

Activated: 06/28/2019
Closed:

Version Date: 11/22/2019
Amendment: 2A

CHILDREN'S ONCOLOGY GROUP**AALL1731**

A Phase 3 Trial Investigating Blinatumomab (IND# 117467, NSC# 765986) in Combination with Chemotherapy in Patients with Newly Diagnosed Standard Risk or Down syndrome B-Lymphoblastic Leukemia (B-ALL) and the Treatment of Patients with Localized B-Lymphoblastic Lymphoma (B-LLy)

A COG Groupwide Phase III Study

NCI Supplied Agent: Blinatumomab (IND# 117467, NSC# 765986),
IV Solution Stabilizer for Blinatumomab (NSC 773150)

IND Sponsor for Blinatumomab: DCTD, NCI

THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, AND SHOULD NOT BE COPIED, REDISTRIBUTED OR USED FOR ANY OTHER PURPOSE. MEDICAL AND SCIENTIFIC INFORMATION CONTAINED WITHIN THIS PROTOCOL IS NOT INCLUDED TO AUTHORIZE OR FACILITATE THE PRACTICE OF MEDICINE BY ANY PERSON OR ENTITY. RESEARCH MEANS A SYSTEMATIC INVESTIGATION, INCLUDING RESEARCH DEVELOPMENT, TESTING AND EVALUATION, DESIGNED TO DEVELOP OR CONTRIBUTE TO GENERALIZABLE KNOWLEDGE. THIS PROTOCOL IS THE RESEARCH PLAN DEVELOPED BY THE CHILDREN'S ONCOLOGY GROUP TO INVESTIGATE A PARTICULAR STUDY QUESTION OR SET OF STUDY QUESTIONS AND SHOULD NOT BE USED TO DIRECT THE PRACTICE OF MEDICINE BY ANY PERSON OR TO PROVIDE INDIVIDUALIZED MEDICAL CARE, TREATMENT, OR ADVICE TO ANY PATIENT OR STUDY SUBJECT. THE PROCEDURES IN THIS PROTOCOL ARE INTENDED ONLY FOR USE BY CLINICAL ONCOLOGISTS IN CAREFULLY STRUCTURED SETTINGS, AND MAY NOT PROVE TO BE MORE EFFECTIVE THAN STANDARD TREATMENT. ANY PERSON WHO REQUIRES MEDICAL CARE IS URGED TO CONSULT WITH HIS OR HER PERSONAL PHYSICIAN OR TREATING PHYSICIAN OR VISIT THE NEAREST LOCAL HOSPITAL OR HEALTHCARE INSTITUTION.

STUDY CO-CHAIR

Sumit Gupta M.D., Ph.D.
Hematology/Oncology
Hospital for Sick Children
555 University Ave.
Room 9415 Black Wing
Toronto, ON, Canada, M5G-1X8
Phone: (416) 513-7654 ext: 201681
Fax: (416) 813-5327
sumit.gupta@sickkids.ca

STUDY CO-CHAIR

Rachel Rau, M.D.
Pediatric Oncology
Baylor College of Medicine
1102 Bates St.
Suite 1025
Houston, TX 77030
Phone: (832) 824-4278
Fax: (832) 825-4846
Rachel.Rau@bcm.edu

| CONTACT INFORMATION | | |
|--|--|--|
| To submit site registration documents: | For patient enrollments: or clinical questions (i.e., patient eligibility or treatment-related) | Submit study data |
| <p>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)</p> <p>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.</p> <p>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</p> | <p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p> | Data collection for this study will be done exclusively through Medidata Rave. Please see the Data Submission Schedule in the CRF packet for further instructions. |
| <p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p> | | |
| <p>For clinical questions (i.e., patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.</p> <p>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p> | | |
| <p>The CTSU Website is located at https://www.ctsu.org.</p> | | |

TABLE OF CONTENTS

| <u>SECTION</u> | <u>PAGE</u> |
|---|-------------|
| STUDY COMMITTEE | 8 |
| ABSTRACT | 12 |
| EXPERIMENTAL DESIGN SCHEMA - B-ALL PATIENTS (INCLUDING SR DS POST-INDUCTION) | 14 |
| EXPERIMENTAL DESIGN SCHEMA – DS B-ALL PATIENTS | 15 |
| EXPERIMENTAL DESIGN SCHEMA – B-LLY PATIENTS (INCLUDING DS) | 16 |
| 1 GOALS AND OBJECTIVES (SCIENTIFIC AIMS) | 17 |
| 1.1 Primary Aims | 17 |
| 1.2 Secondary Aims | 17 |
| 1.3 Exploratory Objectives | 17 |
| 2 BACKGROUND | 18 |
| 2.1 Introduction | 18 |
| 2.2 Rationale for Selected Approach and Trial Design | 21 |
| 2.3 Relevant Data | 24 |
| 2.4 Correlative Studies | 30 |
| 3 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY | 34 |
| 3.1 Study Enrollment | 34 |
| 3.2 Patient Eligibility Criteria | 42 |
| 3.3 Definitions | 45 |
| 4 TREATMENT PLAN | 53 |
| 4.1 Overview of Treatment Plan | 53 |
| 4.2 Non-DS SR B-ALL Patients – Induction | 60 |
| 4.3 All SR-Fav B-ALL (including DS patients) – Consolidation | 66 |
| 4.4 All SR-Fav B-ALL (including DS patients) – Interim Maintenance I EscMTX | 70 |
| 4.5 All SR-Fav B-ALL (including DS patients) – Delayed Intensification | 75 |
| 4.6 All SR-Fav B-ALL (including DS patients) – Interim Maintenance II EscMTX | 82 |
| 4.7 Non-DS SR-Fav B-ALL – Maintenance | 87 |
| 4.8 DS SR-Fav B- ALL – Maintenance | 91 |
| 4.9 All SR-Avg B-ALL (including DS patients) – Consolidation | 96 |
| 4.10 All SR-Avg B-ALL Arm A (including DS patients) – Interim Maintenance I EscMTX101 | |
| 4.11 All SR-Avg B-ALL Arm A (including DS patients) – Delayed Intensification | 106 |
| 4.12 All SR-Avg B-ALL Arm A (including DS patients) – Interim Maintenance II EscMTX | |
| 113 | 113 |
| 4.13 Non-DS SR-Avg B-ALL Arm A – Maintenance | 118 |
| 4.14 DS SR-Avg B-ALL Arm A – Maintenance | 122 |
| 4.15 All SR-Avg B-ALL Arm B (including DS patients) – Blinatumomab Block 1 | 127 |
| 4.16 All SR-Avg B-ALL Arm B (including DS patients) – Interim Maintenance I EscMTX132 | |
| 132 | 132 |
| 4.17 All SR-Avg B-ALL Arm B (including DS patients) – Blinatumomab Block 2 | 137 |

| | | |
|------|--|-----|
| 4.18 | All SR-Avg B-ALL Arm B (including DS patients) – Delayed Intensification | 142 |
| 4.19 | All SR-Avg B-ALL Arm B (including DS patients) – Interim Maintenance II EscMTX | 149 |
| 4.20 | Non-DS SR-Avg B-ALL Arm B – Maintenance | 154 |
| 4.21 | DS SR-Avg B-ALL Arm B – Maintenance | 158 |
| 4.22 | SR-High B-ALL – Consolidation | 163 |
| 4.23 | SR-High B-ALL Arm C – Interim Maintenance I HDMTX | 169 |
| 4.24 | SR-High B-ALL Arm C – Delayed Intensification (DI) | 174 |
| 4.25 | SR-High B-ALL Arm C – Interim Maintenance II CMTX | 181 |
| 4.26 | SR-High B-ALL Arm C – Maintenance Cycles 1-2 | 185 |
| 4.27 | SR-High B-ALL Arm C – Maintenance Cycle 3 and Subsequent Cycles | 189 |
| 4.28 | SR-High B-ALL Arm D – Blinatumomab Block 1 | 193 |
| 4.29 | SR-High B-ALL Arm D – Interim Maintenance I HDMTX | 198 |
| 4.30 | SR-High B-ALL Arm D – Blinatumomab Block 2 | 204 |
| 4.31 | SR-High B-ALL Arm D – Delayed Intensification (DI) | 208 |
| 4.32 | SR-High B-ALL Arm D – Interim Maintenance II CMTX | 215 |
| 4.33 | SR-High B-ALL Arm D – Maintenance Cycles | 220 |
| 4.34 | All DS B-ALL Patients – Induction | 224 |
| 4.35 | DS-HIGH B-ALL – Consolidation | 230 |
| 4.36 | DS-HIGH B-ALL – Blinatumomab Block 1 | 237 |
| 4.37 | DS-HIGH B-ALL – Interim Maintenance with ID MTX | 242 |
| 4.38 | DS-HIGH B-ALL – Blinatumomab Block 2 | 248 |
| 4.39 | DS-HIGH B-ALL – Delayed Intensification | 253 |
| 4.40 | DS-HIGH B-ALL – Blinatumomab Block 3 | 257 |
| 4.41 | DS-HIGH B-ALL – Maintenance | 261 |
| 4.42 | Non-DS B-Ly – Induction | 266 |
| 4.43 | DS B-Ly – Induction | 271 |
| 4.44 | All B-Ly (including DS patients) – Consolidation | 277 |
| 4.45 | All B-Ly (including DS patients) – Interim Maintenance I EscMTX | 281 |
| 4.46 | All B-Ly (including DS patients) – Delayed Intensification | 286 |
| 4.47 | All B-Ly (including DS patients) – Interim Maintenance II EscMTX | 293 |
| 4.48 | All B-Ly (including DS patients) – Maintenance | 298 |
| 5 | DOSE MODIFICATIONS FOR TOXICITIES | 303 |
| 5.1 | Blinatumomab | 303 |
| 5.2 | Asparaginase [Erwinia or Pegasparagase (PEG-Asparaginase)] | 307 |
| 5.3 | Cyclophosphamide | 308 |
| 5.4 | Cytarabine (ARAC) | 308 |
| 5.5 | DOXOrubicin (Anthracyclines) | 309 |
| 5.6 | IT Methotrexate | 311 |
| 5.7 | IV Methotrexate | 313 |
| 5.8 | PO Methotrexate, and 6-Mercaptopurine (6-MP) | 318 |
| 5.9 | Steroids (Dexamethasone and PredniSO(LO)ne) | 323 |
| 5.10 | PO 6-Thioguanine (6-TG) | 324 |
| 5.11 | VinCRIStine | 325 |

| | | |
|-------|---|-----|
| 6 | DRUG INFORMATION | 327 |
| 6.1 | BLINATUMOMAB (11/18/2019) | 327 |
| 6.2 | ASPARAGINASE ERWINIA CHRYSANTHEMI | 341 |
| 6.3 | CYCLOPHOSPHAMIDE INJECTION | 344 |
| 6.4 | CYTARABINE - ALL ROUTES | 345 |
| 6.5 | DEXAMETHASONE | 347 |
| 6.6 | DOXORUBICIN | 349 |
| 6.7 | LEUCOVORIN CALCIUM | 352 |
| 6.8 | MERCAPTOPURINE | 353 |
| 6.9 | METHOTREXATE – ALL ROUTES | 355 |
| 6.10 | PEGASPARGASE | 359 |
| 6.11 | PREDNISO(LO)NE | 361 |
| 6.12 | THIOGUANINE | 363 |
| 6.13 | VINCRISTINE SULFATE | 364 |
| 7 | EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED | 367 |
| 7.1 | Follow-up & End of Therapy | 367 |
| 7.2 | Research Studies for which Patient Participation is REQUIRED | 368 |
| 7.3 | Research Studies for which Patient Participation is OPTIONAL | 369 |
| 8 | CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA | 373 |
| 8.1 | Criteria for Removal from Protocol Therapy (See Section 3.3 for B-ALL definitions and Section 18.0 for B-LLy definitions) | 373 |
| 8.2 | Off Study Criteria | 373 |
| 9 | STATISTICAL CONSIDERATIONS | 374 |
| 9.1 | Statistical Design | 374 |
| 9.2 | Patient Accrual and Expected Duration of Trial | 375 |
| 9.3 | Statistical Analysis Methods | 375 |
| 9.4 | Sex and Minority Accrual Estimates | 380 |
| 10 | EVALUATION CRITERIA | 381 |
| 10.1 | Common Terminology Criteria for Adverse Events (CTCAE) | 381 |
| 10.2 | Response Criteria for Patients with Leukemia and Lymphoma | 381 |
| 11 | ADVERSE EVENT REPORTING REQUIREMENTS | 381 |
| 11.1 | Purpose | 381 |
| 11.2 | Determination of reporting requirements | 381 |
| 11.3 | Expedited Reporting Requirements – Serious Adverse Events (SAEs) | 382 |
| 11.4 | Special Situations for Expedited Reporting | 382 |
| 11.5 | Reporting Requirements for Specialized AEs | 384 |
| 11.6 | Exceptions to Expedited Reporting | 385 |
| 11.7 | Reporting Requirements - Investigator Responsibility | 386 |
| 11.8 | General Instructions for Expedited Reporting via CTEP-AERS | 386 |
| 11.9 | Reporting Table for Late Phase 2 and Phase 3 Studies – Table A | 387 |
| 11.10 | Protocol Specific Additional Instructions and Reporting Exceptions | 388 |

| | | |
|-------|---|-----|
| 11.11 | Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway | 388 |
| 11.12 | Routine Adverse Event Reporting | 389 |
| 11.13 | Syndrome Reporting | 390 |
| 12 | RECORDS AND REPORTING | 390 |
| 12.1 | CDUS | 390 |
| 12.2 | CRADA/CTA | 390 |
| 13 | PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS | 393 |
| 13.1 | Pathology Goals | 393 |
| 13.2 | Requirements for Handling Tissue or Cytology Specimens at Primary Institutions | 393 |
| 13.3 | Immunophenotyping Recommendations for Primary Institutions | 394 |
| 13.4 | Pathology Staging Criteria | 394 |
| 13.5 | Retrospective Central Pathology Review | 395 |
| 14 | SPECIAL STUDIES SPECIMEN REQUIREMENTS | 398 |
| 14.1 | Minimal Residual Testing (MRD) by Flow Cytometry Days 8 and 29 - REQUIRED | 398 |
| 14.2 | MRD by High-Throughput Sequencing (HTS) in Bone Marrow at EOI – REQUIRED | 398 |
| 14.3 | Biobanking for Future Research in Peripheral Blood at End of Induction – OPTIONAL (non-DS NCI SR B-ALL) | 400 |
| 14.4 | MRD by Flow Cytometry at End of Consolidation - REQUIRED for NCI SR B-ALL (with or without DS) with EOI flow MRD $\geq 0.1\%$ and NCI HR DS B-ALL with EOI flow MRD $\geq 0.01\%$ | 401 |
| 14.5 | Biobanking for Future Research in Bone Marrow at End of Consolidation – OPTIONAL (SR-High patients with EOI flow MRD $\geq 0.1\%$, and SR-High patients with EOI flow MRD 0.01-0.099% who have BM assessed for MRD at EOC) | 403 |
| 14.6 | Immune Function in Children with Down Syndrome B-ALL – OPTIONAL (all DS patients) | 405 |
| 14.7 | Biobanking for Future Research on CSF for B-ALL – OPTIONAL | 406 |
| 14.8 | Biobanking for Future Research for B-Lly patients – OPTIONAL | 408 |
| 14.9 | Minimal Marrow Disease for B-Lly patients – Optional | 410 |
| 15 | DS B-ALL IMMUNE FUNCTION STUDIES | 412 |
| 15.1 | Immune Function in DS B-ALL (OPTIONAL) | 412 |
| 15.2 | Host Genetic Susceptibility to Infection in DS B-ALL (OPTIONAL) | 415 |
| 16 | RADIATION THERAPY GUIDELINES | 417 |
| 16.1 | Cranial Irradiation | 417 |
| 16.2 | Testicular Irradiation | 420 |
| 16.3 | Quality Assurance Documentation | 421 |
| 16.4 | Definitions of Deviation in Protocol Performance | 422 |
| 17 | NEUROCOGNITION, HOUSEHOLD MATERIAL HARDSHIP, AND CAREGIVER BURDEN IN B-ALL | 423 |
| 17.1 | Neurocognition, Household Material Hardship and Caregiver Burden in NCI SR B-ALL – OPTIONAL (non-DS only) | 423 |
| 17.2 | Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with Down Syndrome and Acute Lymphoblastic Leukemia – OPTIONAL (DS only) | 440 |

| | | |
|------|--|-----|
| 18 | B-LLY REQUIRED IMAGING STUDIES AND RESPONSE ASSESSMENT | 448 |
| 18.1 | DISEASE PARAMETERS | 448 |
| 18.2 | METHODS FOR EVALUATION OF MEASURABLE DISEASE | 448 |
| 18.3 | EVALUATIONS | 450 |
| 18.4 | RESPONSE CRITERIA | 450 |
| | APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES | 452 |
| | APPENDIX II: YOUTH INFORMATION SHEETS | 455 |
| | APPENDIX III: MERCAPTOPURINE DOSING TABLE | 459 |
| | APPENDIX IV: THIOGUANINE DOSING TABLE | 464 |
| | APPENDIX V-A: HIGH DOSE METHOTREXATE | 466 |
| | APPENDIX V-B: INTERMEDIATE DOSE METHOTREXATE FLOW CHART | 467 |
| | APPENDIX VI: POSSIBLE DRUG INTERACTIONS | 468 |
| | APPENDIX VII: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA | 472 |
| | APPENDIX VIII: CPY3A4 SUBSTRATES, INHIBITORS AND INDUCERS | 474 |
| | APPENDIX IX: SUPPORTIVE CARE GUIDELINES | 476 |
| I. | General Guidelines | 476 |
| II. | Guidelines for Induction | 478 |
| III. | Patients with Down syndrome (DS) | 479 |
| | APPENDIX X-A: CLINICAL SITE MANAGEMENT OF OUT PATIENT TREATMENT USING CTEP-SUPPLIED BLINATUMOMAB | 481 |
| | APPENDIX X-B: SHIPMENT OF BLINATUMOMAB IV BAG FROM SITE/PHARMACY TO PATIENT'S HOME | 484 |
| | APPENDIX XI: PROCEDURES FOR FLOW CYTOMETRY LABORATORIES SUGGESTED FOR AALL1731 | 485 |
| | APPENDIX XII: PROCEDURES FOR HIGH-THROUGHPUT SEQUENCING METHOD OF MRD ANALYSIS | 487 |
| | APPENDIX XIII: FLOW CYTOMETRIC TESTING FOR MINIMAL MARROW AND MINIMAL RESIDUAL DISEASE IN B-LLY PATIENTS | 490 |
| | APPENDIX XIV: CONTACTS FOR TREATMENT PLAN INQUIRIES BY GEOGRAPHICAL DISTRIBUTION | 491 |
| | APPENDIX XV: PATIENT CLINICAL TRIAL WALLET CARD | 492 |
| | REFERENCES | 493 |

STUDY COMMITTEE

STUDY CO-CHAIR

Sumit Gupta, MD, PhD
Hematology/Oncology
Hospital for Sick Children
555 University Ave.
Room 9415 Black Wing
Toronto, ON, Canada, M5G-1X8
Phone: (416) 813-7654 ext:201681
Fax: (416) 813-5327
E-mail: sumit.gupta@sickkids.ca

STUDY CO-CHAIR

Rachel Rau, MD
Pediatric Oncology
Baylor College of Medicine
1102 Bates St. Suite 1025
Houston, TX 77030
Phone: (832) 824-4278
Fax: (832) 825-4846
E-mail: Rachel.Rau@bcm.edu

STUDY VICE CHAIR

Anne Angiolillo, MD
Hematology/Oncology
Children's National Medical Center
111 Michigan Avenue NW
Washington, DC 20010
Phone: (202) 476-2800
Fax: (202) 476-5685
E-mail: aangioli@childrensnational.org

STUDY VICE CHAIR

Karen Rabin, MD, PhD
Hematology/Oncology
Baylor College of Medicine
1102 Bates St., Suite 750.00
Houston, TX 77030
Phone: (832) 824-4213
Fax: (832) 825-1206
E-mail: krrabin@texaschildrens.org

STUDY STATISTICIAN

John Kairalla, PhD
Biostatistics
Children's Oncology Group Statistics and Data Center
6011 NW 1st St. Place
Gainesville, FL 32607
Phone: (352) 273-0574
Fax: (352) 392-8162
E-mail: jkairalla@cog.ufl.edu

STUDY COMMITTEE MEMBERS

Mignon Lee-Cheun Loh, MD
Hematology/Oncology
Helen Diller Family Comprehensive Cancer Center
1450 3rd Street. Rm 284
San Francisco, CA 94158
Phone: (415) 514-0853
Fax: (415) 353-2657
E-mail: mignon.loh@ucsf.edu

Elizabeth Raetz, MD

Hematology/Oncology
Laura and Isaac Perlmutter Cancer Center at NYU Langone
160 East 32nd Street
New York, NY 10016
Phone: (212) 263-9908
E-mail: elizabeth.raetz@nyulangone.org

Julie Gastier-Foster, PhD

Laboratory Science
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215
Phone: (614) 722-2866
Fax: (614) 722-2887
E-mail: Julie.Gastier-Foster@nationwidechildrens.org

Shalini C. Reshma, PhD

Laboratory Science
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215
Phone: (614) 722-2866
Fax: (614) 722-2887
E-mail: Shalini.Reshma@nationwidechildrens.org

Johann Hitzler MD FRCPC

Hematology/Oncology
Hospital for Sick Children
555 University Avenue
Toronto, ON M5G1X8 CA
Phone: (416) 813-8887
Fax: (416) 813-5327
E-mail: johann.hitzler@sickkids.ca

STUDY COMMITTEE MEMBERS

Reuven Schore, MD
Hematology/Oncology
Children's National Medical Center
111 Michigan Avenue NW
Washington, DC 20010
Phone: (202) 476-2800
Fax: (202) 476-5685
E-mail: rschore@childrensnational.org

Lia Gore, MD
Hematology/Oncology
Children's Hospital Colorado
Center for Cancer & Blood Disorders
13124 East 16th Av, Box B115
Aurora, CO 80045
Phone: (720) 777-6458
Fax: (720) 777-7339
E-mail: lia.gore@ucdenver.edu

Brent Wood, MD, PhD
Pathology
Seattle Children's Hospital
M/S G7-800
825 Eastlake Avenue East
Seattle, WA 98109
Phone: (206) 288-7060
Fax: (206) 288-7127
E-mail: woodbl@u.washington.edu

Michael Borowitz, MD, PhD
Pathology
Johns Hopkins University/ Sidney Kimmel Cancer Center
401 N. Broadway
Baltimore, MD 21231
Phone: (410) 614-2889
Fax: (410) 502-1493
E-mail: mborowit@jhmi.edu

Birte Wistinghausen, MD
Division of Oncology
Center for Cancer and Blood Disorders
Children's National Medical Center
111 Michigan Ave NW, Box 1208
Washington, DS 20010
Phone: (202) 476-2800
Fax: (202) 476-5685
E-mail: BWISTINGHA@childrensnational.org

Meenakshi Devidas, PhD
Biostatistics
Children's Oncology Group Statistics and Data Center
6011 NW 1st St. Place
Gainesville, FL 32607
Phone: (352) 273-0551
Fax: (352) 392-8162
E-mail: mdevidas@cog.ufl.edu

Patrick Brown, MD
Hematology/Oncology
Johns Hopkins Univ./Sidney Kimmel Cancer Center
1650 Orleans St. CRB 2M49
Baltimore, MD. 21231
Phone: (410) 614-4915
Fax: (410) 955-8897
E-mail: pbrown2@jhmi.edu

Julie Bradley, MD
Radiation Oncology
UF Health Proton Therapy Institute
2015 North Jefferson Street
Jacksonville, FL 32206
Phone: (904) 588-1441
Fax: (904) 588- 1303
E-mail: jbradley@floridaproton.org

Benjamin Cooper, MD
Radiation Oncology
Laura & Isaac Perlmutter Cancer Center at NYU Langone
160 E. 34th Street
New York, New York 10016
Phone: (212) 731- 5003
E-mail: benjamin.cooper@nyumc.org

Rodney Miles, MD, PhD
Primary Children's Hospital
15 N. Medical Drive East, JMRB 2100
Salt Lake City, UT 84112
Phone: (801) 584-5240
Fax: (801) 584- 5124
E-mail: rodney.miles@path.utah.edu

STUDY COMMITTEE MEMBERS

Maki Okada, RN CPNP
Nursing
Miller Children's and Women's Hospital Long Beach
2801 Atlantic Ave. Suite 100
Long Beach, CA 90806
Phone: (562) 728-5000
Fax: (562) 933-1815
E-mail: mokada@memorialcare.org

Erica Garcia-Frausto, RN MSN CPNP
Nursing
Methodist Children's Hospital of South Texas
Texas Transplant Institute
4410 Medical Drive; Suite 410
San Antonio, TX 78229
Phone: (210) 575-7268
Fax: (210) 575-6319
E-mail: Erica.GarciaFrausto@hcahealthcare.com

Rachel Limbach, LPN, CCRP
Clinical Research Associates
St. Vincent Hospital & Health Care Center
2001 West 86th St.
Indianapolis, IN 46260
Phone: (317) 338- 9825
Fax: (317) 338-8879
E-mail: rachael.limbach@stvincent.org

Lisa Jacola, PhD
Behavioral Science
St Jude Children's Research Hospital
MS740
262 Danny Thomal Place
Memphis, TN 38105
Phone: (901) 595-5042
Fax: (901) 595-4701
Email: lisa.jacola@stjude.org

Kira O'Neil Bona, MD MPH
Hematology/Oncology
Dana-Farber/Harvard Cancer Center
450 Brookline Ave, Dana Building 1134
Boston, MA 02115
Phone: (617) 632-4688
Fax: (617) 632-4410
Email: kira.bona@childrens.harvard.edu

Sarah Alexander, MD
Pediatric Hematology/Oncology
Hospital for Sick Children
555 University Avenue
Toronto, ON M5G 1X8
Canada
Phone: (416) 813-7654 x204068
Fax: (416) 813-5327
E-mail: sarah.alexander@sickkids.ca

Tamara Porter Miller, MD
Pediatric Hematology/Oncology
Children's healthcare of Atlanta Egleston
1405 Clifton Road, 4th Floor
Atlanta, GA 30322
Phone: (404) 785-1200
Fax: (404) 727-4455
E-mail: tamara.miller@emory.edu

Andrew J. Carroll, PhD
Cytogenetics
Children's Hospital of Alabama
1530 3rd Ave. South
Kaul Bldg., Room 314B
Birmingham, AL 35294-2050
Phone: (205) 934-0665
Fax: (205) 934-1078
E-mail: acarroll@uab.edu

Mary Shago, PhD
Cytogenetics
Hospital for Sick Children
555 Universtiay Avenue
Toronto, ON M5G 1X8
Canada
Phone: (416) 813-7654 ext: 201448
E-mail: mary.shago@sickkids.ca

Yassmine Akkari, PhD
Cytogenetics
Randall Children's Hospital at Legacy Emanuel
1225 NE 2nd Avenue
Portland, OR 97232
Phone: (503) 413-5214
Fax: (503) 413-1273
Email: yakkari@lhs.org

Julienne Brackett, MD, MS
Hematology/Oncology
Baylor College of Medicine
6701 Fannin Street, Suite 1510
Houston, TX 77030
Phone: (832) 824-1511
Fax: (832) 825-1503
Email: jxbracke@texaschildrens.org

Amanda Li, MD
Cellular Therapy
British Columbia Children's Hospital
4480 Oak Street, Room B315
Vancouver, BC V6H 3V4 Canada
Phone: (604) 875-2644
Fax: (604) 875-2911
Email: ali3@cw.bc.ca

Amanda M. Termuhlen, MD
Hematology/Oncology
University of Minnesota/ Masonic Cancer Center
420 Delaware Street SE
A672-3 Mayo Building
Minneapolis, MN 55408
Phone: (612) 624-5442
Fax: (612) 626-4911
E-mail: atermuhl@umn.edu

COG RESEARCH COORDINATOR
Susan Conway, BA CCRP
COG Data Center University of Florida
6011 NW 1st Place
Gainesville, FL 32607
Phone: (352) 273-0559
Fax: (352) 392-8162
E-mail: sconway@cog.ufl.edu

COG RESEARCH COORDINATOR
Naira Setrakian, MPH
Children's Oncology Group
222. East Huntington Dr. Suite 100
Monrovia, CA 91016
Phone: (626) 241-1617
Fax: (626) 445- 4334
E-mail: nsetrakian@childrensoncologygroup.org

STUDY PHARMACIST
Tara E. Wright, PharmD
Pharmacy
Seattle Children's Hospital
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 987-2033
E-mail: tara.wright@seattlechildrens.org

COG PROTOCOL COORDINATOR
Christine Petrossian, BS
Children's Oncology Group
222. East Huntington Dr. Suite 100
Monrovia, CA 91016
Phone: (626) 241-1578
Fax: (626) 445- 4334
E-mail: cpetrossian@childrensoncologygroup.org

NCI SUPPLIED AGENT
Blinatumomab NSC#:765986 IND#:117467
IV Solution Stabilizer for Blinatumomab NSC#: 773150

IND SPONSOR: [DCTD, NCI](http://DCTD.NCI)

| OTHER AGENTS | NSC# | IND# |
|----------------------|-------------|-------------|
| Asparaginase Erwinia | 106977 | Exempt |
| Cyclophosphamide | 26271 | Exempt |
| Cytarabine | 63878 | Exempt |
| Dexamethasone | 34521 | Exempt |
| DOXOrubicin | 123127 | Exempt |
| Leucovorin Calcium | 003590 | Exempt |
| Mercaptopurine | 000755 | Exempt |
| Methotrexate | 000740 | Exempt |
| Pegasparagase | 624239 | Exempt |
| Predniso(LO)ne | 9151 | Exempt |
| Thioguanine | 000752 | Exempt |
| VinCRIStine | 67574 | Exempt |

SEE SECTION 13.0 AND SECTION 14.0 FOR SPECIMEN SHIPPING ADDRESSES.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about your subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

While outcomes in Standard Risk (SR) B-lymphoblastic leukemia (B-ALL) have improved significantly, this population still accounts for approximately half of the overall burden of relapse among children with ALL. Despite contemporary intensive chemotherapy, the outcomes for children with relapsed ALL remain dismal, with 5-year overall survival (OS) of approximately 38%.¹ Interventions that further reduce the number of SR ALL relapses will therefore significantly improve the long-term survival of the overall ALL population.

AALL1731 is a group-wide risk-stratified trial for children with newly diagnosed B-ALL and localized B-lymphoblastic lymphoma (B-LLy) that will test if the addition of blinatumomab to standard chemotherapy in patients with NCI SR B-ALL at highest risk for relapse will improve disease-free survival (DFS). Risk stratification will be determined by traditional prognosticators (tumor genetics, extent of extramedullary involvement, early response to therapy as determined by flow cytometry) combined with the new DNA-based MRD detection technology of high throughput sequencing (HTS) of the immunoglobulin heavy chain (IgH).

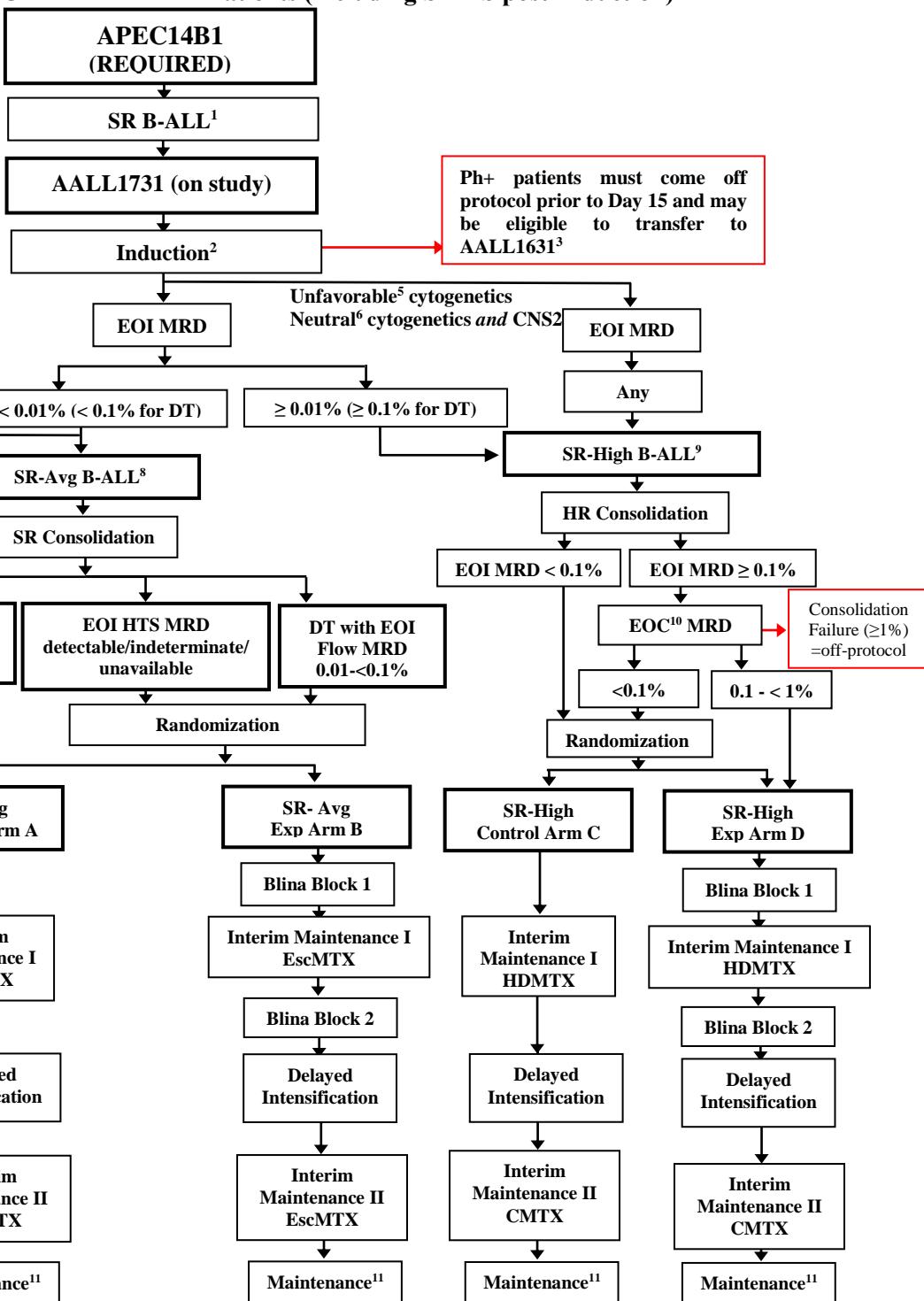
A subset of NCI SR B-ALL children with outstanding outcomes (SR-Favorable) will be identified in whom no new randomized intervention will be tested. Similarly, patients with localized (Murphy stage I/II) B-LLy will receive non-randomized standard risk ALL therapy. NCI SR B-ALL patients without specific adverse clinical features (CNS3, testicular leukemia) and a positive end of Induction (EOI) bone marrow MRD within the context of a genotype-specific threshold will be classified as Standard Risk-Average (SR-Avg) post-Induction. EOI MRD detection by HTS will identify an additional subgroup of these patients with outstanding outcomes (EOI HTS-MRD negative) who will be treated with standard chemotherapy alone, while the remaining SR-Avg patients will be eligible for randomization to either standard chemotherapy alone or standard chemotherapy plus blinatumomab. NCI SR patients with poor prognostic features, such as unfavorable tumor genetics or EOI bone marrow MRD above a genotype specific threshold ($\geq 0.1\%$ for those with double trisomies of chromosomes 4 and 10; $\geq 0.01\%$ for all others), will be classified as Standard Risk-High post-Induction and will be eligible for randomization to augmented Berlin-Frankfurt-Münster (aBFM)-based chemotherapy post-Induction with or without blinatumomab. This trial will also test whether patients can be treated with a uniform duration of therapy (2 years from the start of Interim Maintenance 1) regardless of sex, substantially reducing the burden of therapy for males.

We will also investigate the role of immunotherapy in children with Down Syndrome (DS) and B-ALL, a population traditionally excluded from studies of novel agents, and for which intensification of standard cytotoxic chemotherapy is not feasible due to their significantly increased risk of non-relapse morbidity and mortality. Patients with DS and B-ALL with high-risk features (DS-High) will be non-randomly assigned to receive blinatumomab added to a chemotherapy backbone that omits intensive elements of therapy. Patients with DS lacking high-risk features will be risk stratified in the same fashion as non-DS NCI SR B-ALL patients, including eligibility for randomization to chemotherapy with or without blinatumomab. DS patients with localized B-LLy are eligible for AALL1731 and will non-randomly be assigned to receive standard risk chemotherapy.

AALL1731 also includes studies to identify the effects of household material hardship (HMH) on neurocognitive functioning during treatment, determine the impact of blinatumomab on caregiver burden and patient/proxy-reported symptoms, and explore new applications of the HTS-MRD assay in B-ALL. Additional correlative aims will explore the impact of ALL therapy and its effects on neurocognitive, functional and quality of life outcomes in children with DS, and will identify immune defects underlying the high rates of life-threatening infectious toxicities in patients with DS. This trial will also define the prevalence of minimal marrow disease (MMD) in B-LLy and correlate MMD at diagnosis with outcomes.

EXPERIMENTAL DESIGN SCHEMA - B-ALL Patients (including SR DS post-Induction)

| | |
|--|---------------|
| SR: Standard Risk | Avg: Average |
| Fav: Favorable | HR: High Risk |
| DS: Down syndrome | |
| DT: Double trisomy of chromosomes 4 and 10 | |
| EOC: End of Consolidation | |
| EOI: End of Induction | |
| HTS: High-Throughput Sequencing | |
| IM: Interim Maintenance | |
| MRD: Minimal Residual Disease | |
| Blin: Blinatumomab | |



¹ NCI SR with steroid pretreatment, CNS3, or testicular leukemia transfer to AALL1732 at beginning of Induction;

Induction ³ Ph+ ALL patients go off-study prior to Day 15 of Induction, and if eligible enroll on AALL1631;

patients lacking high risk features and with EOI MRD < 0.01% receive treatment on the SR-Fav or SR-Avg B-ALL arm;

⁵ Unfavorable cytogenetics include KMT2A-R, iAMP21, hypodiploidy, t(17;19); ⁶ Neutral cytogenetics: lacking favorable and unfavorable cytogenetic features.

⁷ SR-Favorable: NCI SR (non-DS and DS) B-ALL, CNS 1 or 2, with favorable cytogenetics [ETV6-RUNX1 fusion or double trisomies (DT) 4 and 10], Day 8 PB MRD <1%, and EOI BM MRD <0.01%; ⁸ Meet features for therapy on the SR chemotherapy backbone; refer to [Section 3.3.6](#);

⁹ Meet features for therapy on the HR chemotherapy backbone; refer to [Section 3.3.6](#); ¹⁰ EOC BM MRD evaluation required for SR-High patients with EOI BM MRD ≥ 0.1%, and is recommended for SR-High with EOI BM MRD 0.01-0.099% require an EOC BM MRD evaluation. Patients with Consolidation Failure as defined in [Section 3.3.5](#) will go off-protocol therapy;

¹¹ Timed from the start of the phase following Consolidation for a total of 2 years for **both females and males**.

² 4 week, ³ drug

⁴ DS SR B-ALL

⁵ Unfavorable

⁶ Neutral cytogenetics: lacking favorable and unfavorable cytogenetic features.

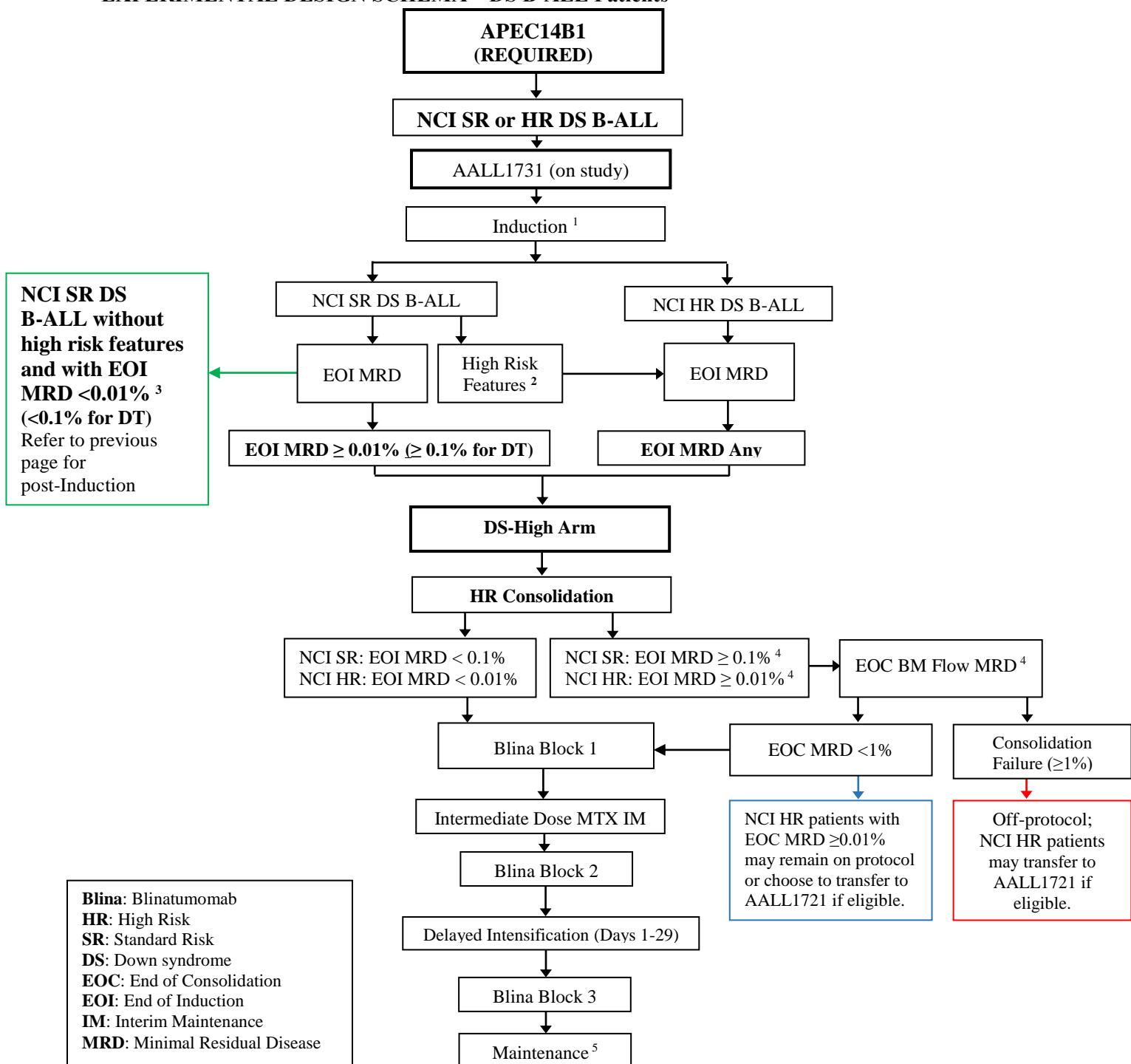
⁷ SR-Favorable: NCI SR (non-DS and DS) B-ALL, CNS 1 or 2, with favorable cytogenetics [ETV6-RUNX1 fusion or double trisomies (DT) 4 and 10], Day 8 PB MRD <1%, and EOI BM MRD <0.01%;

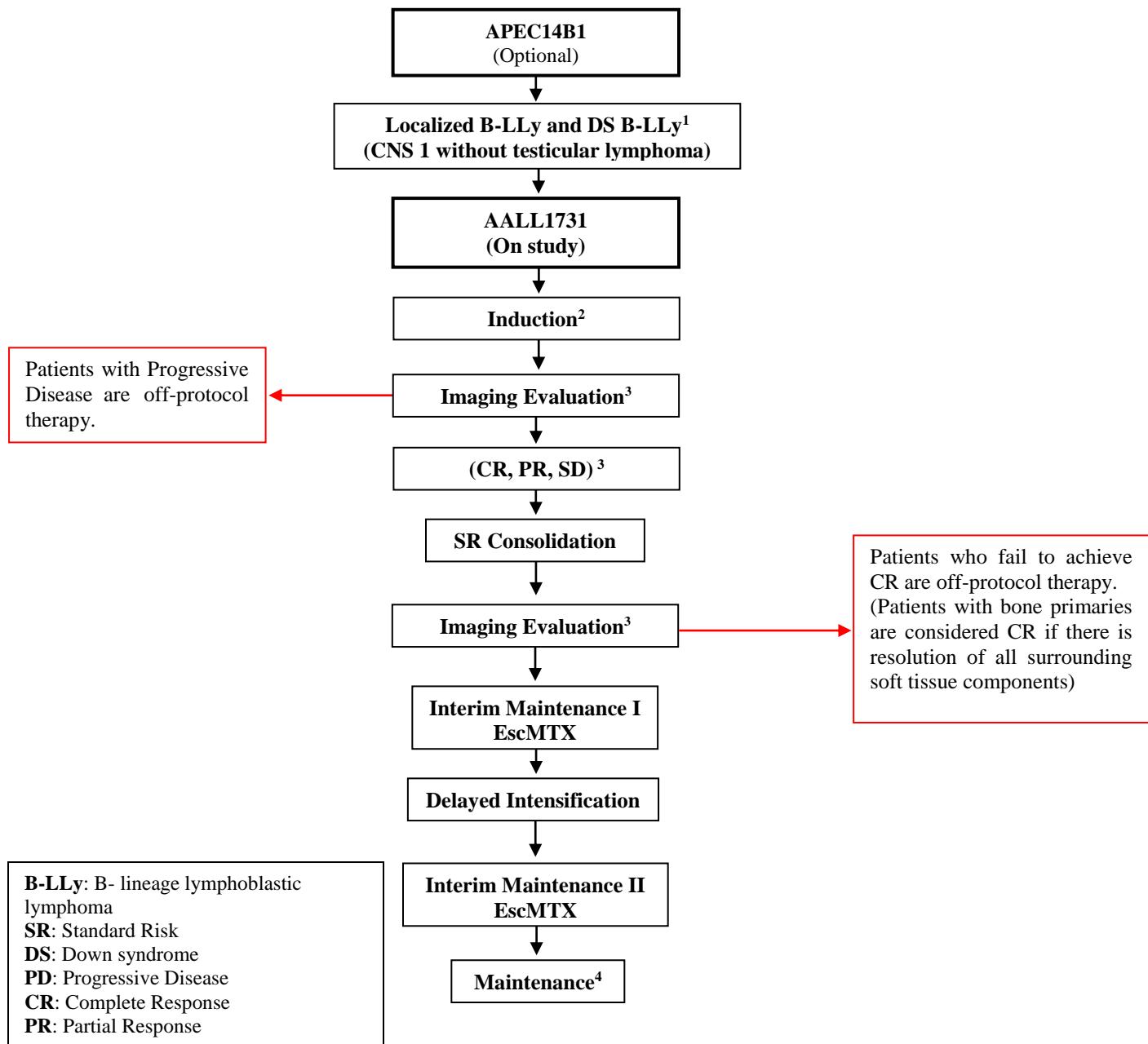
⁸ Meet features for therapy on the SR chemotherapy backbone; refer to [Section 3.3.6](#);

⁹ Meet features for therapy on the HR chemotherapy backbone; refer to [Section 3.3.6](#);

¹⁰ EOC BM

EXPERIMENTAL DESIGN SCHEMA – DS B-ALL Patients

¹ 4 week, 3 drug Induction;² All NCI HR DS and those NCI SR DS patients with EOI MRD $\geq 0.01\%$ ($\geq 0.1\%$ for DT) and unfavorable features, which includes unfavorable cytogenetics, neutral cytogenetics with CNS2, CNS3, testicular disease, or steroid pretreatment > 24 hours in the 2 weeks prior to diagnosis with no CBC obtained within 3 days prior to initiation of steroid. Refer to [Section 3.3.6](#);³ NCI SR DS B-ALL patients without high risk features and with EOI MRD $< 0.01\%$ ($<0.1\%$ for DT) receive treatment on the SR-Fav or SR-Avg B-ALL arm. Refer to schema on previous page and post-Induction risk assignment in [Section 3.3.6](#);⁴ EOC BM MRD evaluation required for NCI SR DS Patients with EOI BM MRD $\geq 0.1\%$ and NCI HR DS patients with EOI BM MRD $\geq 0.01\%$, and is recommended for NCI SR DS patients with EOI BM MRD 0.01-0.099%. Patients with Consolidation Failure as defined in [Section 3.3.5](#) will go off-protocol therapy;⁵ Timed from the start of Blina Block 1 for a total of 2 years for both girls and boys. **Note:** Leucovorin rescue will be given after each dose of IT MTX for all DS during all applicable phases

EXPERIMENTAL DESIGN SCHEMA – B-LLy Patients (including DS)

¹Murphy Stages I and II (See [Appendix VII](#) for classification criteria). CNS 2/3 are not eligible for therapy on AAL1731. See AALL1732; ²4 week, 3 drug Induction; ³See [Section 18.4](#) for definitions of response criteria (progressive disease and relapse);

⁴Timed from the start of Interim Maintenance I for a total of 2 years for both girls and boys.

Note: Leucovorin rescue will be given after each dose of IT MTX for all patients with DS during all applicable phases of therapy.

1 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

- 1.1.1 To determine in a randomized manner if the addition of 2 cycles of blinatumomab to standard therapy improves disease-free survival (DFS) in patients with SR B-ALL and higher risk features (SR-High), and patients with standard-risk average (SR-Avg) B-ALL who are negative for minimal residual disease (MRD) by flow cytometry but have detectable or indeterminate MRD as measured by high-throughput sequencing (HTS) at end of Induction (EOI).
- 1.1.2 To confirm that boys in the standard-risk favorable (SR-Fav) subset of B-ALL, with or without DS, will maintain a 5-year DFS of greater than 93% when treated with a standard chemotherapy regimen with a treatment duration of 2 years from the start of Interim Maintenance I (IM1).

1.2 Secondary Aims

- 1.2.1 To describe the DFS for patients with SR-Avg B-ALL who are negative for MRD measured by flow cytometry and HTS at EOI when treated with standard chemotherapy with a treatment duration of 2 years from the start of IM1, regardless of sex.
- 1.2.2 To describe the DFS for patients with standard-risk favorable (SR-Fav) B-ALL when treated with a standard chemotherapy regimen.
- 1.2.3 To determine if patients with DS-High achieve a reduction of treatment-related mortality (TRM) after replacement of intensive elements of standard chemotherapy (omission of anthracyclines in Induction, omission of the second month of DI) with 3 cycles of blinatumomab.
- 1.2.4 To describe the DFS characterized by the replacement of intensive elements of standard chemotherapy with 3 cycles of blinatumomab in patients with DS-High B-ALL.
- 1.2.5 To describe the DFS for patients with localized (Murphy Stage I and II) B-Lymphoblastic Lymphoma (B-LLy) receiving standard risk B-ALL therapy.
- 1.2.6 To compare the change in neurocognitive functioning, as measured by the CogState Cognitive Composite, from baseline to end-of-therapy among patients with ALL ages 4- <10 years at the time of diagnosis between children from poor families (defined as presence of household material hardship (HMH), including either food, housing or energy insecurity) and non-poor families (absence of HMH).
- 1.2.7 To describe the impact of blinatumomab on caregiver burden and patient/proxy-reported symptoms among a subset of children enrolled in the HMH and neurocognitive outcome study.

1.3 Exploratory Objectives

- 1.3.1 To explore adaptive and innate immune functions and host genetic factors associated with severe infectious complications in children with DS B-ALL.
- 1.3.2 To explore the impact of ALL and its therapy on neurocognitive, functional, and quality of life outcomes in patients with DS and ALL, as measured by caregiver (parent/legal guardian) questionnaires.
- 1.3.3 To define the prevalence of minimal marrow disease (MMD) in B-LLy and to correlate MMD at diagnosis with outcome in patients with B-LLy.

2 BACKGROUND

2.1 Introduction

2.1.1 General Overview

While outcomes in SR B-ALL have improved significantly, this population still accounts for approximately half of the overall burden of relapse among children with ALL. Combining traditional prognosticators with new MRD detection technologies, this trial will identify subsets of SR children with outstanding outcomes in whom no new therapeutic randomized intervention will be tested. The remainder of patients, with expected inferior outcomes, will be randomized to receive or not receive a promising new immunotherapy, blinatumomab, in an effort to improve DFS. We will also investigate the role of immunotherapy in children with DS and B-ALL, a population traditionally excluded from studies of novel agents, and for which intensification of standard cytotoxic chemotherapy is impossible due to their significantly increased risk of non-relapse morbidity and mortality. At the completion of this frontline trial, we envision that an improved risk stratification and treatment approach for all children with ALL will be established incorporating the most effective elements of conventional and novel therapy and emerging diagnostic tools, such as MRD detection using DNA based HTS. If successful, this could also pave the way for replacing the most toxic elements of therapy with immunotherapy in the future. Finally, this trial will also confirm that patients can be treated with a uniform duration of therapy (2 years from the start of Interim Maintenance I) regardless of sex, substantially reducing the burden of therapy for males.

The 5-year event free-survival (EFS) for children with NCI SR B-lineage ALL treated on AALL0331 was 89%, and $77.5 \pm 1.2\%$ for those with HR ALL treated on AALL0232.^{2,3} Approximately twice as many children are diagnosed with NCI SR ALL than NCI HR ALL. Thus, despite their superior outcomes, children with NCI SR disease still account for approximately half of the treatment failures in ALL.^{1,4} On the current COG trial for first relapse of B-ALL (AALL1331), 46% of the first 188 enrollments initially had NCI SR disease at diagnosis; 24% had favorable cytogenetics. Despite contemporary intensive chemotherapy, the outcomes for children with relapsed ALL remain dismal, with 5-year overall survival (OS) of approximately 38%.¹ Interventions that further reduce the number of NCI SR ALL relapses will therefore significantly improve the long-term survival of the overall ALL population. In addition, targetable genomic alterations occur less frequently in the NCI SR population than in the NCI HR population⁵, suggesting that new therapeutic strategies for the NCI SR population will need to be agnostic of somatic molecular lesions.

An attractive strategy is to harness new interventions to treat subsets of the NCI SR ALL population at greatest risk of experiencing relapse. Once SR-Fav patients are identified, the remaining NCI SR patients without adverse clinical features (CNS 3, testicular leukemia or steroid pretreatment) will be classified as SR-Avg or SR-High post-Induction. This study will also incorporate DNA based HTS for MRD detection in order to identify an additional subgroup of these patients with outstanding outcomes while studying the impact of a novel therapeutic agent, blinatumomab, in the remaining NCI SR patients.

2.1.2 Rationale for Overall Approach to Risk Stratification

The AALL1731 and AALL1732 (NCI HR B-ALL) risk stratification algorithm is based on the outcomes of more than 8,000 B-ALL patients enrolled on the first-generation Children's Oncology Group (COG) classification trial, AALL03B1. These patients had detailed information collected including NCI risk group, blast cytogenetics and early response to therapy in the context of 3 therapeutic trials, AALL0331 (NCI SR), AALL0232 (NCI HR), and AALL0031 (Very High Risk, VHR). B-ALL patients will be stratified using a combination of NCI risk group, sentinel genetic lesions, and clinical variables (CNS, testicular status and steroid pretreatment) in combination with early treatment response defined by flow cytometry determined blast percentage in peripheral blood (PB) on Day 8 of Induction, and flow cytometric and HTS evaluations of bone marrow (BM) MRD at the EOI and flow cytometric MRD at the end of Consolidation (EOC) for those patients who are EOI MRD $\geq 0.01\%$ ($\geq 0.1\%$ for patients with double trisomy (DT) – see below). Based on these findings, B-ALL patients will be stratified into one of 6 risk groups for post-Induction and post-Consolidation therapy, with the following projected 5-year EFS rates based on data from AALL03B1: SR-Favorable (SR-Fav, $>95\%$), SR-Average (SR-Avg, 89-95%), SR-High (70-88%), HR-Favorable (HR-Fav, $>94\%$), HR-Average (HR, 65-86%), and VHR ($<50\%$). In addition to these defined risk groups, patients will also be assigned to specific therapeutic interventions based on the presence of CNS2/3 disease and DS.

This risk stratification schema implements several changes from AALL08B1, based on available outcome data from AALL03B1 and the companion therapeutic trials AALL0331 and AALL0232. First, the SR-Fav group will be expanded to include all NCI SR CNS1/2 patients with favorable cytogenetics (*ETV6-RUNX1* or DT of chromosomes 4 and 10) and EOI BM MRD $<0.01\%$ who have Day 8 PB MRD $<1\%$, rather than the more stringent Day 8 PB cutoff of $<0.01\%$ used in AALL08B1. This is based on the outstanding EFS $> 95\%$ recently reported for patients on AALL0331 whose Day 8 PB MRD was in the 0.01-1% range.⁶ Specifically, for NCI SR patients with favorable cytogenetics and EOI MRD $<0.01\%$ treated on AALL0331, the 5 year DFS for the 226 patients with Day 8 PB MRD $<0.01\%$ was $96.8\% \pm 1.3\%$. For the 586 such patients with Day 8 PB MRD 0.01-1%, the 5-year DFS was $95.8\% \pm 0.9\%$ (unpublished). Additionally, NCI SR patients with neutral cytogenetics, CNS1 status and EOI BM MRD $<0.01\%$ will be eligible for the SR-Avg arm regardless of Day 8 PB MRD, unlike on AALL08B1, which would have assigned such patients with a Day 8 PB MRD $\geq 1\%$ to high-risk post-Induction therapy. This change is based on data from AALL03B1, which did not use Day 8 PB MRD for risk stratification and therefore treated all such patients with standard risk post-Induction therapy. On AALL03B1, for NCI SR patients with CNS1 status, neutral cytogenetics and EOI BM MRD $<0.01\%$, the 5-year EFS was 92.8% (90.2-95.4%) versus 89.4% (84.3-94.6%) and the 5-year OS was 97.4% (95.8-99.0%) versus 96.3% (93.1-99.4%) for those with Day 8 PB MRD $<1\%$ and $\geq 1\%$, respectively (unpublished data).

Second, emerging data demonstrates that the clinical significance of the level of MRD at EOI varies depending on genetic subtype. A recent study from the UKALL pediatric ALL consortium reported that NCI SR patients with favorable cytogenetics [defined as patients with *ETV6-RUNX1* fusions or high hyperdiploidy (51-65 chromosomes)] with EOI BM MRD determined by Ig/TCR gene PCR of 0.01-<0.1% had a risk of relapse of only 6% (95% CI 4-10%) even without intensification of post Induction

therapy.⁷ Restricted to high hyperdiploidy patients with EOI MRD 0.01-<0.1%, the 5-year relapse risk was only 5% (95% CI 2-9%), suggesting that the kinetics and significance of MRD clearance of this genetic subtype may differ from other subtypes. While of interest, the MRD methodology used (Ig/TCR PCR) differs from that used by the COG as does the definition of favorable cytogenetics (high hyperdiploidy vs. DT of chromosomes 4 and 10). The COG has also examined genotype-specific MRD cutoffs. Borowitz, et al reported a higher rate of MRD >0.01% at the EOI in patients with DT compared to those with *ETV6-RUNX1* fusions despite having a similarly favorable EFS.⁸ Further analysis of DT patients with EOI MRD 0.01-<0.1% from AALL03B1 found that such patients have excellent expected 5-year EFS of 97.5% ± 5.8% (n = 120) (unpublished). Importantly, patients with this level of MRD would not have received intensified post-Induction therapy on AALL0331 as the cut off for intensification was 0.1%. These data support that NCI SR patient with DT with MRD 0.01-<0.1% do not warrant intensification of post-Induction therapy. Therefore, on AALL1731 such patients will be assigned to the SR-Avg arm rather than the SR-High arm. While the baseline 5-year EFS for this group is excellent (97.5%), it should be noted that the confidence intervals are quite wide given the relatively small number of patients falling into this group (n=120). Thus, given the lower end of this range is less than the 95% EFS baseline for the SR-Fav group, including them in the blinatumomab randomization is justifiable. This classification system will also use HTS to refine risk grouping for SR-Avg patients with flow based MRD at EOI of < 0.01% as described herein.

Finally, CNS2 status will be introduced as a risk factor for SR patients based on the significantly inferior outcomes for CNS 2 patients on AALL0331 and AALL0232, with the exception of those with favorable cytogenetics.⁹ While most cooperative trial groups add extra intrathecal therapy during Induction for patients with CNS2 disease, but do not otherwise change their risk stratification, these consortia (unlike COG) also include High Dose Methotrexate (HDMTX) for SR therapy. Accordingly, treating these patients with CNS2 disease lacking favorable cytogenetics with extra intrathecal therapy during 3-drug Induction and then treating them with an augmented BFM chemotherapy backbone on the SR-High arm after Induction will provide systemic and CNS directed therapy comparable to successful published regimens for patients with CNS2 disease.

Conceptually, this risk stratification algorithm seeks to accomplish several goals; (1) to identify patients with an outstanding outcome for whom further intensification of therapy is not warranted and for whom future de-escalation may be feasible (SR-Fav, and SR-Avg with undetectable HTS MRD); (2) to continue to allocate patients to risk adapted therapy based on NCI Rome risk group, blast genetics, and response to therapy; and (3) to provide a uniform method for risk allocation and/or treatment for rare subsets of patients including those with B-Lly or DS. Table 1 illustrates the overall approach to risk stratification for the non-DS NCI SR B-ALL patients who will be enrolled on AALL1731.

Table 1: Classification of NCI Non-DS SR B-ALL patients (excluding patients with steroid pretreatment, CNS3 or testicular leukemia)

| Risk Group | SR-Favorable (SR-Fav) | SR-Average (SR-Avg) | | | SR-High (SR-High) | | |
|--|--------------------------|------------------------|---------------|--------|----------------------|--------|--------------------|
| Projected 5-year EFS | >95% | 92-95% | 92-97% | 89-93% | 75-90% | 70-88% | 80-88% |
| CNS ¹ | 1/2 | 1/2 | 1/2 | 1 | 2 | 1/2 | 1/2 |
| Cytogenetics ² | Fav | Fav | DT | Neut | Neut | Unfav | Any |
| Day 8 PB MRD (%) | <1 | ≥1 | Any | Any | Any | Any | Any |
| EOI MRD (%) | <0.01 | <0.01 | ≥0.01 to <0.1 | <0.01 | <0.01 | <0.01 | ≥0.01 ³ |
| EOC MRD (%) | n/a | n/a | n/a | n/a | n/a | n/a | <1% |
| Pt accrual/year | 631 | 71 | 22 | 357 | 34 | 11 | 124 |
| Fraction of NCI SR patients (%) ^{1,4} | 51 | 36 | | | 13 | | |

¹ All NCI SR B-ALL patients with steroid pretreatment, CNS3 or testicular leukemia will be eligible for the HR AALL1732 study at initiation of Induction

² Favorable cytogenetics (Fav) = presence of double trisomies of 4 and 10 (DT) OR *ETV6-RUNX1* fusion; Unfavorable cytogenetics (Unfav) = presence of iAMP21, *KMT2A*-R (formerly *MLL*-R), hypodiploidy (modal chromosome number less than 44, DNA index <0.81, or other clear evidence of a hypodiploid clone), OR t(17;19); Neutral cytogenetics (Neut) = lack of favorable and unfavorable cytogenetics

³ ≥0.1% in patients with DT

⁴ Patients with Ph+ ALL will come off protocol therapy prior to Day 15 of Induction to receive therapy incorporating tyrosine kinase inhibition.

2.2 Rationale for Selected Approach and Trial Design

2.2.1 Overall approach to NCI Standard Risk (SR) B-lineage Acute Lymphoblastic Leukemia (ALL)

Previous COG trials for the treatment of NCI SR B-ALL have successfully identified a chemotherapy regimen that yields excellent outcomes and acceptable toxicity in the context of a risk classification schema including sentinel genetic lesions, clinical variables, and early treatment response.² NCI SR B-ALL patients without steroid pretreatment, CNS3, or testicular leukemia will receive a standard 3-drug Induction. Given their outstanding outcomes, patients classified as SR-Fav will receive standard therapy post-Induction but with a uniform duration of Maintenance therapy, regardless of sex. No randomized questions will be asked of this population. For patients classified as SR-Avg post-Induction, we will confirm a DFS of ≥ 95% for the subgroup of patients with undetectable MRD as measured by flow cytometry and HTS at the end of Induction (EOI). These patients will also receive standard therapy post-Induction but with a uniform duration of Maintenance therapy, regardless of sex. For the remaining SR-Avg patients (EOI flow cytometry negative but HTS positive, indeterminate, or unavailable, or DT with EOI MRD 0.01- <0.1%) and for the SR-High patients, we will determine, in a randomized fashion, whether DFS will be improved by the addition of 2 cycles of blinatumomab to risk-adapted standard post-Induction therapy. Of note recent data available from AALL0932 demonstrated no detectable benefit of intensifying oral methotrexate therapy during Maintenance for NCI SR patients, and no difference in outcome between patients receiving every 4 week pulses of vincristine (VCR) and dexamethasone (DEX) vs. every 12 week pulses.¹⁰ Thus, a standard dose of 20 mg/m² will be used as the recommended starting dose for patients

with NCI SR B-ALL during Maintenance and every 12 weeks pulses of VCR/steroid for all patients enrolled on AALL1731, regardless of arm.

2.2.2 Rationale for uniform treatment duration regardless of sex

COG ALL trials have historically used sex-based therapy duration, with females receiving treatment for a total of 2 years from the start of IM1 and males a total of 3 years from the start of IM1.¹¹ This practice was established by the Children's Cancer Group in response to the inferior outcome for males, and a 1983 meta-analysis suggesting that longer Maintenance may have provided some EFS, though not OS, advantage for males.¹² Treating males for a longer duration has not been adopted by almost any other cooperative group in Europe or the US. Even within the COG, the additional year of Maintenance has failed to eliminate the difference in outcome between males and females with 5-year EFS rates of $83.7 \pm 0.6\%$ vs. $85.5 \pm 0.6\%$, for males and females enrolled on COG trials AALL0331 and AALL0232 ($p=0.005$). Overall, the outcome for all patients with ALL has improved dramatically over the past three decades through the identification and incorporation of powerful prognostic markers and the evolution of effective cytotoxic and now targeted therapies. Thus, the absence of data supporting the initial use of an additional year of therapy for males, the absence of a dramatic difference in outcome among males and females treated on St Jude, DFCI, NOPHO and BFM trials using sex neutral duration of therapy¹³⁻¹⁵, and the dramatic improvement in outcomes associated with current classification-risk-genetics based COG therapies strongly suggest that the additional year of therapy for males is not warranted. Thus, the proposed treatment duration in AALL1731 and AALL1732 will be 2 years from the start of post-Consolidation treatment (Blinatumomab Block 1 for patients randomized to receive blinatumomab, and IM1 for all others) for all patients. A secondary benefit to shortening therapy for all patients is that males will receive 4 fewer intrathecal chemotherapy treatments during Maintenance, which is appealing given the potential for long-term neurocognitive impacts of intensive intrathecal chemotherapy.¹⁶⁻¹⁸ Outcomes will be followed closely in males to ensure no erosion in DFS occurs as each of the current generation of ALL trials progresses.

2.2.3 Rationale for treating patients with SR-Fav B-ALL with standard therapy post-Induction

Borowitz et al. demonstrated that the combination of NCI risk factors, blast cytogenetics, and early MRD response could be used to predict outcome after the therapy delivered on POG 9900. Indeed, a significant number of patients with outstanding outcomes using less intensive therapy were identified.¹⁹ This was confirmed on COG AALL0331 where NCI SR patients with favorable cytogenetics (triple trisomies 4+10+17 or *ETV6-RUNX1*), Day 8 PB MRD < 1% and EOI BM MRD < 0.01% experienced a 5-year complete continuous remission rate (CCR) of $95.3 \pm 0.5\%$ with an OS of at least $98.6 \pm 0.8\%$.² Given their outstanding outcomes, the SR-Fav subset of NCI SR patients (based on cytogenetics, CNS status and MRD response) will receive non-randomized post-Induction therapy with a standard Consolidation, two IV escalating Methotrexate (EscMTX) IM phases, a standard DI phase, and Maintenance. As above, treatment duration will be 2 years from the start of IM1 regardless of sex. Close monitoring will ensure that no erosion in outcome occurs in males who are treated with a shorter duration of Maintenance compared to those treated on AALL0331.

2.2.4 Rationale for treating all NCI SR patients with every 12 week pulses in Maintenance

A primary objective of COG AALL0932 was to determine if a reduced-pulses Maintenance regimen with VCR/DEX pulses delivered every 12 weeks could be used without adversely impacting DFS as compared to pulses given every 4 weeks in the average risk (AR) subset of patients with SR B-ALL. The 5-year DFS estimate for VCR/DEX pulses every 12 weeks vs. every 4 weeks was 95.1% (0.9%) and 94.1% (1.0%), respectively (1-sided p=0.86); 5-year OS was 98.6% (0.5%) and 98.3% (0.5%), respectively (1-sided p=0.69). On AALL0932, low risk (LR) patients randomized to the LR-C arm already received every 12 week VCR/DEX pulses. The 5-year DFS for LR-C patients on AALL0932 was outstanding at 98.5% (0.9%). Thus SR-Fav and SR-Avg patients on AALL1731 will receive every 12 week pulses during Maintenance.

AALL0932 did not include SR patients with higher risk features, such as end of Induction bone marrow MRD positivity or unfavorable cytogenetics, who on AALL1731 are categorized as SR-High. It should be noted that the BFM cooperative group, who do not use any VCR/steroid pulses during Maintenance therapy, achieved outcomes equivalent to those on recent COG trials. Notably, AALL1731 SR-High patients will receive a chemotherapy backbone very similar to BFM therapy (e.g. inclusion of high-dose methotrexate) and that in some phases is actually more intensive (e.g. augmented vs. non augmented Consolidation) than BFM therapy. The proven success of Maintenance therapy without pulses in BFM protocols, the similar but higher intensity chemotherapy backbone used in COG for higher risk patients, and the AALL0932 AR results together justify the use of every 12 week VCR/steroid pulses in SR-High patients as well.

2.2.5 Rationale for inclusion of patients with B-lymphoblastic lymphoma

Children and adolescents with B-LLy are currently treated with mBFM therapy derived from ALL protocols with DFS approaching 80%-90%.^{20,21} On COG 5971, these patients received a 4-drug Induction, a 4 week augmented Consolidation, IM with oral methotrexate followed by a standard DI and Maintenance therapy, with a total therapy length of 2 years. While both the BFM and French groups have shown that dose reduction of anthracycline and cyclophosphamide can be achieved in localized lymphoblastic lymphoma, both studies combined B- and T-lymphoblastic lymphoma patients. Thus, the standard of care for treatment of B-LLy patients remains undefined. Currently, patients with localized B-LLy on AALL0932 are being treated with significantly less intense therapy with a 3-drug Induction, standard Consolidation and EscMTX in IM. From March 2013 to June 2016, 30 patients were enrolled for an annual accrual rate of 10 patients/year. The expected total patient accrual is 44 patients with 17 patients greater than 10 years of age. A descriptive analysis for DFS and OS is planned. Since this therapy is a dose reduction, especially in the older patient population, a larger sample size is needed to confirm outcome. Therapy will remain broadly consistent from AALL0932 to AALL1731. This will result in a localized B-LLy patient cohort of 99 patients, and will represent the largest ever cohort of consistently treated localized B-LLy patients. It will thus define the standard of care for this patient population and identify prognostic markers for future studies.

2.3 Relevant Data

2.3.1 Rationale for using HTS to identify a further patient subset with outstanding outcomes

Current MRD assessment (flow cytometry, qPCR) is the most powerful predictor of outcome in ALL.¹² Enhancing the sensitivity to detect MRD will likely serve to advance risk based classification and therapy assignment. HTS of the IgH loci represent a novel DNA-based method of MRD detection with thresholds of 1.0×10^{-6} , significantly lower than flow cytometry. Preliminary data from Wu et al. found that of 91 patients on AALL0932 who were MRD-negative by flow cytometry (< 0.01%), HTS detected MRD levels $> 10^{-6}$ in 38 (42%), $> 10^{-5}$ in 20 (22%), and $> 10^{-4}$ in 5 (5%).²² A small Czech study recently concluded that among a group of patients treated with BFM backbone therapy, HTS-determined MRD was more predictive of relapse than qPCR-based MRD.²³

In a recent analysis of paired pre-treatment and EOI samples from patients enrolled on AALL0331 and AALL0232 who had EOI MRD < 0.1% by flow cytometry, HTS detected a dominant clonal sequence in 93.2% of patients. Among NCI SR patients treated on AALL0331 with a single IM phase, 19.9% had no detectable residual clonal sequence at any detection level at the EOI; these patients had outstanding DFS of $98.1\% \pm 0.2\%$.²⁴ Indeed, only one event occurred in the 56 patients with HTS undetectable disease experienced only one event. Importantly, the proportion of patients with undetectable HTS-MRD did not vary significantly among cytogenetic risk groups (20.9% among those with neutral cytogenetics). Additionally, preliminary analysis of the same cohort found that of the 215 NCI SR patients with EOI MRD < 0.01% by flow, 53 (24.7%) had no residual clonal sequence detectable by HTS. Together these data imply that the proportion of SR-Avg patients on AALL1731 meeting this criterion will also be approximately 20%. In this study, SR-Avg patients who are EOI HTS-MRD undetectable will be non-randomly assigned to standard therapy with two IM phases and a treatment duration of 2 years from the start of IM1, regardless of sex, in order to prospectively confirm their excellent outcomes (DFS of at least 95%, and therefore similar to that historically seen for SR-Fav patients). Outcomes for this group will also be compared to those of SR-Avg HTS-MRD detectable, indeterminate, or unavailable patients treated on the control arm (see below).

2.3.2 Rationale for blinatumomab randomization in NCI SR B-ALL patients

If we conservatively estimate a true post-Consolidation DFS among HTS MRD undetectable patients of 96% comprising 20% of SR-Avg children, we can project the outcome for patients with detectable HTS-MRD to be approximately 91% with standard therapy. EOI HTS-MRD positive patients will therefore be randomly assigned to receive standard therapy vs. standard therapy plus the addition of two 28-day cycles of blinatumomab, one each after Consolidation and IM1. In addition, the 2.8% of SR-Avg patients who had an indeterminate HTS MRD had a 5-year DFS of approximately 90%; these patients as well as those patients without an available HTS MRD result (patients without an available sample or a sample that does not meet QA/QC standards), will also be eligible for this randomization. SR-High patients (i.e., those with EOI flow MRD positivity, unfavorable cytogenetics, and/or neutral cytogenetics with CNS2 status) will be treated with the high-risk augmented BFM chemotherapy backbone and are estimated to have a 5-year post-Consolidation DFS of

86.9% \pm 4.4%. Given no *a priori* reason to suspect an interaction between chemotherapy backbone and blinatumomab efficacy, they will also be included in the blinatumomab randomization. Of note, given the recently approved FDA indication for blinatumomab for patients with MRD positivity of $\geq 0.1\%$, SR-High patients with EOI MRD $\geq 0.1\%$ and end of Consolidation (EOC) MRD of 0.1-<1% will be nonrandomly assigned to receive blinatumomab. SR-High patients with EOC MRD $\geq 1\%$ are considered to have Consolidation Failure and will be taken off protocol (see below).

Blinatumomab is a bispecific single-chain antibody that targets the CD19 antigen and redirects CD3+ T cells for the selective lysis of tumor cells. A recently published single-arm phase 2 study among adults with primary refractory or relapsed B-lineage ALL found that treatment with single-agent blinatumomab resulted in CR in 33% of patients; 82% of these achieved MRD negativity.²⁵ Based in part on these outstanding results, the FDA granted accelerated approval of blinatumomab for the treatment of Philadelphia chromosome (Ph)-negative relapsed or refractory B-lineage ALL in December 2014, which was extended to full approval for Ph⁺ and Ph-negative patients with relapsed/refractory B-ALL in July 2016. The results of the confirmatory Phase 3 TOWER study were recently published. Adults with relapsed/refractory Ph-negative B-ALL were randomized 2:1 to blinatumomab or one of four standard of care (SOC) chemotherapy regimens. Patients receiving blinatumomab experienced CR rates double those receiving chemotherapy (34% vs. 16%; p < 0.001) and exhibited a significant 2-fold improvement in median overall survival (7.7 months vs. 4 months; p= 0.01).²⁶ In addition, Gokbuget et al. reported the results of a phase 2 trial using blinatumomab in adults with newly diagnosed B-ALL who had achieved CR with conventional chemotherapy but remained MRD positive.²⁷ Patients could receive up to 4 cycles of single agent blinatumomab or proceed to hematopoietic stem cell transplant (HSCT) after the first cycle. The rate of MRD response was 80% (16 of 20 evaluable patients) with all MRD responses occurring in the first cycle. Nine of the 20 patients proceeded to HSCT. In the final analysis, with a median follow-up of 50.8 months, the 5-year EFS for all patients was 50%, superior in comparison to generally accepted outcomes of 25% for adult patients with B-ALL and residual MRD.

AALL1121, a Phase 1/2 study conducted by COG and the I-BFM European childhood leukemia cooperative group enrolled 70 patients with relapsed/refractory B-ALL. Among patients receiving the recommended dose of blinatumomab, 39% achieved CR within two cycles, with 52% achieving MRD negativity.²⁷ When restricted to patients with relapsed disease (i.e., not refractory), the CR rate was 48%. Given the unfavorable characteristics of the cohort (>70% of patients had relapsed within 6 months of the previous treatment attempt) these data are highly encouraging. These data led the FDA to grant accelerated approval for the use of blinatumomab in the treatment of pediatric patients with Ph-negative relapsed/refractory BCP-ALL in 2016, the first agent to receive such approval since 2004. On AALL1731, blinatumomab will be delivered using cycles of 28-day continuous infusions with a flat dose of 15 µg/m²/day, followed by a one-week break prior to the initiation of the next cycle of therapy.

New data from the recently published adult study of blinatumomab in the persistent MRD setting provide support for using multiple cycles.²⁸ While the majority of the MRD responses below the level of detection were seen after one cycle, of the 20% of patients that did not achieve MRD negativity after one cycle, 10% achieved MRD-negativity with a second cycle of therapy. Perhaps most convincingly, one-third

of patients on the trial did not receive HSCT or any additional therapy after receiving 3 or more cycles of blinatumomab; these patients had identical survival to those that received HSCT. This suggests that even in patients achieving MRD-negativity, further courses of blinatumomab may eradicate disease below the threshold of detection. These data led to the FDA expanding the indications for blinatumomab to include persistent MRD positivity in March 2018.

Finally, AALL1331 randomized patients with high and intermediate risk (HR/IR) first relapse B-ALL between standard chemotherapy vs. standard re-induction therapy but with two blocks of intensive chemotherapy replaced with two cycles of blinatumomab for post-induction therapy. In September 2019, the HR/IR randomization was closed early due to efficacy. Patients receiving the experimental arm including blinatumomab were found to have superior DFS and OS, higher rates of MRD negativity, and lower rates of toxicity compared to patients receiving standard therapy (AALL1331 memo, September 18, 2019). While these data are very encouraging, caution is warranted in extrapolating these results to a newly diagnosed NCI SR population until definitively tested on the current study.

Blinatumomab represents the ideal candidate for investigation in the NCI SR B-ALL population for several reasons. First, as noted above, evidence in the relapsed population has been highly promising. Adult and pediatric data suggesting an association between lower leukemia burden (< 50% bone marrow blasts) at the time of administration and better response rates to blinatumomab also argues for investigation in newly diagnosed patients who have already attained CR.²⁷ In the BLAST trial, among adults in hematologic CR with measurable MRD who then received blinatumomab, 88/116 (78%) achieved MRD negativity. These data make its use in a population with positive MRD, either by flow or by HTS, highly appealing.²⁹ Second, any agent considered for incorporation into NCI SR therapy must carry minimal risk of toxicity given generally favorable DFS with standard treatment.²⁹ As noted above, preliminary data from AALL1331 demonstrates a highly favorable toxicity profile associated with blinatumomab when compared to conventional chemotherapy.

Cytokine release syndrome (CRS) remains a concern with blinatumomab and other immunotherapies. However, in the Phase 1/2 study by von Stackelberg et al. described above, of the 70 patients with > 25% blasts at study entry and receiving the recommended blinatumomab dose, only 8 (11%) experienced CRS of any grade, with 4 (6%) experiencing Grade 3 or higher CRS.³⁰ The risk of CRS has been shown to depend heavily on disease burden at the time of administration.³¹ This is evidenced by the low rates of CRS in a recent study of blinatumomab in adults with MRD positive BCP-ALL.^{27,29} Thus in AALL1731, the risk of significant CRS is anticipated to be very low.

Neurotoxicity (seizures, encephalopathy, tremors) has been associated with blinatumomab administration. Seen with some frequency in adults, these toxicities occur less commonly in children. In AALL1121, nine (13%) patients experienced neurologic events (mainly tremor and dizziness) that were considered treatment-related. All were Grade 2 and resolved, with no permanent discontinuations due to neurologic events.³⁰ Two patients interrupted treatment because of Grade 2 seizures. Similar findings have been seen on AALL1331, with all cases of neurotoxicity rapidly reversible upon discontinuation of blinatumomab and not recurring on re-challenge (personal communication, Patrick Brown, M.D.).

Finally, over 180 COG institutions have obtained IRB approval for AALL1331, indicating that the logistical challenges associated with blinatumomab are manageable and that a high level of enthusiasm for this agent exists among the clinical community. The recommended frequency for blinatumomab bag changes has now been extended to every 7 days for patients $\geq 22\text{kg}$, which will also ease the burden of outpatient administration.

Thus, blinatumomab offers a unique approach to leukemia therapy with no overlap in mechanism of action when compared to standard cytotoxic agents, and is therefore potentially more likely to yield larger improvements in outcome. This study will allow a complete assessment of the advantages and disadvantages of incorporating blinatumomab into standard therapy for NCI SR B-ALL patients.

2.3.3 Rationale for incorporating blinatumomab in therapy for children with Down syndrome

Approximately 3% of children with ALL also have a diagnosis of DS. Survival outcomes after treatment of ALL remain inferior in this group compared to the non-DS population.³²⁻³⁴ The causes of treatment failure are excessive TRM, chiefly due to infections, a higher rate of relapse, and low success rate of both relapse chemotherapy and hematopoietic stem cell transplantation.³²⁻³⁴ On previous COG studies, AALL0331 (SR ALL) and AALL0232 (HR ALL), the strata for children with DS were temporarily suspended due to excessive TRM (primarily due to overwhelming sepsis during times of neutropenia) during both Induction and post-Induction therapy. Safety amendments were implemented, but ultimately the DS stratum of the AALL0232 HR B-ALL trial was permanently closed due to continued excess TRM. The successor trials AALL0932 (SR ALL) and AALL1131 (HR ALL) preserved the safety amendment measures from the predecessor studies and implemented additional modifications for DS patients, including: 1) reduced exposure to anthracyclines during Induction; 2) modified intermediate dose methotrexate during IM for DS-High patients; 3) reduced frequency of vincristine/glucocorticoid pulses during Maintenance; 4) shortened duration of therapy for males; 5) intensified supportive care guidelines for both HR and SR DS patients. TRM for DS patients on these trials has not reached stopping rules, but has remained significantly higher for DS-High patients compared to non-DS patients.³⁵ These modifications will remain in place for DS patients treated on AALL1731. Importantly, analyses of previous trials has shown a higher rate of neurotoxicity in DS versus non-DS patients despite current leucovorin rescue. Earlier rescue has been used by other cooperative groups. Therefore, on AALL1731, patients with DS will receive leucovorin rescue after every intrathecal methotrexate at Hour 24 and 30 as compared to Hour 48 and 60 on past studies.

In an attempt to reduce TRM in patients with DS and high-risk features [DS-High - All NCI HR DS, NCI SR DS patients with EOI MRD $\geq 0.01\%$ ($\geq 0.1\%$ for DT), unfavorable cytogenetics, steroid pretreatment, neutral cytogenetics with CNS2 status, CNS3, or testicular disease], the current study will replace intensive immunosuppressive and myelosuppressive elements of standard chemotherapy, with blinatumomab, which we hypothesize will preserve or even enhance anti-leukemic efficacy while reducing toxicity. Specific therapy reductions include: 1) omission of anthracycline in all DS-High patients during Induction, during which approximately half of TRM in AALL1131 has occurred; 2) omission of the

cyclophosphamide/cytarabine-based second half of DI (Day 29-56), which accounts for most of the remaining TRM in DS-High ALL. Thus, anthracycline exposure will be eliminated during Induction but retained during the first half of DI while the portion of DI that duplicates Consolidation therapy is omitted. To compensate for these therapy reductions, three cycles of blinatumomab will be administered, one each after the Consolidation and IM phases and one in the place of the second half of DI. These patients will receive 3 courses of therapy, as opposed to the 2 courses that will be received by non DS patients on the SR-Avg or SR-High strata. The higher numbers of courses is justified by 1) the elevated risk of relapse of DS patients, 2) blinatumomab replacing and not just being added to elements of standard therapy, and 3) the potential improvement in quality of life with blinatumomab as compared to prolonged inpatient admissions during courses of intensive chemotherapy.

Importantly, blinatumomab has been safely used in children with DS.^{30,36} DS-High ALL patients will continue to receive intensified supportive care. A single-arm study design will be used for this study with the predecessor study AALL1131 serving as comparator. NCI HR DS patients with EOC MRD $\geq 0.01\%$ will be classified as VHR and will be eligible to either remain on protocol therapy on AALL1731 (provided they do not meet criteria for consolidation failure) or will be eligible for treatment on the AALL1721 study with CD19 CAR T cells (CTL019). These patients will not have been exposed to blinatumomab by this time point in therapy.

Current COG therapy (AALL0331) has proven safe for children with DS and NCI SR B-ALL, who do not experience the magnitude of TRM observed in DS-High ALL. Therefore, patients with DS and SR-Avg B-ALL will be included in the SR-Avg stratum, which will evaluate the addition of blinatumomab to SR ALL chemotherapy in a randomized design for patients who are HTS-MRD positive or indeterminate. NCI SR DS-ALL patients with MRD $\geq 0.01\%$ at the EOI, or unfavorable cytogenetics, or steroid pretreatment, CNS3 or testicular leukemia will receive augmented post-Induction therapy on the DS-High ALL stratum.

2.3.4 Multiparameter flow cytometry (MPF) for measurement of minimal residual disease (MRD) for NCI Standard Risk B-lineage ALL at the end of Consolidation (EOC)

Bone marrow MPF MRD at EOC will be used to identify patients who meet the definition of Consolidation failure (see [Section 14.4](#)) with bone marrow MRD $\geq 1\%$ and are not eligible to continue on protocol therapy. However, the majority of patients who have MPF MRD performed at the EOC are likely to have values less than 1%, and the prognostic significance of lower levels of EOC MRD in the NCI SR population has not been established. Therefore, this correlative biology study proposes to examine the prognostic impact of EOC MPF MRD in NCI SR patients who will remain on AALL1731 post-Consolidation.

Data from the Italian Association of Pediatric Hematology and Oncology (AIEOP) and Berlin-Frankfurt-Münster (BFM) Acute Lymphoblastic Leukemia 2,000 studies demonstrated that patients who are MRD-positive at EOI, but who are MRD-negative by EOC, still have favorable outcomes.³⁷ More recently, data from COG NCI HR B-ALL trial, AALL0232 supported this finding.³⁸ In this trial, patients with $>0.1\%$ EOI MRD were provided with more intensive post-Induction therapy, with the result that the outcome curves of those patients were shifted in comparison to patients with

0.01-0.1% MRD. Among patients with a slow early response to Induction defined by bone marrow morphology at Day 15 (blasts $\geq 5\%$) or bone marrow MRD at Day 29 of Induction ($MRD \geq 0.1\%$), subsequent MRD measurement by MPF at EOC was prognostic of EFS; see Figure 1). Those with $MRD <0.01\%$ at EOC had a 5-year disease-free survival (DFS) of $79\% \pm 5\%$ versus only $39\% \pm 7\%$ for those with $MRD \geq 0.01\%$ at EOC. However, these data were restricted to NCI HR B-ALL patients.

The measurement of BM MRD at the EOC (also known as time point 2) is considered standard of care in centers using BFM based therapy in both NCI SR and NCI HR patients who are MRD positive at the EOI.³⁷ Survey data of 27 medium-large COG centers also indicates that 100% of centers polled follow this practice as well, with 93% considering changing therapy based on the results. Indeed, 86% of those polled change therapy for patients with NCI SR ALL who are EOC MRD positive, most commonly employing hematopoietic stem cell transplant. Notably, other immunotherapies such as blinatumomab and CAR-T were also alternative therapies delivered. This is despite the fact that a study of the prognostic impact of EOC MRD levels in a large cohort of uniformly treated NCI SR patients has not yet been conducted.

A limited number of NCI SR B-ALL patients on AALL0932 with EOI MRD positivity subsequently enrolled on AALL1131. Of 368 such patients who submitted EOC MRD data, 25 (6.8%) were EOC MRD positive and experienced a 4-year DFS of $82\% \pm 25\%$. While superior to the published outcomes of NCI HR EOC MRD positive patients, large standard errors prevent robust conclusions from being drawn. In addition, follow-up inquiries reveal that at least 7 of these 25 patients received transplant in CR1.

Of note, given the recently approved FDA indication for blinatumomab for patients with MRD positivity of $\geq 0.1\%$, SR-High patients with end of Consolidation (EOC) MRD of $0.1\%-<1\%$ will be nonrandomly assigned to receive blinatumomab. Therefore, all SR-High patients with EOI BM MPF MRD $\geq 0.1\%$, will be required to have a BM MRD assessment at the EOC to determine treatment arm assignment. For SR-High patients with EOI BM MPF MRD $0.01\%-<0.1\%$ (approximately 10% of SR patients), the picture is less clear. Only approximately 2% of these patients will have EOC MRD $>0.01\%$. On AALL0932, no relapses occurred in patients with both EOI and EOC MRD of $0.01\%-<0.1\%$, though data were available on only 5 such patients. For SR-High patients with EOI BM MPF MRD $0.01\%-<0.1\%$, the study committee cannot therefore make recommendations as to whether an EOC BMA should be performed. Should treating clinicians choose to obtain EOC BMAs in these patients, MRD results will be collected and patients will have to option to submit extra material for biobanking. With any submitted data, we will determine the rate of conversion from EOI MRD $\geq 0.01\%$ to EOC MRD-negative by MPF in NCI SR patients treated with a mBFM Consolidation, and examine the impact on outcome of persistent MRD positivity by MPF.

NCI HR DS B-ALL patients may be eligible for enrollment on the VHR B-ALL trials, AALL1721, which requires an EOC BM MPF MRD $\geq 0.01\%$. Therefore, all NCI HR DS patients with EOI BM MRD $\geq 0.01\%$ will be required to have a BM MRD assessment at EOC. NCI SR DS patients who have an EOI BM MRD by MPF $\geq 0.01\%-0.99\%$ treated on the DS-High arm, will be required to have a BM MRD assessment at EOC or Day 1 of Blinatumomab Block 1, whereas it will be up to treating clinicians for NCI SR DS patients with EOI BM MPF MRD $0.01\%-0.099\%$.

ALL MRD testing has traditionally been performed at two centralized laboratories, but recently was decentralized. Multiple COG institutions are now approved to detect EOI MRD for patients enrolled on COG therapeutic studies. This validation however, does not include time points for B-ALL beyond EOI. EOC MRD analysis is more challenging to interpret due to the increased frequency of hematogones. On AALL1731, MPF for MRD at EOC will be performed centrally at the University of Washington, Seattle, a COG centralized laboratory with extensive experience.

2.4 Correlative Studies

2.4.1 Application of High Throughput Sequencing of IgH loci for minimal residual disease (MRD) detection in peripheral blood (PB) at end of Induction (EOI) and in bone marrow (BM) at end of Consolidation (EOC)

This potential correlative biology study on banked samples aims to determine the strength of association between BM and PB MRD as determined by the highly sensitive DNA-based MRD detection method of HTS of IgH loci in NCI SR B-ALL patients at EOI, and to determine the strength of association between flow cytometry determined MRD and HTS of IgH loci determined-MRD from the BM at EOC in NCI SR B-ALL patients who are MRD positive by flow cytometry at EOI.

The early clonal dynamics of B-ALL during treatment are highly predictive of relapse^{39,40} as is the detection of MRD at later stages.^{38,40} Currently, early response to therapy is assessed by bone marrow MRD using either flow cytometry or qPCR methodologies. We hypothesize that with the more sensitive assay, HTS of the IgH loci, MRD can be effectively monitored in the PB as well. Coustan-Smith et al. reported that for B-ALL patients enrolled on the St. Jude Total Therapy trials, PB MRD as measured by flow cytometry during treatment correlated with outcome, but was less sensitive than BM MRD at the same time point.⁴¹ Lower detection threshold, however, should allow HTS methods to detect MRD in the PB with greater sensitivity. Indeed, Logan, et al found that PB MRD by HTS was sufficiently sensitive to quantify MRD in adult ALL patients in the pre- and post-hematopoietic transplant period, being highly predictive of impending relapse.⁴² To date, however only a few small studies of ALL patients have been performed assessing the strength of association between paired BM and PB MRD as determined by HTS.^{42,43} Here, we will determine the concordance between MRD in the BM and PB in a large cohort of B-ALL patients at EOI. This will establish the lower limit of MRD detection in the PB relative the level of MRD in the BM. If our findings demonstrate that MRD can be sufficiently quantified from the PB of pediatric patients with B-ALL, it could ultimately obviate the need for bone marrow aspirations in the future for MRD monitoring.

Recent data have demonstrated the prognostic significance of MRD status at later time points in therapy. On the COG high-risk B-ALL trial, AALL0232, patients who remained MRD positive at EOC at a threshold of 0.01% by flow cytometry, had a dismal outcome with 5-year disease-free survival (DFS) of $39\% \pm 7\%$.³⁸ Similarly, of patients enrolled on the P9900 series of B-ALL clinical trials, those with flow cytometry-determined MRD $\geq 0.01\%$ at the EOC had a 5-year event-free survival (EFS) of $43\% \pm 7\%$.¹⁹ It is important to note that all the flow cytometry MRD assays included in these studies were performed at one of two centralized reference labs. Studies of the reproducibility of flow cytometry determined MRD, particularly at later

time points in therapy, are scant but suggest extensive training and validation of labs are necessary, potentially limiting the wide-spread application of this technique. Therefore, demonstrating high concordance between HTS-determined MRD and flow cytometry-determined MRD performed in centralized reference labs would allow HTS-MRD to be used for EOC risk-stratification in the future, eliminating the need to either rely on a handful of reference labs or the need to certify numerous additional flow cytometry labs for this assay.

Additionally, while patients who are MRD positive at the EOI but clear by EOC have significantly better outcomes compared to those with persistent MRD positivity,^{19,38} patient outcomes vary substantially. On AALL0232, NCI-HR patients who were flow-determined EOI MRD positive but MRD <0.01% by EOC had a 5-year DFS of 79% ± 5%. Similarly, such patients enrolled on the P9900 series had a 5-year EFS of 83% ± 1%. Therefore, more sensitive determination of BM MRD using HTS may further delineate flow MRD negative patients who are at high risk for relapse warranting novel therapies, and may also define a group likely to do well with conventional chemotherapy alone.

2.4.2 Correlative studies in the DS B-ALL population

2.4.2.1 **Immune dysfunction in DS B-ALL (See [Section 15.1](#) for details)**

About 7% of DS-ALL patients suffer infection-related mortality (IRM) with approximately 65% of those occurring during Maintenance therapy.^{32,44} This suggests that ALL therapy causes a long-lasting immune deficiency in DS children. IRM in DS ALL is associated with multiple types of bacterial, fungal and viral infections,^{44,35} suggesting globally defective "Type 1" and/or "Type 17" cell-mediated immune responses. This study will utilize mass cytometry (MC) to investigate the complex network of innate and adaptive immune cell types and functions, and the balance of pro-inflammatory TH1/TH17 versus anti-inflammatory TH2 and FoxP3+ T-regulatory (Treg) cells, that are important for anti-microbial immunity.

2.4.2.2 **Host genetic susceptibility to infection (See [Section 15.2](#) for details)**

Recently, there has been growing awareness of the role of genetic factors affecting susceptibility to infection in childhood ALL.^{45,46} Variant alleles of genes involved in the immune response and genes affecting metabolism of immunosuppressive chemotherapeutic agents have been implicated in the risk of severe infectious complications. The presence of a variant allele with adverse immunologic effects may be particularly profound when superimposed on these generalized immune defects of children with DS.

2.4.2.3 **Longitudinal assessment of neurocognitive, functional, and quality of life outcomes in patients with DS B-ALL (See [Section 17.2](#) for details)**

Compared to other children, children with DS have inferior survival outcomes, higher relapse rates, and higher rates of treatment-related morbidity and mortality.³² Unfortunately, we know very little of the impact of ALL and its therapy on neuropsychological function and QOL in patients with DS-ALL as these patients have been systematically excluded from nearly all studies examining such issues. A recent single-institution study of

neuropsychological late effects in children with DS and acute leukemia found that children with DS-ALL performed significantly worse than controls on a variety of measures of neurocognition and adaptive function.⁴⁷ These deficits far exceeded those observed among children with DS-AML, suggesting that neuropsychological morbidities observed in DS-ALL may be related to CNS-directed therapy. Outcome data from a large, uniformly treated, cooperative group study cohort are needed to guide modifications to therapy, inform supportive care guidelines (e.g., rehabilitative therapies and educational programming), and to provide families with evidence-based information about neurodevelopmental outcomes, in a manner similar to that which has been afforded to the non-DS ALL population. Since such data are lacking⁴⁸, an exploratory aim will focus on closing this gap of knowledge, using parent questionnaires to assess the impact of ALL and its therapy on neurocognitive, functional, and quality of life outcomes, adjusting for effect of potential covariates (e.g., socioeconomic status, frequency and severity of hospitalization). We will use a longitudinal design that includes time points on therapy and off therapy for this study.

2.4.3 Household Material Hardship and Neurocognitive Outcomes (See [Section 17.1](#) for details)

One in five children in the U.S. lives in poverty⁴⁹ and children living in poverty are at higher risk of impaired cognitive function as compared to their non-poor counterparts.⁵⁰ Neurocognitive deficits have been reported in 20-40% of childhood ALL survivors and are associated with inferior child quality-of-life⁵¹ and increased parental stress.⁵² Despite this, almost no data exist elucidating the impact of pre-existing poverty on neurocognitive outcomes in childhood leukemia survivors. In the context of AALL06N1, we previously found that children with public insurance were at increased risk of neurotoxicity (mean estimated IQ US Public Insurance = 93.1 vs. US Private or Military Insurance = 106.2; p < 0.001). These data suggest an important outcome disparity but provide no target for intervention. Furthermore, extremely limited data on neurocognitive toxicity in NCI SR ALL exist, despite the fact that a majority of this population will be long-term survivors for whom neurotoxicity is highly relevant. As such, identifying targetable predictors and mechanistic pathways driving neurocognitive toxicity is essential. We hypothesize that children living in poverty at the time of their leukemia diagnosis are at risk of experiencing greater declines in neurocognitive function from baseline than their non-poor counterparts. We propose to investigate this hypothesis using a concrete measure of poverty, household material hardship (HMH), which is both associated with inferior child health outcomes and remediable with intervention.⁵³⁻⁵⁶ HMH is defined as unmet basic needs including food, heat, housing or transportation. Prior work by our group has identified HMH in 20% of pediatric cancer families at diagnosis and 30% after the initial six months of chemotherapy.⁵⁷ We have extensive experience utilizing Cogstate to longitudinally evaluate neurocognition in the context of COG trials and have demonstrated in the context of AALL1131 that CogState evaluation is both feasible and sensitive to changes in function during therapy. Early data from this trial suggest that almost one third of the children have scores >1.5 SD below the mean on at least two CogState tasks two years from diagnosis. This study will provide the first comprehensive investigation of poverty-related neurocognitive outcome disparities in pediatric NCI SR ALL, leveraging the uniform care delivery setting of a cooperative group clinical trial. As such, this trial will lay the groundwork for future comprehensive

risk-based neurocognitive screening and targeted intervention including both pharmacological and poverty-targeted interventions.

2.4.4 Caregiver burden and patient symptoms in children with NCI SR B-ALL receiving blinatumomab (See [Section 17.1](#) for details)

Few longitudinal studies exist to measure the burdens of leukemia therapy on pediatric patients and their parents. The impact of novel leukemia directed therapies on parental burden are unknown. Blinatumomab is a promising new agent for the treatment of children with ALL. Its administration requires 28 days continuous infusion and as such is hypothesized to be associated with unique caregiver demands. Health related quality of life (QOL) has recently been investigated in adult patients with relapsed ALL receiving blinatumomab.⁵⁸ The symptom burden in children being treated with blinatumomab has not been evaluated to date.

This study aims to fill these knowledge gaps. Data from this study will allow for anticipatory guidance to families with children receiving blocks of blinatumomab and chemotherapy post-Induction for SR-Avg and SR-High ALL. Identification of unique burdens will inform future investigations of interventions to mitigate burden and caregiver demands, thereby improving the QOL for patients with ALL and their families.

Experience from the embedded QOL secondary aim in AAML1031 demonstrated that 73-83% of families completed QOL assessments at each of the first 5 of 8 planned time-points.⁵⁹ The most common reason for non-completion in this population was that the child was too sick at the assessment time point. The NCI SR B-ALL population is less likely to be as sick during therapy so completion rates are expected to be higher. In addition, the measures to be used in the currently proposed study for AALL1731 can be completed within a shorter time frame.

2.4.5 Rationale for evaluating Minimal Marrow Disease (MMD) in B-Ly

The importance of MRD as a prognostic factor and the value for risk classification is well established for B-ALL. However, there are little data on whether MMD and MRD correlate with prognosis in B-Ly. Coustan-Smith et al. showed that flow cytometric analysis of peripheral blood samples can be used to detect evidence of disseminated T-Ly, rendering it a valuable method to monitor blast clearance during therapy.⁶⁰ Out of 99 pediatric T-Ly patients, 72% had detectable levels (>0.01%) of T-lymphoblasts in their bone marrow. The level of detectable disease correlated with outcome with a 2-year EFS of 68% for patients with >1% lymphoblasts in the bone marrow versus 91% for patients with <1% involvement ($p=0.031$).⁶⁰ In a more recent study conducted by the Italian AIEOP study group, the prognostic value of MMD analyzed by multiparameter flow cytometry (MPF) in bone marrow and peripheral blood samples was evaluated in a cohort of 65 children affected by T- and B-lineage lymphoblastic lymphoma.⁶¹ MMD was detected in 49% (32/65) of bone marrow samples, whereas only 21% (14/65) were positive at standard morphological evaluation. Using an MMD cut-off level of 3% by flow cytometry, 5-year EFS is 60% for patients with MMD >3% LLy cells versus 83% for the remaining patients ($p=0.04$).⁶¹ This protocol will prospectively evaluate the level of MMD and MRD by flow cytometry using established methods for ALL and correlate it with outcome.

3 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In order for an institution to maintain COG membership requirements, every patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project: EveryChild A Registry, Eligibility Screening, Biology and Outcome Study*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see [Appendix I](#) for detailed CTEP Registration Procedures for Investigators and Associates, and Cancer Trials Support Unit (CTSU) Registration Procedures, including: how to download site registration documents, requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see [Appendix I](#).

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff must verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (<https://open.ctsu.org>). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

PATIENTS WITH B-ALL MUST CONSENT TO ELIGIBILITY SCREENING (PART A) AND BE ENROLLED ON PROJECT:EVERYCHILD (APEC14B1) BEFORE RECEIVING ANY SYSTEMIC PROTOCOL THERAPY ON AALL1731. (For the purpose of this study, "systemic protocol therapy" does not include the first dose of intrathecal chemotherapy or selected cases of steroid pretreatment). **PATIENTS THAT BEGIN SYSTEMIC PROTOCOL THERAPY ON AALL1731 PRIOR TO ENROLLMENT ON APEC14B1 ARE INELIGIBLE FOR AALL1731.**

B-LLy PATIENTS MUST SUBMIT SAMPLES FOR CENTRAL RETROSPECTIVE PATHOLOGY REVIEW. SPECIFIC INSTRUCTIONS REGARDING REQUIRED TISSUE SUBMISSION ARE OUTLINED IN SECTION 13.0. EVERY EFFORT SHOULD BE MADE TO ACQUIRE AS MUCH TISSUE AS POSSIBLE.

PATIENTS WITH B-LLy ARE ELIGIBLE FOR PROJECT:EVERYCHILD (APEC14B1) BUT ENROLLMENT IS NOT AN ELIGIBILITY REQUIREMENT FOR AALL1731.

All Patients:

Study enrollment must take place within **five (5)** calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **five (5)** calendar days after enrollment.

Patients must meet all eligibility criteria prior to the start of protocol therapy or enrollment, whichever occurs first. All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to protocol-directed systemic therapy, unless otherwise indicated in the eligibility section below. Diagnostic biopsy for B-LLy must be performed within 14 days of starting therapy.

Initiation of systemic protocol therapy: Systemic Induction chemotherapy, with the exception of steroid pretreatment as outlined below, must begin within 72 hours of the first dose of intrathecal chemotherapy.

3.1.5 Staged Consent

Informed consent will be obtained at critical stages of treatment for the different groups of patients on this study.

Informed consent: Except for administration of intrathecal cytarabine or allowable steroid pretreatment ([Section 3.3](#)), informed consent/parental permission MUST be signed before protocol therapy begins.

Informed consent that describes the first 4 weeks of Induction therapy will be obtained for B-ALL patients prior to starting treatment. All patients will receive a common Induction regimen with the exception of children with DS who will also receive 2 doses of oral leucovorin following each dose of intrathecal methotrexate, and age-based steroid treatment that includes either dexamethasone for 28 days (for patients aged <10 years) or predniSO(LO)ne for 28 days (for patients aged ≥10 years). Patients with B-LLy and DS B-LLy will be approached with a single consent prior to starting Induction therapy, which describes all therapy to be received on study. DS B-LLy patients will also receive Induction treatment that includes either dexamethasone for 28 days (for patients aged <10 years) or predniSO(LO)ne for 28 days (for patients aged ≥10 years). Patients with B-LLy and DS B-LLy will be consented to treatment for the duration of the study at enrollment.

At the end of Induction, after B-ALL patients have been stratified into risk subgroups, a second consent that describes all post-Induction therapy will be discussed with patients and their families. There are separate post-Induction consents for children with SR-Fav B-ALL (including DS patients), SR-Avg B-ALL (including DS patients), SR-High B-ALL, and DS-High B-ALL. For patients with SR-Fav B-ALL, the post-Induction consent describes standard chemotherapy that will be administered on this study. For patients with SR-Avg and SR-High subsets of NCI SR B-ALL, the post-Induction consent describes the assignment to post-Induction chemotherapy and the possible randomization to 1 of 2 different post-Consolidation regimens. For patients with DS-High B-ALL the post-Induction consent describes the non-random therapy including three cycles of blinatumomab.

Summary of Required Consents for AALL1731:

| Consent Document | Time Point for Obtaining Consent | Population for Consent |
|-----------------------|--|--|
| APEC14B1 | Prior to the start of Protocol Therapy | B-ALL (required) B-LLy (optional, but strongly encouraged) |
| Induction | Prior to the start of Induction | SR B-ALL DS B-ALL |
| Post-Induction | Prior to the start of Consolidation | SR-Fav B-ALL DS SR-Fav B-ALL (non-randomized) SR-Avg B-ALL DS SR-Avg B-ALL (possibility of randomization) SR-High B-ALL (possibility of randomization) DS-High B-ALL (non-randomized) |
| All phases of therapy | Prior to the start of Induction | B-LLy and DS B-LLy |

Consent for Optional Studies

See [Section 7.3](#) for schedule of optional research studies.

Biobanking for EOI Peripheral Blood MRD by High-Throughput Sequencing

All non-DS B-ALL patients are eligible to participate in this optional study. Consent will be obtained prior to the start of therapy using the B-ALL Induction consent document. See [Section 14.3](#) for further details.

Biobanking for EOC Bone Marrow MRD by High-Throughput Sequencing

All SR-High B-ALL patients with EOI BM MRD $\geq 0.1\%$ by flow cytometry, and those SR-High B-ALL patients with EOI BM MRD 0.01-0.099% who had BM MRD assessed at end of Consolidation, are eligible to participate in this optional study. Consent will be obtained prior to the start of Consolidation therapy using the SR-High post-Induction consent document. See [Section 14.5](#) for further details.

Biobanking for Future Research – B-ALL

Non-DS B-ALL patients are eligible to participate in banking CSF samples. Consent will be obtained prior to the start of therapy using the B-ALL Induction consent document. See [Section 14.7](#) for further details.

Biobanking for Future Research – B-LLy

All B-LLy patients are eligible to participate in banking residual masses leftover from any scheduled biopsies. B-LLy patients are also eligible to participate in banking bone marrow samples at relapse, if it occurs. Consent will be obtained prior to the start of therapy using the B-LLy consent document. See [Section 14.8](#) for further details.

Down syndrome and Immune Function

All DS B-ALL patients are eligible to participate in this optional study. Consent will be obtained prior to the start of therapy using the B-ALL Induction consent document. See [Section 14.6](#) for further details.

Household Material Hardship (HMH) and Neurocognition

Non-DS B-ALL patients may be eligible to participate in assessments for this optional study. See [Section 17.1.6](#) for eligibility criteria. Consent for this study will be obtained prior to the start of therapy using the B-ALL Induction consent document. The institutional CRA will be responsible for ensuring the HMH surveys and neurocognitive assessments are completed at the appropriate time points. See [Section 17.1](#) for further details.

Caregiver Burden and Symptom Assessment

Non-DS SR-Avg, and SR-High B-ALL patients who have enrolled on the HMH and neurocognition study are eligible to participate in assessments for this optional study. Consent for this study will be obtained prior to the start of Consolidation therapy using the SR-Avg and SR-High post-Induction consent documents. The institutional CRA will be responsible for ensuring the caregiver burden and symptom assessments are completed at the appropriate time points. See [Section 17.1](#) for further details.

Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL

Patients with Down syndrome and B-ALL may be eligible to participate in assessments for this optional study. See [Section 17.2.3](#) for eligibility criteria. Consent for this study will be obtained using the B-ALL appropriate DS post-Induction consent document. The institutional CRA will be responsible for ensuring the quality of life assessments are completed at the appropriate time points. See [Section 17.2](#) for further details.

Minimal Marrow Disease (MMD) Study for B-LLY

All B-LLY patients are eligible to participate. Consent for this study will be obtained prior to the start of therapy using the B-LLY consent document. See [Section 14.9](#) for further details.

3.1.6 Inclusion of Women and Minorities

Both males and females of all races and ethnic groups are eligible for this study.

3.1.7 Callback for Treatment Assignment/Randomization for B-ALL

There will be 2 Callback procedures performed during this study. The first Callback (Callback #1 – post-Induction for all B-ALL patients) is performed after completion of Induction therapy, subsequent to Risk Assignment for the B-ALL patients, and prior to beginning Consolidation therapy. Callback #1 will:

1. Assign remaining therapy for SR-Fav B-ALL patients to the SR-Fav Arm.
2. Assign remaining therapy for DS SR-Fav B-ALL patients to the SR-Fav Arm.
3. Assign post-Induction therapy for SR-Avg B-ALL patients.
4. Assign post-Induction therapy for DS SR-Avg B-ALL patients.
5. Assign post-Induction therapy for SR-High B-ALL patients.
6. Assign post-Induction therapy for DS-High B-ALL patients.

Callback #1 and risk group assignment must be completed prior to beginning post-Induction therapy or the patient will be made inevaluable.

If Callback #1 has been completed and risk group assignment is confirmed to be SR-Avg (except patients with DT with EOI flow MRD 0.01-<0.1%), the institution must enter both the clonality order and the tracking test order for HTS MRD testing via the Adaptive within 7 days of beginning Consolidation therapy in order to receive HTS MRD results and enter them into RAVE by the completion of Consolidation therapy. If results are not entered in RAVE by the completion of Consolidation therapy, the patient will be made inevaluable and must be taken off protocol therapy. See the Adaptive Portal Walk-Through Slides and Adaptive SOP for instructions for initial set-up of Adaptive Portal account, ordering high-throughput sequencing (HTS) MRD assessments, and interpreting HTS MRD results. Sites must set up accounts ahead of ordering their first HTS MRD assessment since set-up of Adaptive Portal account may take 24 hours or longer to activate.

The second Callback (Callback #2 – post-Consolidation therapy for all SR-Avg and DS SR-Avg B-ALL and SR-High B-ALL patients) is to be performed post-Consolidation therapy. **The next phase of therapy (Interim Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2.**

Patients who have not begun the next phase of therapy within 7 days will be declared inevaluable and will have to come off study. Thus, Callback #2 should only be completed if the treating physician is confident that the patient will meet criteria to start the next phase of therapy. As predicting the timing of count recovery is difficult, particularly for SR-High B-ALL patients, teams may therefore choose to wait until patients have actually met criteria to start the next phase of therapy prior to completing Callback #2.

Institutions should take into account that the logistics of starting blinatumomab infusions can take time to arrange. For DS and non-DS SR-Avg patients, Callback #2 will assign DS and non-DS SR-Avg B-ALL HTS EOI MRD undetectable patients to Arm A, or randomly assign DS and non-DS SR-Avg B-ALL HTS EOI MRD detectable/indeterminate/unavailable patients to either treatment Arm A or B (See [experimental design schema](#)). For SR-High patients, Callback #2 will randomly assign SR-High patients to either treatment Arm C or D (See [experimental design schema](#)).

Callback #2 for SR-Avg and SR-High must be completed prior to beginning post-Consolidation therapy or the patient will be made inevaluable.

3.1.7.1 **SR-Fav B-ALL (including DS patients)**

Post-Induction therapy assignment for patients with SR-fav subset of SR B-ALL is accomplished by completing the Callback in OPEN, after the risk assignment has been completed and consent signed, and prior to the start of Consolidation therapy.

3.1.7.2 **SR-Avg B-ALL (including DS patients)**

Post-Induction therapy assignment for patients with SR-Avg B-ALL is accomplished by completing the Callback in OPEN, after the risk assignment has been completed and consent signed, prior to the start of Consolidation therapy.

Patients who are risk assigned to SR-Avg B-ALL will sign consent prior to Consolidation therapy including the possibility of future randomization, based on HTS MRD results. At this time, they will be treatment assigned to Consolidation therapy via the callback application in the OPEN system. At the end of Consolidation therapy, patients will then be risk stratified based on EOI HTS MRD results. Patients (including DS) who are risk assigned to SR-Avg B-ALL with undetectable EOI HTS MRD will continue to receive therapy on control Arm A. Patients who are risk assigned to SR-Avg B-ALL with detectable or indeterminate EOI HTS MRD, or have double DT with EOI flow MRD 0.01-<0.1% will be randomized to 1 of 2 post-Consolidation therapy regimens [Treatment Arms A and B (see [experimental design schema](#))]. Patients for whom BM HTS MRD specimens are not obtained, or do not meet QA/QC standards, referred to as unavailable, will be randomized and receive treatment on either Arm A or Arm B. Randomization for SR-Avg B-ALL with detectable, indeterminate, or unavailable EOI HTS MRD patients (including DS) or DT with EOI flow MRD 0.01-<0.1% is accomplished by going to the

Callback application in the OPEN system for a second time. The next phase of therapy (Interim Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2. Institutions should take into account that the logistics of starting blinatumomab infusions can take time to arrange.

3.1.7.3 **SR-High B-ALL**

Post-Induction therapy assignment for patients with SR-High B-ALL is accomplished by completing the Callback in OPEN, after the risk assignment has been completed and consent signed, prior to the start of Consolidation therapy.

Patients who are risk assigned as SR-High B-ALL will sign consent prior to Consolidation and subsequent randomization. At this time, they will be treatment assigned to this Consolidation therapy via the Callback application in the OPEN system. At the end of Consolidation therapy, patients will be randomized to 1 of 2 post-Consolidation therapy regimens [Treatment Arms C and D (see [experimental design schema](#))]. Randomization for SR-High B-ALL is accomplished by going to the Callback application in the OPEN system for a second time. The next phase of therapy (Interim Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2. Institutions should take into account that the logistics of starting blinatumomab infusions can take time to arrange. Note that SR-High patients who are EOC MRD positive between 0.1 - <1% will be non-randomly assigned to Treatment Arm D with blinatumomab.

3.1.7.4 **DS-High B-ALL**

Patients with DS-High B-ALL may consent to non-randomized post-Induction treatment, after risk assignment and prior to the beginning of Consolidation therapy. Treatment assignment for these patients is accomplished by going to the Callback application in the OPEN system at the end of Induction but prior to the start of Consolidation therapy.

3.1.8 **Required Sample Submissions for Risk Stratification**

Adequate samples must be provided to the COG ALL Reference Laboratory and/or COG-approved cytogenetics laboratories to allow completion of the studies needed for risk-stratification to determine post-Induction treatment.

As part of APEC14B1 Part A, patients must submit specimens to a COG-Approved Cytogenetics Laboratory, and results must be submitted for central review within 3 weeks of diagnosis. It is essential that *BCR-ABL1* FISH data for AALL1731 be entered by the local institution in RAVE by Day 10 of Induction; all other FISH data must be entered by the local institution by Day 21 of Induction. All chromosome analysis must be submitted by Day 21 to ensure that central review can be completed before the end of Induction.

At diagnosis, if a BM aspirate is performed, sample submission guidelines as specified in [Section 14.1](#) and [Section 14.2](#) must be followed.

If a BM aspirate is not performed, or adequate material cannot be obtained, PB can be substituted for BM if there are at least 1,000 circulating blasts/ μ L (i.e., a WBC count of 10,000/ μ L with 10% blasts or a WBC count of 5,000/ μ L with 20% blasts). If only PB is submitted, please obtain and send twice the volume of PB as the recommended BM volume specified in the tables. As long as there are at least 1,000/ μ L PB blasts, institutions are encouraged to submit PB in addition to BM samples to make sure that adequate material is available to perform the required studies. If an adequate BM aspirate cannot be obtained and there are fewer than 1,000/ μ L PB blasts, the patient is not eligible for AALL1731.

Samples must be sent to a COG-approved cytogenetics laboratory, and COG Reference Laboratory studies must be performed as per [Section 14.1](#) and [Section 14.2](#) so that the data needed for post-Induction risk assignment are available. *If informative results needed for treatment stratification are not available at specified time-points during Induction, patients will not be eligible to receive post-Induction therapy on this trial.*

3.2 Patient Eligibility Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to protocol-directed systemic therapy, unless otherwise indicated. Diagnostic biopsy for B-LLy must be performed within 14 days prior to enrollment. Imaging studies, if applicable, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

3.2.1 Eligibility Screening

All B-ALL patients must be enrolled on APEC14B1 and consented to Eligibility Screening (Part A) prior to treatment and enrollment on AALL1731. See [Section 3.1.4](#) for timing details.

APEC 14B1 is not a requirement for B-LLy patients. B-LLy patients may directly enroll on AALL1731 and MUST submit eligibility studies as outlined in [Section 13.0](#).

3.2.2 Age at diagnosis

Patients must be \geq 365 days and $<$ 10 years of age (B-ALL patients without DS)

Patients must be \geq 365 days and \leq 31 years of age (B-ALL patients with DS)

Patients must be \geq 365 days and \leq 31 years of age (B-LLy patients with or without DS)

3.2.3 White Blood Cell Count (WBC) Criteria

- B-ALL patients without DS must have an initial white blood cell count $< 50,000/\mu\text{L}$
- B-ALL patients with DS are eligible regardless of the presenting WBC

3.2.4 Diagnosis

- Patient has newly diagnosed B-cell ALL, with or without Down syndrome:
 $> 25\%$ blasts on a BM aspirate;

OR if a BM aspirate is not obtained or is not diagnostic of B-ALL, the diagnosis can be established by a pathologic diagnosis of B-ALL on a BM biopsy;

OR a complete blood count (CBC) documenting the presence of at least 1,000/ μ L circulating leukemic cells;

- OR Patient has newly diagnosed B-cell LLy Murphy Stages I or II (see [Appendix VII](#) for staging), with or without Down syndrome.

Note: For B-LLy patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to B-ALL. For tissue processed by other means (i.e., paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of B-LLy defined by the submitting institution will be accepted.

3.2.5 Exclusion Criteria

- 3.2.5.1 Patient must not have secondary ALL that developed after treatment of a prior malignancy with cytotoxic chemotherapy. Note: patients with Down syndrome with a prior history of transient myeloproliferative disease (TMD) are not considered to have had a prior malignancy. They would therefore be eligible whether or not the TMD was treated with cytarabine.

3.2.5.2 Prior Therapy

With the exception of steroid pretreatment (defined in [Section 3.3.3](#)) or the administration of intrathecal cytarabine, patients must not have received any prior cytotoxic chemotherapy for either the current diagnosis of B-ALL or B-LLy or for any cancer diagnosed prior to initiation of protocol therapy on AALL1731.

Please see [Section 4.1.4](#) for the concomitant therapy restrictions for patients during treatment.

- 3.2.5.3 For patients receiving steroid pretreatment (See [Section 3.3.3](#)), the following additional exclusion criteria apply:

- Non-DS B-ALL patients must not have received steroids for more than 24 hours in the 2 weeks prior to diagnosis without a CBC obtained within 3 days prior to initiation of the steroids.
- DS and non-DS B-LLy patients must not have received > 48 hours of oral or IV steroids within 4 weeks of diagnosis.

- 3.2.5.4 B-ALL who do not have sufficient diagnostic bone marrow submitted for APEC14B1 diagnostic testing and who do not have a peripheral blood sample submitted containing >1,000/ μ L circulating leukemia cells.
- 3.2.5.5 Patient must not have acute undifferentiated leukemia (AUL).
- 3.2.5.6 Non-DS B-ALL patients with CNS3 leukemia (see definition in [Section 3.3.4](#), CNS status must be known prior to enrollment)
- Note: DS patients with CNS3 disease are eligible but will be assigned to the DS-High B-ALL arm. CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in [Section 3.3.3](#).
- 3.2.5.7 Non-DS B-ALL patients with testicular leukemia. (Note: DS patients with testicular disease are eligible but will be assigned to the DS-High B-ALL arm)
- 3.2.5.8 For LLy patients, the following additional exclusion criteria apply:
- T-Lymphoblastic Lymphoma.
 - Morphologically unclassifiable lymphoma.
 - Absence of both B-cell and T-cell phenotype markers in a case submitted as lymphoblastic lymphoma.
 - CNS positive disease (see [Section 3.3.4](#) for details) or testicular involvement.
 - M2 (5%-25% blasts) or M3 (>25% blasts) marrow.
- 3.2.5.9 Patients with known Charcot-Marie-Tooth disease.
- 3.2.5.10 Patients with evidence of a MYC translocation associated with mature (Burkitt) B-cell ALL, regardless of blast immunophenotype.
- 3.2.5.11 Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.
- 3.2.5.12 Lactating females who plan to breastfeed their infants.
- 3.2.5.13 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.6 Regulatory Requirements

- 3.2.6.1 All patients and/or their parents or legal guardians must sign a written informed consent.
- 3.2.6.2 All institutional, FDA, and NCI requirements for human studies must be met.

3.3 Definitions

COMMON ABBREVIATIONS:

EOI = End of induction

EOC = End of consolidation

MRD = Minimal Residual Disease (MRD)

EM = Extramedullary *NOTE: for the purposes of this protocol, EM excludes extramedullary hematopoietic sites (lymphoid tissue, liver, spleen, thymus), and refers only to non-hematopoietic extramedullary sites (CNS, testicular and other sites, such as soft tissue, bone, skin, other organ parenchyma, etc.)*

3.3.1 Disease Assessment

INITIAL WBC: The first WBC at the treating COG institution, or the WBC prior to intravenous fluids, whichever occurs first. If prior therapy (i.e., steroids) has been administered and a CBC is available that was obtained within 72 hours prior to steroid therapy, then this pre-steroid WBC should be used.

INITIAL PLATELET COUNT: The first platelet count at the treating COG institution, or the count before transfusion of platelets if transfused prior to arrival.

INITIAL HEMOGLOBIN: The first hemoglobin at the treating COG institution, or the hemoglobin prior to intravenous fluid or red cell transfusions, whichever occurred first.

B-ALL: The presence of > 25% B-lymphoblasts in the bone marrow (either via aspirate or biopsy if an aspirate is not obtained) OR > 1,000/ μ L circulating B-lymphoblasts on a CBC at the treating COG institution if a marrow is not obtained. Note: Every attempt should be made to obtain marrow unless medically contraindicated and documented.

B-L_y: For B-L_y patients with tissue available for flow cytometry, the criterion for diagnosis should be analogous to B-ALL. For tissue processed by other means (i.e., paraffin blocks), the methodology and criteria for immunophenotypic analysis to establish the diagnosis of B-L_y defined by the submitting institution will be accepted. Marrow must have <25% morphologic blasts to be considered B-L_y. See [Appendix VII](#) for details about Murphy Staging classification for lymphoma.

BONE MARROW STATUS

M1: < 5% leukemic blasts

M2: 5%-25% leukemic blasts

M3: > 25% leukemic blasts

BONE MARROW MRD STATUS (Day 29) FOR PATIENTS WITH B-ALL

Positive: $\geq 0.01\%$ detectable leukemia cells by flow cytometry

Negative: < 0.01% detectable leukemia cells by flow cytometry

TESTICULAR LEUKEMIA AT DIAGNOSIS

Unilateral or bilateral testiculomegaly as determined by ultrasound and physical examination. Biopsy is required if clinical findings are equivocal or suggestive of hydrocele or a non-leukemic mass. These non-DS B-ALL patients are not eligible for this study, but may be eligible to enroll in AALL1732. DS patients with testicular leukemia are eligible, but will be assigned to the DS-High B-ALL arm.

3.3.2 **Genetics**

It is essential that *BCR-ABL1* FISH data for all patients enrolling on AALL1731 be entered by the local institution in RAVE by Day 10 of Induction; all other FISH data must be entered by the local institution by Day 21 of Induction. All chromosome analysis must be submitted by Day 21 to ensure that central review can be completed before the end of Induction. Note that these studies will be done as part of APEC14B1.

FAVORABLE CYTOGENETICS FOR B-ALL PATIENTS

1. *ETV6-RUNX1* as identified by cytogenetics, fluorescence in-situ hybridization (FISH) or molecular studies
2. Double trisomies 4, 10 (DT) as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies

UNFAVORABLE CYTOGENETICS FOR B-ALL PATIENTS

1. iAMP21 as identified by central cytogenetic review (fluorescence in-situ hybridization (FISH) or SNP array).
2. *KMT2A* (formerly *MLL*) rearrangements as identified by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.
3. HYPODIPLOIDY: Fewer than 44 chromosomes and/or DNA index < 0.81, or other clear evidence of a hypodiploid clone.
4. t(17;19)(q21-q22;p13.3) or resultant *E2A-HLF* fusion transcript determined by cytogenetics, fluorescence in-situ hybridization (FISH), or molecular studies.
5. PHILADELPHIA CHROMOSOME POSITIVE (Ph+) ALL:
 - a) *BCR-ABL1* fusion transcript determined by FISH or RT-PCR
 - b) t(9;22)(q34;q11) determined by cytogenetics

Note: Patients enrolled on AALL1731 who are later found to have Ph+ ALL should be taken off protocol therapy prior to Day 15 of Induction therapy. Those patients who meet eligibility criteria may enroll on AALL1631 (or its successor COG Ph+ ALL trial).

NEUTRAL CYTOGENETICS FOR B-ALL PATIENTS

Lacking favorable and unfavorable cytogenetic features

3.3.3 **Steroid Pretreatment**

STEROID PRETREATMENT FOR B-ALL PATIENTS:

1. For DS patients ≥ 10 years of age:

The use of steroids prior to diagnosis will not affect their Induction therapy. Patients must meet all eligibility criteria (including an M3 bone marrow at diagnosis, or peripheral count of at least 1,000/ μ L leukemic blasts for patients in whom there is a medical contraindication to a bone marrow aspirate). Post-Induction risk assignment will be refined by leukemia specific genetic features and the level of bone marrow MRD at Day 29. Note: this definition applies only to children with DS and NCI HR-ALL. (Non-DS patients with NCI HR B-ALL are not eligible for this trial but may be eligible for AALL1732).

2. For non-DS patients younger than 10 years of age:

If steroids are given for more than 24 hours in the 2 weeks prior to diagnosis and a CBC is obtained within 3 days prior to initiation of the steroid, the patient will be assigned to Induction based on NCI risk group using the pre-steroid WBC. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29,

except that SR patients in this group will not be eligible for the SR-Fav arm of AALL1731. If there is no pre-steroid CBC obtained, non-DS patients are not eligible for AALL1731 but may be eligible for AALL1732. If steroids are given for less than 24 hours in the 2 weeks prior to diagnosis, Induction risk group will be based on NCI risk group using the initial WBC, though patients will not be eligible for the SR-Fav arm.

For DS B-ALL patients younger than 10 years of age:

If steroids are given for more than 24 hours in the 2 weeks prior to diagnosis and a CBC is obtained within 3 days prior to initiation of the steroid, the patient will be assigned to Induction based on NCI risk group using the pre-steroid WBC. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29, except that SR patients in this group will not be eligible for the SR-Fav arm of AALL1731. DS patients who have received steroid pretreatment for more than 24 hours in the 2 weeks prior to diagnosis and no CBC is obtained within 3 days prior to initiation of the steroid will be assigned to the DS-High B-ALL arm on AALL1731.

3. For all patients younger than 10 years of age:

Any amount of steroid pretreatment at any time prior to 2 weeks before diagnosis will not affect initial Induction assignment as long as the patient meets all other eligibility criteria including the presence of an M3 marrow at diagnosis. The presenting WBC at the time of diagnosis will be used to assign the patient to SR or HR Induction therapy. Post-Induction risk assignment will be refined by leukemia-specific genetic features and the level of bone marrow MRD at Day 29. SR patients in this group may be eligible for the SR-Fav arm only if they did not receive steroids within the month prior to diagnosis.

4. Inhalational and topical steroids are not considered pretreatment.
5. A single dose of dexamethasone used as an antiemetic or during sedation to prevent or treat airway edema is allowed and not considered steroid pretreatment or protocol specified therapy.

STEROID PRETREATMENT FOR B-LLy PATIENTS: Patients receiving steroids within 4 weeks of diagnosis:

1. B-LLy Patients with Murphy stage I and II who have received \leq 48 hours of oral or IV steroids will be eligible for AALL1731.
2. B-LLy Patients with Murphy stage I and II who have received $>$ 48 hours of oral or IV steroids, will not be eligible for AALL1731 because they cannot reasonably be classified as localized, but are eligible for AALL1732.
3. B-LLy Patients with Murphy stage III and IV are eligible for AALL1732 regardless of prior steroid exposure.

3.3.4 CNS

CNS LEUKEMIA AT DIAGNOSIS (B-ALL):

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytopsin preparation, regardless of the number of white blood cells (WBCs).

CNS 2: In CSF, presence $< 5/\mu\text{L}$ WBCs and cytopsin positive for blasts, or traumatic LP, $> 5/\mu\text{L}$ WBCs, cytopsin positive for blasts, but negative by Steinherz/Bleyer algorithm (see below):

CNS 2a: $< 10/\mu\text{L}$ RBCs; $< 5/\mu\text{L}$ WBCs and cytopsin positive for blasts;

CNS 2b: $\geq 10/\mu\text{L}$ RBCs; $< 5/\mu\text{L}$ WBCs and cytopsin positive for blasts; and

CNS 2c: $\geq 10/\mu\text{L}$ RBCs; $\geq 5/\mu\text{L}$ WBCs and cytopspin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).

CNS3: In CSF, presence of $\geq 5/\mu\text{L}$ WBCs and cytopspin positive for blasts and/or clinical signs of CNS leukemia:

CNS 3a: $< 10/\mu\text{L}$ RBCs; $\geq 5/\mu\text{L}$ WBCs and cytopspin positive for blasts;

CNS 3b: $\geq 10/\mu\text{L}$ RBCs, $\geq 5/\mu\text{L}$ WBCs and positive by Steinherz/Bleyer algorithm (see below);

CNS 3c: Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

B-Ly DEFINITION OF CNS POSITIVE DISEASE:

CNS Positive: Any CSF WBC and a cyt centrifuge preparation demonstrating lymphoblasts. CNS1, 2, 3 definitions are identical to those listed above for B-ALL.

Note: CNS2 and CNS3 B-Ly patients are not eligible for AALL1731, but may be eligible for AALL1732

CNS lymphoma may also be diagnosed when the CSF WBC is normal but clinical signs of CNS involvement are present:

- Cranial nerve palsy (if not explained by extracranial tumor)
- Clinical spinal cord compression
- Isolated intracerebral mass

METHOD OF EVALUATING INITIAL TRAUMATIC LUMBAR PUNCTURES:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/ μL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2 \times \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC $\geq 5/\mu\text{L}$ blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = $60/\mu\text{L}$; CSF RBC = $1,500/\mu\text{L}$; blood WBC $46,000/\mu\text{L}$; blood RBC = $3.0 \times 10^6/\mu\text{L}$

$$\frac{60}{1500} = 0.04 > 2 \times \frac{46000}{3.0 \times 10^6} = 0.015$$

3.3.5 Response and Relapse Definitions for B-ALL

FOR RESPONSE AND RELAPSE DEFINITIONS FOR B-Ly, REFER TO [SECTION 18.4](#)

REMISSION 1 (Rem-1) STATUS FOR PATIENTS WITH B-ALL

Achievement of MRD $< 1\%$ blasts and resolution of EM disease (for CNS disease, requires CNS1). Rem-1 is subclassified by timing of achievement:

- **Early Rem-1:** Achievement of Rem-1 as of EOI evaluation
- **OR, Late Rem-1:** If EOI MRD $\geq 1\%$ blasts or residual EM disease, achievement of Rem-1 as part of EOC evaluation

NOTE: Failure to achieve Rem-1 by the end of Consolidation (i.e., failure to meet criteria for both early Rem-1 and late Rem-1) is equivalent to consolidation failure (CF, defined below) and is a required off-protocol criterion.

NOTE: For patients who do NOT meet criteria for early Rem-1, the EOC MRD must be performed when there is evidence of early marrow recovery from Consolidation therapy, as evidenced by an absolute phagocyte count (APC, defined as absolute neutrophil count plus absolute monocyte count) of at least 500/ μ L after Day 56.

INDUCTION FAILURE (IF)

- EOI M3 (**IF-M3**)
- OR, EOI MRD \geq 5% blasts (**IF-MRD**)
- OR, Residual EM disease (for CNS, includes CNS2 and CNS3) (**IF-EM**)

NOTE: IF does not require that the patient be removed from protocol therapy; patients who meet criteria for IF can still achieve Late Rem-1 as defined above. The primary purpose of defining IF is to facilitate estimates of IF rates that can be compared with other clinical trials, both within and outside of COG.

CONSOLIDATION FAILURE (CF)

NOTE: CF is a required off-protocol criterion

- EOC MRD \geq 1% blasts (**CF-MRD**)
- OR, Residual EM disease (for CNS, includes CNS2 and CNS3) (**CF-EM**)

RELAPSE for B-ALL PATIENTS

NOTE: Definitive relapse as defined here is a required off-protocol criterion; detection of disease that does not meet definitive relapse criteria (i.e., equivocal marrow or CNS) is not a required off-protocol criterion.

Relapse occurs in a patient who achieves Rem-1 and then meets the criteria for any of the four anatomic locations below:

1) BONE MARROW RELAPSE

Definitive Relapse:

- **Rel-M3:** A single bone marrow sample with M3 morphology
- **Rel-M2:** A single bone marrow sample with M2 morphology and at least one confirmatory test
- **Rel-M1:** A single bone marrow sample with M1/M2 morphology and at least two confirmatory tests

Acceptable confirmatory tests include:

- flow cytometry showing leukemia \geq 1% of all cells
- karyotypic abnormality (must display at least 1 metaphase similar/identical to diagnosis; central cytogenetic review by COG required)
- FISH abnormality identical to one present at diagnosis (must be above level of sensitivity of specific FISH probe; central cytogenetic review by COG required)
- PCR or NGS-based demonstration of Ig or TCR rearrangement that matches diagnosis and is quantifiable as \geq 1% in a CLIA approved laboratory.
- PCR or NGS-based demonstration of validated leukemogenic lesion (e.g., fusion, mutation) that matches diagnosis and is quantifiable as \geq 1% in a CLIA approved laboratory.

Equivocal Marrow (Equiv-M):

- A single bone marrow sample with M1 morphology, but also with at least one evaluation that suggests recurrence of leukemia (e.g., flow cytometry, karyotype, FISH, PCR, NGS) but does not meet the definition of a definitive relapse.
 - In the case of Equiv-M, bone marrow evaluation should be repeated at least 1 week and at most, 4 weeks later; for repeat marrow, flow cytometric testing *must* be sent to a COG-approved flow cytometry laboratory
 - To convert to definitive relapse, the repeat marrow must either:
 - a. meet criteria for definitive relapse (Rel-M3, Rel-M2 or Rel-M1), or
 - b. demonstrate $\geq 1\%$ MRD in a COG approved flow cytometry lab (Rel-M1)

2) CNS RELAPSE:**Definitive Relapse:**

- **Rel-CNS3a/b:** A single CSF sample with CNS3 status
- **Rel-CNS3c:** Clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome
- **Rel-CNS2:** two consecutive CSF samples with CNS2 status confirmed by flow cytometry and/or FISH. See below for details.

Equivocal CNS (Equiv-CNS):

A single CSF sample with CNS2 status (Equiv-CNS)

- In the case of Equiv-CNS, CSF evaluation should be repeated at least 1 week and at most 4 weeks later; for repeat CSF, flow cytometric testing and FISH (if a diagnostic FISH marker is available) should be sent
- To convert to definitive relapse, the repeat CSF or clinical status must:
 - Meet criteria for definitive relapse (Rel-CNS3a/b/c), OR
 - Re-demonstrate CNS2 status, but with lymphoblasts confirmed by flow cytometry and/or FISH (Rel-CNS2) Note: For Rel-CNS2, the two CSF samples MUST BE CONSECUTIVE

3) TESTICULAR RELAPSE (Rel-T):

After achieving Rem-1, biopsy-proven recurrence

4) OTHER EXTRAMEDULLARY RELAPSE (Rel-OEM):

After achieving Rem-1, biopsy-proven recurrence

CATEGORIES OF RELAPSE

| Categories | BM | CNS | Testicular | Other EM site |
|-------------------------|----|----------------|------------|---------------|
| Isolated bone marrow | Y | N | N | N |
| Combined | Y | At least one Y | | |
| Isolated extramedullary | N | At least one Y | | |

DISEASE EVALUATION DURING FOLLOW-UP

A disease evaluation is a procedure ordered with the intent to measure or assess the disease status of a patient. The most common evaluations are a bone marrow aspirate and/or biopsy and a lumbar puncture (LP). If a CBC has findings that raise suspicion for relapse, a bone marrow aspirate must be performed to confirm the relapse as defined above.

3.3.6 Post-Induction Risk Groups for B-ALL Patients

3.3.6.1 Standard Risk-Favorable (SR-Fav) B-ALL

Standard Risk-Favorable (SR-Fav) B-ALL, Non-DS and DS

| NCI Risk Group | CNS stage | Steroid Pretreatment | Favorable Genetics (ETV6-RUNX1 or DT) | PB MRD D8 | BM MRD D29 |
|----------------|-----------|----------------------|---------------------------------------|-----------|------------|
| SR | 1, 2 | None ¹ | Yes | < 1% | < 0.01% |

¹ Within one month prior to diagnosis.

3.3.6.2 Standard Risk-Average (SR-Avg) B-ALL

Standard Risk-Average¹, Non-DS and DS

| NCI Risk Group | CNS stage | ETV6-RUNX1 | DT | Neutral Cytogenetics ² | PB MRD D8 | BM MRD D29 ³ |
|-----------------|-----------|---------------|-----|-----------------------------------|-----------|-------------------------|
| SR | 1, 2 | Yes to Either | | No | ≥ 1% | < 0.01% |
| SR ⁴ | 1, 2 | Yes to Either | | No | < 1% | < 0.01% |
| SR | 1, 2 | No | Yes | No | Any | ≥ 0.01-< 0.1% |
| SR | 1 | No | No | Yes | Any | < 0.01% |

¹ Note that certain cases of steroid pretreatment are allowed, see [Section 3.3.3](#) for details. For DS, patients who have received steroid pretreatment for more than 24 hours in the 2 weeks prior to diagnosis and no CBC is obtained within 3 days prior to initiation of the steroid will automatically be assigned to the DS-High B-ALL risk group, regardless of other features.

² Neutral cytogenetics is defined as the absence of favorable and unfavorable cytogenetics.

³ Note that all SR-Avg patients will also be evaluated at EOI using HTS-MRD, except for patients with both Double Trisomies 4, 10 and EOI BM flow MRD ≥ 0.01% to < 0.1%. HTS-MRD results will be available by end of Consolidation. HTS undetectable patients will be treated with standard therapy, while patients HTS-MRD detectable, indeterminate, or unavailable (as well as patients with Double Trisomies 4, 10 and EOI BM flow MRD ≥ 0.01% to < 0.1%) will be randomized to blinatumomab.

⁴ Received steroid pretreatment within one month prior to diagnosis (see [Section 3.3.3](#) for details).

3.3.6.3 Standard Risk-High (SR-High) B-ALL

Standard Risk-High¹

| NCI Risk Group | CNS stage | ETV6-RUNX1 | DT | Neutral Cytogenetics ² | Unfavorable Cytogenetics ³ | PB MRD D8 | BM MRD D29 |
|-----------------|-----------|------------|-----|-----------------------------------|---------------------------------------|-----------|------------|
| SR ⁴ | 1, 2 | Yes | No | No | No | Any | ≥ 0.01% |
| SR | 1, 2 | No | Yes | No | No | Any | ≥ 0.1% |
| SR | 1 | No | No | Yes | No | Any | ≥ 0.01% |
| SR | 2 | No | No | Yes | No | Any | Any |
| SR | 1, 2 | No | No | No | Yes | Any | Any |

¹ Note that certain cases of steroid pretreatment are allowed, see [Section 3.3.3](#) for details.

² Neutral cytogenetics is defined as the absence of favorable and unfavorable cytogenetics.

³ Unfavorable cytogenetics: Presence of iAMP21, KMT2A-R (formerly MLL-R), hypodiploidy (modal chromosome number less than 44, DNA index < 0.81, or other clear evidence of a hypodiploid clone), OR t(17;19).

⁴ Note that all SR-High patients with a BM MRD D29 ≥ 0.1% are required to have an End of Consolidation (EOC) Bone Marrow performed. If this EOC MRD level is ≥ 1%, the patient must go off protocol therapy. If this EOC MRD level is between 0.1% - <1%, the patient will be non-randomly assigned to receive the experimental

blinatumomab arm. Patients with EOI MRD 0.01-0.099% are not required to have an EOC MRD assessment but have the option of sending and submitting centrally acquired flow cytometry data on this timepoint if performed, as well as a banked optional research sample.

3.3.6.4 DS-High B-ALL

DS-High B-ALL¹

| NCI Risk Group | CNS stage | Testicular Leukemia | ETV6-RUNX1 | DT | Neutral Cytogenetics ² | Unfavorable Cytogenetics ³ | BM MRD D29 ⁴ |
|----------------|-----------|---------------------|------------|-----|-----------------------------------|---------------------------------------|-------------------------|
| SR | 1, 2 | No | Yes | No | No | No | ≥ 0.01% |
| SR | 1, 2 | No | No | No | Yes | No | ≥ 0.01% |
| SR | 1, 2 | No | No | Yes | No | No | ≥ 0.1% |
| SR | Any | Yes | Any | Any | Any | Any | Any |
| SR | 3 | Any | Any | Any | Any | Any | Any |
| SR | 2 | No | No | No | Yes | No | Any |
| SR | Any | No | No | No | No | Yes | Any |
| HR | Any | Any | Any | Any | Any | Any | Any |

¹Note that NCI SR DS patients who have received steroid pretreatment for more than 24 hours in the 2 weeks prior to diagnosis and no CBC is obtained within 3 days prior to initiation of the steroid will automatically be assigned to the DS-High B-ALL risk group, regardless of other features.

²Neutral cytogenetics is defined as the absence of favorable and unfavorable cytogenetics.

³Unfavorable cytogenetics: Presence of iAMP21, KMT2A-R (formerly MLL-R), hypodiploidy (modal chromosome number less than 44, DNA index < 0.81, or other clear evidence of a hypodiploid clone), OR t(17;19).

⁴Note that NCI HR DS patients with a BM MRD D29 ≥ 0.01% and any NCI SR DS patients with a BM MRD D29 ≥ 0.1% are required to have an End of Consolidation (EOC) Bone Marrow performed. If this EOC level is ≥ 1%, the patient is off protocol therapy. NCI HR DS patients with an EOC BM MRD ≥ 0.01% may be eligible for the Very High Risk B-ALL trial, AALL1721, however if they are not able or not willing to enroll on AALL1721, they may continue on AALL1731 provided they do not meet criteria for Consolidation Failure.

4 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Informed consent that describes the first 4 weeks of Induction therapy for patients is required. Separate Induction consents will be used for B-ALL, DS B-ALL, and B-Lly patients.

At the end of Induction, after B-ALL patients have been stratified into risk subgroups, a second informed consent that describes the next portions of therapy must be signed prior to the start of Consolidation. There will be separate post-Induction consents for different risk groups eligible for this study.

- Post-Induction consent for SR-Fav B-ALL patients (DS and non-DS) will include consent to assignment on the SR-Fav B-ALL Arm, with no randomization.
- Post-Induction consent for SR-Avg patients (DS and non-DS) will include consent to the possibility of non-randomized standard chemotherapy (Arm A) in the case of undetectable (EOI) high-throughput sequencing (HTS) minimal residual disease (MRD), and the possibility of randomization in the case of detectable, indeterminate, or unavailable EOI HTS-MRD or SR-Avg with Double Trisomies 4, 10 and EOI BM Flow MRD $\geq 0.01\%$ to $< 0.1\%$. Randomization will be to either Arm A (control) or Arm B (experimental).
- Post-Induction consent for SR-High B-ALL patients will include consent to the possibility of post-Consolidation randomization to either Arm C (control) or Arm D (experimental) for patients with with MRD $< 0.1\%$ by EOC, and the possibility of non-random assignment to Arm D for patients with EOI MRD $\geq 0.1\%$ who have EOC MRD between 0.1% - <1%.
- Post-Induction consent for patients with DS and high risk features will include consent to assignment on the DS-High Arm, which includes blinatumomab, with no randomization.

Localized (Murphy Stage I or II) B-Lly patients with or without DS will sign one consent that describes all therapy to be received on study, prior to beginning Induction therapy.

CNS status must be known prior to enrollment because patients with non-DS B-ALL CNS3 disease and patients with B-Lly with CNS positive disease are not eligible for AALL1731 but may be eligible for the COG HR B-ALL protocol AALL1732. It is recommended that intrathecal cytarabine be administered at the time of the diagnostic lumbar puncture. This is usually done at the time of the diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. (Note: The CNS status must be determined based on a sample obtained prior to administration of any systemic or intrathecal chemotherapy, except for steroid pretreatment as discussed in [Section 3.3](#)). This is allowed prior to registration. **Systemic**

chemotherapy must begin within 72 hours of this intrathecal therapy. Non-DS B-ALL and non-DS and DS B-LLy patients with testicular leukemia are not eligible for this study.

FOR ALL NCI SR B-ALL PATIENTS WITH OR WITHOUT DS, IF DAY 8 PB AND DAY 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE AALL1731 FOLLOWING COMPLETION OF INDUCTION THERAPY AND WILL BE REMOVED FROM PROTOCOL THERAPY.

FOR NCI HR B-ALL PATIENTS WITH DS, IF DAY 29 BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO A COG-APPROVED ALL FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE AALL1731 FOLLOWING COMPLETION OF INDUCTION THERAPY AND WILL BE REMOVED FROM PROTOCOL THERAPY.

FOR ALL NCI SR B-ALL PATIENTS WITH OR WITHOUT DS WITH DAY 29 BM MRD $\geq 0.1\%$ AND NCI HR DS B-ALL PATIENTS WITH DAY 29 BM MRD $\geq 0.01\%$, IF END OF CONSOLIDATION BM MRD SAMPLES ARE NOT OBTAINED AND SHIPPED TO THE UNIVERSITY OF WASHINGTON FLOW CYTOMETRY REFERENCE LABORATORY, THEN THE PATIENT WILL NOT BE ELIGIBLE TO CONTINUE AALL1731 FOLLOWING COMPLETION OF CONSOLIDATION THERAPY AND WILL BE REMOVED FROM PROTOCOL THERAPY.

4.1.1 Non-Down syndrome (non-DS) Standard Risk (SR) B-ALL patients

Induction Therapy

All patients will receive a common 3-drug dexamethasone based Induction. Patients with CNS2 disease will also receive twice weekly IT ARAC in addition to their initial dose (except on Days 8 & 29 when IT MTX is administered) until 3 consecutive CSF samples are clear of blasts.

At the end of Induction, all eligible **B-ALL patients without DS** are stratified into 3 risk groups (See [Section 3.3.6](#) for defining criteria):

- 1) Standard Risk-Favorable (SR-Fav) B-ALL
- 2) Standard Risk-Average (SR-Avg) B-ALL
- 3) Standard Risk-High (SR-High) B-ALL

Post Induction Therapy

Patients whose disease meets the criteria for consolidation failure (as described in [Section 3.3.5](#)) are not eligible to continue on AALL1731.

STANDARD RISK-FAVORABLE (SR-FAV) B-ALL

Patients who meet the SR-Fav criteria as outlined in [Section 3.3.6](#) will be treated with standard chemotherapy, including standard Consolidation therapy, two phases of Interim Maintenance (IM I & II) with escalating methotrexate, Delayed Intensification (DI), and Maintenance with every 12 week vinCRISTine and dexamethasone pulses. There is no randomization for patients with SR-Fav B-ALL.

STANDARD RISK-AVERAGE (SR-AVG) B-ALL

SR-Avg patients with DT and BM EOI MRD $\geq 0.01\%$ to $< 0.1\%$ will be treated with standard Consolidation therapy. These patients do not require having EOI HTS MRD testing ordered through the Adaptive Portal, and will be randomized to receive post-Consolidation therapy on either Arm A or Arm B. All other patients who meet the SR-Avg criteria as defined in [Section 3.3.6](#) will be treated with standard Consolidation therapy then further stratified on the basis of EOI HTS MRD as follows (results returned prior to end of Consolidation).

SR-Avg B-ALL EOI HTS MRD undetectable (Arm A): SR-Avg B-ALL patients with undetectable EOI HTS MRD will be non-randomly assigned to receive standard chemotherapy with two IM phases (IM I & II) with escalating methotrexate, one DI, and Maintenance with every 12 week vinCRISTine and dexamethasone pulses.

SR-Avg B-ALL patients with detectable/indeterminate/unavailable EOI HTS MRD and SR-Avg patients with DT with BM EOI MRD $\geq 0.01\%$ to $< 0.1\%$ are randomized at the end of Consolidation to one of two treatment arms:

Control Arm A: Standard therapy with two IM phases (IM I & II) with escalating methotrexate phases, one DI, and Maintenance with every 12-week vinCRISTine and dexamethasone pulses.

Experimental Arm B: Patients receive standard therapy as in Arm A plus two 28-day courses of Blinatumomab after Consolidation and after IM I chemotherapy courses.

Modifications specific to patients with Down syndrome

- 1) Leucovorin rescue following intrathecal methotrexate in all phases of therapy.

STANDARD RISK-HIGH (SR-HIGH) B-ALL

Patient who meet the SR-High criteria as outlined in [Section 3.3.6](#) will receive aBMF Consolidation therapy, then be randomized at the end of Consolidation to one of two treatment arms, with the exception of SR-High patients with EOC BM MRD 0.1-0.99% who will be non-randomly assigned to Arm D:

Control Arm C: High risk therapy with an augmented Berlin-Frankfurt-Münster (aBFM) backbone including high risk Consolidation, two phases of Interim Maintenance (IM I with high-dose methotrexate and IM II with Capizzi style methotrexate), DI, and Maintenance with every 12 week vinCRISTine and predniSO(LO)ne pulses.

Experimental Arm D: aBFM therapy, as in Arm C, plus two 28-day courses of Blinatumomab after Consolidation and after IM I chemotherapy courses.

Patients whose disease meets the criteria for consolidation failure (as described in [Section 3.3.5](#)) will not be eligible to continue on AALL1731.

NOTE: ALL PATIENTS TREATED ON AALL1731 WILL RECEIVE MAINTENANCE THERAPY FOR 2 YEARS FROM THE BEGINNING OF INTERIM MAINTENANCE I (SR-FAV, ARM A, ARM C, B-LLy) OR

BLINATUMOMAB BLOCK 1 (ARM B, ARM D, DS-HIGH), REGARDLESS OF SEX.**4.1.2 Patients with DS and NCI SR or NCI HR B-ALL****Induction Therapy**

NCI SR and HR B-ALL patients with DS will receive a 3-drug Induction with age-based steroid therapy.

- Patients 1 to < 10 years receive dexamethasone 6 mg/m²/day x 28 days.
- Patients ≥ 10 years of age receive predniSO(LO)ne 60 mg/m²/day x 28 days.

Patients will also receive leucovorin rescue after each IT MTX. Patients with CNS2 disease will also receive twice weekly IT ARAC in addition to their initial dose (except on Days 8 & 29 when IT MTX is administered) until 3 consecutive CSF samples are clear of blasts.

At the end of Induction, all eligible **patients with Down syndrome** will be stratified into 3 risk groups (See [Section 3.3.6](#) for defining criteria):

- 1) Standard Risk-Favorable (SR-Fav) DS B-ALL
- 2) Standard Risk-Average (SR-Avg) DS B-ALL
- 3) DS-High B-ALL

Post-Induction Therapy

Patients with DS who meet either SR-Fav or SR-Avg criteria will receive post-Induction therapy similar to that of non-DS patients as above.

Patients with DS NCI HR B-ALL or with DS NCI SR-ALL with additional high-risk features (CNS3 disease, testicular leukemia, steroid pretreatment, EOI MRD ≥ 0.01%, unfavorable cytogenetics, or neutral cytogenetics with CNS2 disease) are eligible for post-Induction therapy on the DS-High B-ALL arm of AALL1731.

NCI SR DS patients with EOI BM flow MRD of ≥ 0.1% and NCI HR DS patients with EOI MRD ≥ 0.01% are required to have an EOC BM MRD by flow cytometry evaluation. For NCI SR DS, those with EOC MRD < 1% may remain on therapy on the DS-High arm. Those with NCI HR DS B-ALL with EOC MRD ≥ 0.01% may remain on therapy on the DS-High arm in AALL1731, provided they do not meet criteria for Consolidation Failure (as described in [Section 3.3.5](#)), but may also be eligible for AALL1721.

Patients with Consolidation failure (as described in [Section 3.3.5](#)) will not be eligible to continue on AALL1731.

Post-Induction therapy consists of the Modified Berlin-Frankfurt-Munster interim maintenance intermediate-dose methotrexate (MBFM-IMHDM) backbone with modifications specific to DS patients. This backbone includes high-risk Consolidation, one IM phase with intermediate dose methotrexate (ID MTX), a reduced intensity DI phase with only the first 29 days of the MBFM DI, and Maintenance. Blinatumomab will be given as 28-day courses after Consolidation, IM, and one month of DI. Modifications to the MBFM-IMHDM backbone specific to DS patients will include:

- Leucovorin rescue following IT MTX in all phases of therapy.
- IM with ID MTX beginning at a dose of 2,000 mg/m² with early leucovorin rescue starting at hour 30. If this dose is tolerated, the dose will continue at 2,000 mg/m² for the second and subsequent courses with leucovorin rescue starting at hour 36.

Testicular Radiation Therapy:

Males with DS and testicular leukemia at diagnosis, as determined by ultrasound and physical examination, and continued clinical evidence of testicular leukemia at EOI will receive radiation to the testes (2400 cGy in 12 fractions) during Consolidation (see [Section 4.37](#) and [Section 16.2](#)). A testicular biopsy should be performed if the clinical findings are equivocal. **Patients with testicular leukemia at diagnosis that resolves completely by the EOI, and those who have a negative testicular biopsy at EOI, will NOT receive testicular irradiation.**

Cranial Radiation Therapy:

DS patients with CNS3 status at diagnosis receive cranial irradiation, 1800 cGy in 10 fractions, during the first cycle of Maintenance therapy (see [Section 4.43](#) and [Section 16.1](#)).

4.1.3 Patients with Localized B-Lymphoblastic Lymphoma

Induction Therapy

B-LLy patients without DS will receive a 3-drug Induction with dexamethasone

- Patients 1 to ≤ 30 years receive dexamethasone 6 mg/m²/day x 28 days.

B-LLy patients with DS will receive a 3-drug Induction with age-based steroid therapy.

- Patients 1 to < 10 years receive dexamethasone 6 mg/m²/day x 28 days.
- Patients ≥ 10 years of age receive predniSO(LO)ne 60 mg/m²/day x 28 days.

Patients with DS will also receive leucovorin rescue after each IT MTX.

Patients with progressive disease (as described in [Section 18.0](#)) at the end of Induction therapy are not eligible to continue on AALL1731.

Post-Induction Therapy

Patient with B-LLy will be treated non-randomly with standard chemotherapy including standard Consolidation, two IM phases (IM I & II) with escalating methotrexate, DI, and Maintenance with every 12-week vinCRIStine and dexamethasone pulses for 2 years from the beginning of IM I regardless of sex.

Modifications specific to patients with Down syndrome

- Leucovorin rescue following each IT in all phases of therapy

4.1.4 Concomitant Therapy Restrictions

4.1.4.1 **Cytochrome P450 Interactions with Antileukemic Drugs**

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with anti-leukemic therapy has been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces hepatic drug metabolizing enzymes. Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes and may be suitable alternative anticonvulsants. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes. Patients receiving some anti-leukemic drugs (e.g., vinCRISTine, anthracyclines, etoposide) may experience excess toxicity when these agents are given concomitantly; alternate antifungal and antibacterial therapy should be used where possible (see table below).

| DRUGS | POTENTIAL INTERACTION | ACTION TO BE TAKEN |
|---|---|--|
| Anticonvulsants | Induction of drug metabolizing enzymes Lowered EFS | AVOID phenytoin, phenobarbital, carbamazepine Consider gabapentin or levetiracetam as alternative |
| Rifampin | Induction of drug metabolizing enzymes | DO NOT USE |
| Azole Antifungals (fluconazole, itraconazole*, isavuconazole, posaconazole, voriconazole, ketoconazole) | Inhibition of drug metabolizing enzymes | CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vinCRISTine*, anthracyclines, etoposide, steroids |
| Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, roxithromycin, telithromycin) | Inhibition of drug metabolizing enzymes | CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vinCRISTine, anthracyclines, etoposide, steroids |

* Itraconazole should NOT be used in patients who are receiving vinCRISTine due to a serious drug-drug interaction leading to severe neurotoxicity. [62](#) [63](#)

For a more complete list of CYP3A4/5 Inhibitors and Inducers, see [Appendix VIII](#).

4.1.4.2 **Possible Drug Interactions with High or Intermediate Dose Methotrexate**

Avoid non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim/sulfamethoxazole (TMP/SMX), penicillins, probenecid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin. Urinary acidifiers can cause methotrexate to precipitate in the urinary tract.

4.1.5 COG Supportive Care Guidelines

<https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines>

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

4.1.6 Contacts for Questions Regarding Treatment Plan

Questions regarding study treatment should be directed to the contacts listed below according to the institution's geographic location in either the Eastern Division or Western Division. For US institutions, refer to the map in [Appendix XIV](#) for a description of Eastern US and Western US.

Institutions in the Eastern Division: Eastern US, and Eastern Canada (Ontario, Quebec, Nova Scotia, and Newfoundland)

- Address questions regarding treatment plans to the following:
 - Study Co-Chair:
Dr. Sumit Gupta
The Hospital for Sick Children
 - Study Vice Chair:
Dr. Anne Angiolillo
Children's National Medical Center

Institutions in the Western Division: Western US, Australia, New Zealand, and Western Canada (British Columbia, Alberta, Saskatchewan and Manitoba)

- Address questions regarding treatment plans to the following:
 - Study Co-Chair:
Dr. Rachel Rau
Baylor College of Medicine
 - Study Vice Chair:
Dr. Karen Rabin
Baylor College of Medicine

Questions regarding subjects with Down syndrome

- Address questions to:
 - Dr. Amanda Li
British Columbia Children's Hospital

Questions regarding subjects with B-LLy

- Address questions to:
 - Dr. Birte Wistinghausen
Children's National Medical Center
 - Dr. Amanda M. Termuhlen
University of Minnesota/ Masonic Cancer Center

4.2 Non-DS SR B-ALL Patients – Induction

4.2.1 Therapy Delivery Map – Non-DS SR B-ALL INDUCTION

Induction therapy in [Section 4.2.1](#) is for non-DS SR B-ALL patients. Refer to [Section 4.36](#) for DS SR B-ALL and [Sections 4.44](#) and [4.45](#) for B-Lly Induction therapy. Induction therapy is 5 weeks (35 days).

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.2.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|-----------------------------------|---|--|------------------------|---|--------|-------|--------|-------|--------|-------|--|---|----------|--|
| Intrathecal Cytarabine (IT ARAC) | IT | <table> <thead> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>1-1.99</td> <td>30 mg</td> </tr> <tr> <td>2-2.99</td> <td>50 mg</td> </tr> <tr> <td>≥ 3</td> <td>70 mg</td> </tr> </tbody> </table> | Age (yrs) | Dose | 1-1.99 | 30 mg | 2-2.99 | 50 mg | ≥ 3 | 70 mg | Given at time of diagnostic LP <u>OR</u> Day 1* | <p>See Section 4.2.3 for administration guidelines.</p> <p>Note age-based dosing.</p> | | |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 30 mg | | | | | | | | | | | | | |
| 2-2.99 | 50 mg | | | | | | | | | | | | | |
| ≥ 3 | 70 mg | | | | | | | | | | | | | |
| Intrathecal Cytarabine (IT ARAC) | IT | <table> <thead> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>1-1.99</td> <td>20 mg</td> </tr> <tr> <td>2-2.99</td> <td>30 mg</td> </tr> <tr> <td>≥ 3</td> <td>40 mg</td> </tr> </tbody> </table> | Age (yrs) | Dose | 1-1.99 | 20 mg | 2-2.99 | 30 mg | ≥ 3 | 40 mg | CNS2: twice weekly [†] | <p>[†]For CNS2, the initial dose is followed by twice weekly IT ARAC except during weeks when Days 8 & 29 IT MTX is administered</p> <p>Note: IT therapy is administered until 3 consecutive CSF samples are clear of blasts.</p> | | |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 20 mg | | | | | | | | | | | | | |
| 2-2.99 | 30 mg | | | | | | | | | | | | | |
| ≥ 3 | 40 mg | | | | | | | | | | | | | |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 8, 15 & 22 | <p>⁺Or infusion via minibag as per institutional policy.</p> <p>Maximum dose: 2 mg</p> | | | | | | | | | | |
| Dexamethasone (DEX) | PO (may be given IV) | 3 mg/m ² /dose BID | 1-28 (do not taper) | <p>Total daily dose: 6 mg/m²/day, divided BID</p> <p>See Section 4.2.3 for administration guidelines.</p> | | | | | | | | | | |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or intramuscular (IM) injection) | 2,500 International Units/m ² /dose | 4 | <p>Note: pegaspargase should be administered on Day 4.</p> <p>Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl</p> | | | | | | | | | | |
| Intrathecal Methotrexate (IT MTX) | IT | <table> <thead> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>≥ 9</td> <td>15 mg</td> </tr> </tbody> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | ≥ 9 | 15 mg | 8 and 29 | <p>See Section 4.2.3 for administration guidelines.</p> <p>Note age-based dosing</p> <p>Note: All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation.</p> |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| ≥ 9 | 15 mg | | | | | | | | | | | | | |

Continue to the next page for the therapy log.

4.2.1 Therapy Delivery Map – Non-DS SR B-ALL INDUCTION

Induction therapy in [Section 4.2.1](#) is for Non-DS SR B-ALL patients. Refer to [Section 4.36](#) for DS SR and HR B-ALL patients. Refer to [Section 4.44](#) and [4.45](#) for B-Lly Induction therapy. Induction therapy is 5 weeks (35 days).

| Ht _____ cm Wt _____ kg BSA _____ m ² | | | | | | | | | |
|---|------------|-------------|--|---------------------------------|----------------|---------------------------|--------------------|-------------------|---------|
| Date Due | Date Given | Day | IT ARAC ____ mg | IT ARAC (if CNS2) ____ mg | VCR ____ mg | DEX ____ mg ____ mg | PEG-ASP ____ IU | IT MTX ____ mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | | | | |
| | | -2/-1/0/LP* | ____ mg | | | | | | a-f |
| | | 1 | | | ____ mg | ____ mg | | | |
| | | 4† | | ____ mg† | | | ____ IU | | e† |
| | | 8 | | | ____ mg | | | ____ mg | e, g |
| | | 10 | | | | | | | |
| | | 11† | | ____ mg† | | | | | e† |
| | | 15 | | | ____ mg | | | | |
| | | 22 | | | ____ mg | | | | |
| | | 28 | | | | | | | |
| | | 29 | | | | | | ____ mg | e, h-l |
| | | 31 | | | | | | | |
| | | 32 | | | | | | | |
| | | 35 | Begin Consolidation therapy on Day 36 or when blood count criteria have been met (whichever occurs later). SR-Fav B-ALL refer to Section 4.3 , SR-Avg B-ALL patients refer to Section 4.9 , and SR-High B-ALL patients refer to Section 4.23 . | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

Page 3 of 3

4.2.2 Required Observations in Induction – Non-DS SR B-ALL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Hx/PE/Wt/Ht/BSA (Note: Height is only required at the beginning of this course)
- b. CBC/diff/platelets
- c. Creatinine
- d. Total bilirubin, ALT
- e. CSF cell count and cytopsin (obtain with each IT administration)
- f. *TPMT and NUDT15 genotype (TPMT highly recommended for all subjects; NUDT15 is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects.*
- g. **Required peripheral blood (PB).** Send Day 8 PB sample to COG-approved ALL Flow Cytometry Lab for MRD testing. This sample should be drawn prior to Day 8 IT MTX or VCR. This sample should be drawn no more than one day early or late. **If Day 8 PB sample is not obtained and shipped to COG-approved ALL flow cytometry reference laboratory, then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. This sample is absolutely essential.** See [Section 14.1](#) for a list of COG-approved labs.
- h. **Required bone marrow (BM) evaluation to assess response by morphology (at local institution), flow minimal residual disease (MRD), and high-throughput sequencing (HTS) MRD.** BM specimen for flow MRD testing should be sent to a COG-approved flow MRD laboratory (See [Section 14.1](#) for a list of labs). BM specimen for HTS MRD should be sent to the COG ALL Molecular Reference Lab (See [Section 14.2](#) for additional details). This sample should be drawn no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level. **If Day 29 BM sample is not obtained and shipped to a COG-approved flow lab for MRD testing and to the COG ALL Molecular Reference lab then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. These samples are absolutely essential.**
- i. For patients who consent, send Day 29 PB and BM specimens to the ALL Molecular Reference Lab for cell banking. Done through APEC14B1. Refer to the APEC14B1 protocol for additional details.
- j. For patients who consent to optional biobanking for EOI PB, send specimen to the COG ALL Molecular Reference Lab. Refer to [Section 14.3](#) for additional details.
- k. For patients who consent, send CSF specimens to the ALL Molecular Reference Lab for optional biobanking. Refer to [Section 14.7](#) for additional details.
- l. For patients who consent, complete assessment for the Household Material Hardship study prior to Day 29 LP. Refer to [Section 17.1](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.2.3 Induction Treatment Details – Non-DS SR B-ALL

All Non-DS SR B-ALL patients will receive common Induction therapy. For patients with DS and B-ALL refer to [Section 4.36](#). For patients with non-DS B-LLy see [Section 4.44](#). For patients with DS B-LLy see [Section 4.45](#).

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Note: Systemic chemotherapy must begin within 72 hours of the first dose of intrathecal therapy.

Cytarabine: Intrathecal (IT)

All patients: Day 1 or at the time of diagnostic LP

May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing for Day 1/diagnostic LP:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1-1.99 | 30 mg |
| 2-2.99 | 50 mg |
| ≥ 3 | 70 mg |

B-ALL CNS2 patients ONLY: In addition to the initial dose (above), patients will receive additional IT Cytarabine on either Day 4, 5 or 6 during Induction, IT Methotrexate on Day 8, and then receive IT Cytarabine on Days 11 or 12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy on Day 29 with methotrexate. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 8 and 29 of Induction regardless of CSF evaluations.

Age-based dosing for additional IT Cytarabine for **B-ALL CNS2 patients ONLY (Days 4, 5 or 6 and Days 11 or 12) and additional IT Cytarabine until clear for three consecutive LPs:**

Age-based dosing for CNS2 additional doses:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 20 mg |
| 2 – 2.99 | 30 mg |
| ≥ 3 | 40 mg |

Use preservative free formulation. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.4](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8, 15 and 22

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: Oral (PO; may be given Intravenous (IV))

Days: 1 - 28 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Pegaspargase: Intravenous (IV) over 1 - 2 hours (may also be given IM)

Day: 4*

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

***PLEASE NOTE: FOR B-ALL PATIENTS, DUE TO THE IMPORTANCE OF DAY 8 EARLY RESPONSE ASSESSMENT, PEGASPARGASE SHOULD BE ADMINISTERED ON DAY 4.** Deviation from Day 4 administration may adversely impact risk categorization.

See dose modifications in [Section 5.2](#).

Methotrexate: Intrathecal (IT)

Days: 8 and 29

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of Induction, begin Consolidation therapy on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later). All SR-favorable patients refer to [Section 4.3](#). SR-Avg B-ALL patients refer to [Section 4.7](#). Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

4.3 All SR-Fav B-ALL (including DS patients) – Consolidation

| | |
|---|--|
| 4.3.1 Therapy Delivery Map – CONSOLIDATION | Patient COG ID number _____ DOB _____ |
| Consolidation therapy in this TDM is for all SR-Fav B-ALL patients, including DS patients. Consolidation therapy is 4 weeks (28 days). Begin Consolidation on Day 36 of Induction therapy or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.3.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|------------------------------------|--|-----------|---|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1 ONLY | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-28 | See Section 4.3.3 and Appendix III for administration guidelines. *See Section 5.8 for suggested dose based on <i>TPMT</i> and <i>NUDT15</i> status. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1, 8 & 15 | See Section 4.3.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2, 9 & 16 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.3.3 for administration guidelines. |

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | VCR ____ mg | MP ____ mg | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | Studies |
|---|------------|-----|--|---------------|-------------------|---|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | | a-e |
| | | 2 | | | | ____ mg** ____ mg** | |
| | | 8 | | | ____ mg | | d |
| | | 9 | | | | ____ mg** ____ mg** | |
| | | 15 | | | ____ mg | | d, f |
| | | 16 | | | | ____ mg** ____ mg** | |
| | | 22 | | | | | |
| | | 28 | | | | | |
| | | 29 | Begin Interim Maintenance I (Section 4.4) on Day 29 or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.3.2 Required Observations in Consolidation – All SR-Fav B-ALL (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only
- f. For non-DS patients who consent, send CSF for cell banking at **the final LP**. Refer to [Section 14.7](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.3.3 Consolidation Treatment Details – All SR-Fav B-ALL (including DS patients)

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For all SR-Fav B-ALL patients, Consolidation therapy begins on Day 36 of Induction (7 days following Day 29 LP) or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day 1 ONLY

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Mercaptopurine: Oral (PO)

Days 1 - 28

Dose: 75 mg/m²/dose* once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to $525 \text{ mg/m}^2/\text{week}$ as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate dose based on blood counts during this cycle (see [Section 5.8](#)).

Methotrexate: Intrathecal (IT)

Days: 1, 8 & 15

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days: 2, 9 and 16

Dose: $5 \text{ mg/m}^2/\text{dose} \times 2 \text{ doses}$ given 24 and 30 hours after each IT methotrexate dose

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Consolidation therapy, Interim Maintenance I ([Section 4.4](#)) should begin on Day 29 or when peripheral counts recover with an ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

4.4 All SR-Fav B-ALL (including DS patients) – Interim Maintenance I EscMTX

Page 1 of 2

| | |
|--|--|
| 4.4.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE I (IM I EscMTX)</u> | Patient COG ID number _____ DOB _____ |
| IM I therapy in this TDM is for all SR-Fav B-ALL patients, including DS patients. IM I therapy is 8 weeks (56 days). Begin IM I on Day 29 of Consolidation or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.4.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|---|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (IV MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose 100 mg/m ² & escalate by 50 mg/m²/dose | 1, 11, 21, 31 & 41 | See Section 4.4.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 31 ONLY | See Section 4.4.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.4.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | IV MTX ____mg (escalating dose) | IT MTX ____mg | LCV (DS pts only) ____mg ____mg | Studies |
|---|------------|-----|---|---------------------------------------|------------------|---------------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____mg | ____mg | | | a-c, e |
| | | --- | | | | | |
| | | 11 | ____mg | ____mg | | | a-c |
| | | --- | | | | | |
| | | 21 | ____mg | ____mg | | | a-c |
| | | --- | | | | | |
| | | 31 | ____mg | ____mg | ____mg | | a-d |
| | | 32 | | | | ____mg** ____mg** | |
| | | --- | | | | | |
| | | 41 | ____mg | ____mg | | | a-c |
| | | --- | | | | | |
| | | 56 | | | | | |
| | | 57 | Begin Delayed Intensification (Section 4.5) on Day 57 or when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.4.2 Required Observations in Interim Maintenance I with EscMTX – All SR-Fav B-ALL (including DS patients)

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.4.3 Interim Maintenance I with EscMTX Treatment Details – All SR-Fav B-ALL (including DS patients)

For SR-Fav B-ALL, IM I begins on Day 29 of Consolidation or when peripheral counts recover with an ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and Vincristine doses in 10 days.
 2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give Vincristine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled Vincristine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled Vincristine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate MTX by 50 mg/m²/dose.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m²/dose; **thereafter, escalate by 50 mg/m²/dose**

Methotrexate: IT

Day: 31 ONLY

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after the IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by

timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Interim Maintenance (IM) I, Delayed Intensification ([**Section 4.5**](#)) should begin on Day 57 of IM I or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.5 All SR-Fav B-ALL (including DS patients) – Delayed Intensification

| | |
|---|--|
| 4.5.1 Therapy Delivery Map – Delayed Intensification (DI) Part 1 | Patient COG ID number _____ DOB _____ |
| Delayed Intensification Part 1 therapy in this TDM is for all SR-Fav B-ALL patients, including DS patients. DI therapy is 8 weeks (56 days). Begin DI on Day 57 of IM I or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.5.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|--|-------------|---|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day See Section 4.5.3 for administration guidelines. |
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXOrubicin (DOXO) | IV push/infusion over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.5.3 for administration guidelines. *Obtain ECHO (f) prior to the first dose of DOXO. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Administer through the tubing of a freely infusing solution of DsW or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.5.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.5.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | DEX ____ mg | VCR ____ mg | DOXO ____ mg | PEG-ASP ____ IU | IT MTX ____ mg | LCV (DS pts only) ____ mg | Studies |
|--|------------|-----|----------------|----------------|-----------------|--------------------|-------------------|------------------------------|-----------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | a-e, f* |
| | | 2 | | | | | | ____ mg** | ____ mg** |
| | | 3 | | | | | | | |
| | | 4 | | | | ____ IU | | | |
| | | 5 | | | | | | | |
| | | 6 | | | | | | | |
| | | 7 | | | | | | | |
| | | 8 | | ____ mg | ____ mg | | | | b |
| | | 15 | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | b |
| | | 16 | | | | | | | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 19 | | | | | | | |
| | | 20 | | | | | | | |
| | | 21 | | | | | | | |
| | | 22 | | | | | | | |

This Therapy Delivery Map continues on the next page.

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

All SR-Fav B-ALL – Delayed Intensification

| | |
|---|--|
| 4.5.1 Therapy Delivery Map – Delayed Intensification (DI) Part 2 | Patient COG ID number _____ DOB _____ |
| Delayed Intensification Part 2 therapy in this TDM is for all SR-Fav B-ALL patients, including DS patients. DI therapy is 8 weeks (56 days). Begin DI Part 2 on Day 29 of DI Part 1 or when criteria to start are met (whichever occurs later). Patients should have ANC ≥ 750/μL and platelets ≥ 75,000/μL to begin Day 29 of DI. | |

Treatment details and criteria to start are in [Section 4.5.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--------------------------|--|---------------|--|
| Cyclophosphamide (CPM) | IV over 30-60 minutes | 1,000 mg/m ² /dose | 29 | See Section 4.5.3 for administration guidelines |
| Thioguanine (TG) | PO | 60 mg/m ² /dose daily | 29-42 | See Section 4.5.3 & Appendix IV for administration guidelines. See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/m ² /dose daily | 29-32 & 36-39 | See Section 4.5.3 for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 29 | See Section 4.5.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6h x2 | 30 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.5.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | CPM ____ mg | TG ____ mg | ARAC ____ mg | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | Studies |
|--|------------|-----|---|---------------|-----------------|-------------------|---|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 29 | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg ** ____ mg ** | a-e |
| | | 30 | | | | | | |
| | | 31 | | | | | | |
| | | 32 | | | | | | |
| | | 36 | | | | | | b |
| | | 37 | | | | | | |
| | | 38 | | | | | | |
| | | 39 | | | | | | |
| | | 40 | | | | | | |
| | | 41 | | | | | | |
| | | 42 | | | | | | |
| | | 43 | | | | | | |
| | | 50 | | | | | | |
| | | 56 | | | | | | |
| | | 57 | Begin Interim Maintenance II therapy (Section 4.6) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.5.2 Required Observations in Delayed Intensification – All SR-Fav B-ALL (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only
- f. ECHO prior to the first dose of DOXOrubicin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.5.3 Delayed Intensification Treatment Details – All SR-Fav B-ALL (including DS patients)

Delayed Intensification is given in 2 parts. For all SR-Fav B-ALL, Delayed Intensification Part 1 begins on Day 57 of Interim Maintenance I or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2 - 28 or Days 30 - 43, but Day 29 does not begin until ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Dexamethasone: PO (may give IV)

Days: 1 - 7 and 15 - 21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8 and 15

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: Intravenous (IV) push/infusion over 1 - 15 minutes

Days 1, 8 and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pegaspargase: Intravenous (IV) over 1 - 2 hours (may also be given IM.)

Day 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#).

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Cyclophosphamide: Intravenous (IV) over 30 - 60 minutes

Day 29

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: Oral (PO)

Days 29 - 42

Dose: 60 mg/m²/dose * once daily

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

Cytarabine: Intravenous (IV) over 1 - 30 minutes or subcutaneous

Days 29 - 32 and 36 - 39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)

Day 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 30

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Delayed Intensification, Interim Maintenance II therapy ([**Section 4.6**](#)) starts on Day 57 or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.6 All SR-Fav B-ALL (including DS patients) – Interim Maintenance II EscMTX

| | |
|---|---|
| 4.6.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE II (IM II) EscMTX</u> | Patient COG ID number _____ DOB _____ _____ |
|---|---|

Treatment details and criteria to start are in [Section 4.6.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|---|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Intravenous Methotrexate (IV MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | ___mg/m ² /dose* | 1, 11, 21, 31 & 41 | *Starting dose for IM II is two-thirds of the maximum tolerated dose attained in IM I. Thereafter, escalate by 50 mg/m²/dose . See Section 4.6.3 for details. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 31 | See Section 4.6.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 & 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.6.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ___mg | IV MTX ___mg (escalating dose) | IT MTX ___mg | LCV (DS pts only) ___mg ___mg | Studies |
|---|------------|-----|--|--------------------------------------|-----------------|-------------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ___mg | ___mg | ___mg | | a-c, e |
| | | 2 | | | | ___mg** ___mg** | |
| | | --- | | | | | |
| | | 11 | ___mg | ___mg | | | a-c |
| | | --- | | | | | |
| | | 21 | ___mg | ___mg | | | a-c |
| | | --- | | | | | |
| | | 31 | ___mg | ___mg | ___mg | | a-d |
| | | 32 | | | | ___mg** ___mg** | |
| | | --- | | | | | |
| | | 41 | ___mg | ___mg | | | a-c |
| | | --- | | | | | |
| | | 56 | | | | | |
| | | 57 | Begin Maintenance therapy (Section 4.7 for non-DS SR-Fav and Section 4.8 for DS SR-Fav) on Day 57 of IM II or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.6.2 Required Observations in Interim Maintenance II with EscMTX – All SR-Fav B-ALL (including DS patients)

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.6.3 Interim Maintenance II with EscMTX Treatment Details – All SR-Fav B-ALL (including DS patients)

For all SR-Fav B-ALL patients, Interim Maintenance II therapy starts on Day 57 of Delayed Intensification, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate MTX by 50 mg/m²/dose.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days 1, 11, 21, 31 and 41

Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two thirds of 200 mg/m² (or 130 mg/m²) IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (\pm 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: Intrathecal (IT)

Days 1 and 31

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2 & 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Interim Maintenance (IM) II, Maintenance therapy, [Section 4.7](#) for non-DS SR Fav B-ALL and [Section 4.8](#) for DS SR-Fav B-ALL, begins on Day 57 or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.7 Non-DS SR-Fav B-ALL – Maintenance

4.7.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for non-DS SR-Fav B-ALL patients. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance therapy on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all cycles of Maintenance therapy.

Patient COG ID number _____
DOB _____

Treatment details and criteria to start are in [Section 4.7.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|--|--|--|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.7.3 & Appendix III for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.7.3 for administration guidelines Note age-based dosing |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit Day 1 dose as it coincides with IT MTX |

Enter Cycle #:

Ht _____ cm

Wt _____

kg _____

BSA _____

m² _____

| Date Due | Date Given | Day | VCR mg | DEX mg | MP mg | IT MTX mg | PO MTX mg | Studies |
|---|------------|-----|--|----------|----------|-----------|-----------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-f |
| | | 2 | | | | | | |
| | | 3 | | | | | | |
| | | 4 | | | | | | |
| | | 5 | | | | | | |
| | | 8 | | | | | _____ mg | |
| | | 15 | | | | | _____ mg | |
| | | 22 | | | | | _____ mg | |
| | | 29 | | | | | _____ mg | a, b |
| | | 36 | | | | | _____ mg | |
| | | 43 | | | | | _____ mg | |
| | | 50 | | | | | _____ mg | |
| | | 57 | | | | | _____ mg | a, b |
| | | 64 | | | | | _____ mg | |
| | | 71 | | | | | _____ mg | |
| | | 78 | | | | | _____ mg | |
| | | 84 | | | | | | |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of IM I. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.7.2 Required Observations in Maintenance – Non-DS SR-Fav B-ALL

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship study anytime **between Day 1 of Cycle 1 and end of Cycle 2**, and at 1st off-therapy visit and 1 year off-therapy visit. Refer to [Section 17.1](#) for additional information.
- f. For non-DS patients who consent, send CSF for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.7.3 Maintenance – Non-DS SR-Fav B-ALL

For non-DS SR-Fav B-ALL patients, Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day: 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days: 1 - 5 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 - 84

Dose: $75 \text{ mg/m}^2/\text{dose}^*$ once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). The liquid or tablet formulation may be used. If using tablets, adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to $525 \text{ mg/m}^2/\text{week}$ as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: Intrathecal (IT)

Day: 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**

Dose: $20 \text{ mg/m}^2/\text{dose}$

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: $>40 \text{ mg/m}^2$; adult patients: $>80 \text{ mg/m}^2$) possibly due to saturation effect.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Interim Maintenance I is reached for both males and females.

4.8 DS SR-Fav B- ALL – Maintenance

4.8.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for DS SR-Fav B-ALL patients. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance therapy on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all cycles of Maintenance therapy.

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.8.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|--|--|--|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.8.3 & Appendix III for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.8.3 for administration guidelines Note age-based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.8.3 for administration guidelines. |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit Day 1 dose as it coincides with IT MTX |

Enter Cycle #: _____

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | VCR mg | DEX mg | MP mg | IT MTX mg | LCV mg | PO MTX mg | Studies |
|---|------------|-----|--|----------|----------|-----------|----------|-----------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-e, g |
| | | 2 | | | | | | | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 8 | | | | | _____ mg | | |
| | | 15 | | | | | _____ mg | | |
| - | | 22 | | | | | _____ mg | | |
| | | 29 | | | | | _____ mg | | a, b, f |
| | | 36 | | | | | _____ mg | | |
| | | 43 | | | | | _____ mg | | |
| | | 50 | | | | | _____ mg | | |
| | | 57 | | | | | _____ mg | | a, b |
| - | | 64 | | | | | _____ mg | | |
| | | 71 | | | | | _____ mg | | |
| | | 78 | | | | | _____ mg | | |
| | | 84 | | | | | | | |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of IM I. | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.8.2 Required Observations in Maintenance – DS SR-Fav B-ALL

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG
- f. For patients who consent, complete the assessment for the Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS B-ALL study on **Day 29 of Cycles 1 and 5, and 1 year after end of therapy**. Refer to [Section 17.2](#) for additional information. Note: flexible time point, must be obtained/administered within ±4 weeks of time point.
- g. For patients who consent, collect peripheral blood specimen for Immune Function in DS B-ALL patients on **Day 1 of Cycle 2**. Refer to [Section 14.6](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.8.3 Maintenance – DS SR-Fav B-ALL

For DS SR-Fav B-ALL patients, Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12-week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day: 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days 1 - 5 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 - 84

Dose: $75 \text{ mg/m}^2/\text{dose}^*$ once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). The liquid or tablet formulation may be used. If using tablets, adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to $525 \text{ mg/m}^2/\text{week}$ as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV)

Days: 2

Dose: $5 \text{ mg/m}^2/\text{dose} \times 2$ doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**

Dose: 20 mg/m²/dose

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Interim Maintenance I is reached for both males and females.

4.9 All SR-Avg B-ALL (including DS patients) – Consolidation

| | |
|---|--|
| 4.9.1 Therapy Delivery Map – CONSOLIDATION | Patient COG ID number _____ DOB _____ |
| Consolidation therapy in this TDM is for all SR-Avg B-ALL patients, with or without DS. Consolidation therapy is 4 weeks (28 days). Begin Consolidation on Day 36 or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.9.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|------------------------------------|--|-----------|---|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1 ONLY | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-28 | See Section 4.9.3 and Appendix III for administration guidelines. *See Section 5.8 for suggested dose based on TPMT and NUDT15 status. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1, 8 & 15 | See Section 4.9.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2, 9 & 16 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.9.3 for administration guidelines. |

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | VCR ____ mg | MP ____ mg | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | Studies |
|---|------------|-----|--|---------------|-------------------|--------------------------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | | a-e, g |
| | | 2 | | | | ____ mg** ____ mg** | |
| | | 8 | | | ____ mg | | d |
| | | 9 | | | | ____ mg** ____ mg** | |
| | | 15 | | | ____ mg | | d, f |
| | | 16 | | | | ____ mg** ____ mg** | |
| | | 22 | | | | | |
| | | 28 | | | | | b^ |
| | | 29 | After EOI HTS MRD results have been received, begin next course when blood count parameters are met and Callback #2 is completed. The next phase of therapy (Interim Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2. SR-Avg B-ALL EOI HTS MRD undetectable patients refer to IM I in Section 4.9 . SR-Avg B-ALL EOI HTS MRD detectable, indeterminate or unavailable and DT patients with EOI BM flow MRD ≥0.01 to <0.1% randomized to Arm A refer to Section 4.9 for IM I therapy. SR-Avg B-ALL EOI HTS MRD detectable, indeterminate or unavailable, and DT patients with EOI BM flow MRD ≥0.01 to <0.1% randomized to the Arm B refer to Section 4.17 for Blinatumomab Block 1 therapy. | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

Page 2 of 2

4.9.2 Required Observations in Consolidation – All SR-Avg B-ALL (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets ^Day 29 CBC is meant to determine count recovery criteria to continue on to the next phase of therapy.
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only
- f. For non-DS patients who consent, send CSF specimens to the ALL Molecular Reference Lab for cell banking **at the final LP**. Refer to [Section 14.7](#) for additional details.
- g. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed +14 days from Day 1.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.9.3 Consolidation Treatment Details – All SR-Avg B-ALL (including DS patients)

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For all SR-Avg B-ALL patients, Consolidation therapy begins on Day 36 of Induction (7 days following Day 29 LP) or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/dsc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day 1 ONLY

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Mercaptopurine: Oral (PO)

Days 1 – 28

Dose: 75 mg/m²/dose* once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate dose based on blood counts during this cycle (see [Section 5.8](#)).

Methotrexate: Intrathecal (IT)

Days: 1, 8 & 15

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2, 9 and 16

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of Consolidation therapy, the next course should begin when peripheral counts recover with an ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ and Callback#2 is completed. **The next phase of therapy (Interim Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2. Only complete Callback #2 if the treating physician is confident the patient will meet count recovery criteria prior to starting the next phase.**

END CONSOLIDATION CALLBACK #2 OCCURS PRIOR TO STARTING POST-CONSOLIDATION THERAPY FOR ALL SR-AVG B-ALL PATIENTS.

- SR-Avg B-ALL EOI HTS MRD undetectable patients assigned to Arm A refer to Interim Maintenance I in [Section 4.10](#).
- SR-Avg B-ALL EOI HTS MRD detectable, indeterminate or unavailable, and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the Control arm (Arm A) refer to [Section 4.10](#) for Interim Maintenance I therapy.
- SR-Avg B-ALL EOI HTS MRD detectable, indeterminate, or unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the Experimental arm (Arm B) refer to [Section 4.15](#) for Blinatumomab Block 1 therapy.

4.10 All SR-Avg B-ALL Arm A (including DS patients) – Interim Maintenance I EscMTX

4.10.1 Therapy Delivery Map – INTERIM MAINTENANCE (IM I EscMTX)

IM I therapy in this TDM is for all SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to Arm A, or EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A. IM I therapy is 8 weeks (56 days). Begin IM I when peripheral counts recover and no more than 7 days after Callback #2.

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.10.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|--|
| VinCRIStine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose 100 mg/m ² & escalate by 50 mg/m ² /dose | 1, 11, 21, 31 & 41 | See Section 4.10.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 31 ONLY | See Section 4.10.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 32 | **Down-syndrome patients only. Admin 24 & 30 hours after each IT MTX. See Section 4.10.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | IV MTX ____mg (escalating dose) | IT MTX ____mg | LCV (DS pts only) ____mg ____mg | Studies |
|---|------------|-----|--|---------------------------------------|------------------|---------------------------------------|----------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____mg | ____mg | | | a-c, e-g |
| | | 11 | ____mg | ____mg | | | a-c |
| | | 21 | ____mg | ____mg | | | a-c, h |
| | | 31 | ____mg | ____mg | ____mg | | a-d |
| | | 32 | | | | ____mg** ____mg** | |
| | | 41 | ____mg | ____mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Delayed Intensification (Section 4.11) on Day 57 or when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.10.2 Required Observations in Interim Maintenance I with EscMTX – All SR-Avg B-ALL Arm A (including DS patients)

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG and IgM
- f. Absolute CD19 count
- g. Absolute lymphocyte count
- h. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 21.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.10.3 Interim Maintenance I with EscMTX Treatment Details – SR-Avg B-ALL Arm A (including DS patients)

For all SR-Avg B-ALL EOI HTS MRD undetectable patients assigned to Arm A and all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on Control Arm A, IM I begins when peripheral counts recover with an ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ and **no more than 7 days after Callback #2 is completed.**

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$ resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, hold therapy until counts recover to ANC $> 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$. When ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC $\geq 500/\mu\text{L}$ but $< 750/\mu\text{L}$ and/or platelets $\geq 50,000/\mu\text{L}$ but $< 75,000/\mu\text{L}$, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ escalate MTX by $50 \text{ mg/m}^2/\text{dose}$.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days: 1, 11, 21, 31 and 41

Starting dose of 100 mg/m²/dose; **thereafter, escalate by 50 mg/m²/dose**

Methotrexate: Intrathecal (IT)

Day 31 ONLY

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days: 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of Interim Maintenance I, Delayed Intensification should begin on Day 57 ([Section 4.11](#)) or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.11 All SR-Avg B-ALL Arm A (including DS patients) – Delayed Intensification

| | |
|--|--|
| 4.11.1 <u>Therapy Delivery Map – Delayed Intensification (DI) Part 1</u> | Patient COG ID number _____ DOB _____ |
| Delayed Intensification Part 1 therapy in this TDM is for all SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to Arm A. This TDM is also for EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A. DI therapy is 8 weeks (56 days). Begin DI on Day 57 of IM I or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.11.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|---|-------------|--|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day See Section 4.11.3 for administration guidelines. |
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXORubicin (DOXO) | IV push/infusion over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.11.3 for administration guidelines. *Obtain ECHO (f) prior to the first dose of DOXO. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.11.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.11.3 for administration guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | DEX ____ mg ____ mg | VCR ____ mg | DOXO ____ mg | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | PEG-ASP IU | Studies |
|--|------------|-----|---------------------------|----------------|-----------------|-------------------|---|---------------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | ____ mg ____ mg | ____ mg | ____ mg | ____ mg | | | a-e, f* |
| | | 2 | | | | | ____ mg** ____ mg** | | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | ____ IU | |
| | | 5 | | | | | | | |
| | | 6 | | | | | | | |
| | | 7 | | | | | | | |
| | | 8 | | ____ mg | ____ mg | | | | b |
| | | 15 | ____ mg ____ mg | ____ mg | ____ mg | | | | b |
| | | 16 | | | | | | | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 19 | | | | | | | |
| | | 20 | | | | | | | |
| | | 21 | | | | | | | |
| | | 22 | | | | | | | |
| This Therapy Delivery Map continues on the next page. | | | | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

| | |
|--|--|
| 4.11.1 <u>Therapy Delivery Map – Delayed Intensification (DI) Part 2</u> | Patient COG ID number _____ DOB _____ |
| Delayed Intensification Part 2 therapy in this TDM is for all SR-Avg B-ALL who are EOI HTS MRD undetectable assigned to Arm A. This TDM is also for patients who are EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A. DI therapy is 8 weeks (56 days). Begin DI Part 2 on Day 29 of DI Part 1 or when criteria to start are met (whichever occurs later). Patients should have ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ to begin Day 29 of DI. | |

Treatment details and criteria to start are in [Section 4.11.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--------------------------|---|---------------|--|
| Cyclophosphamide (CPM) | IV over 30-60 minutes | 1,000 mg/m ² /dose | 29 | See Section 4.11.3 for administration guidelines |
| Thioguanine (TG) | PO | 60 mg/m ² /dose daily | 29-42 | See Section 4.11.3 & Appendix IV for administration guidelines See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/m ² /dose daily | 29-32 & 36-39 | See Section 4.11.3 for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 29 | See Section 4.11.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 30 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.11.3 for administration guidelines. |

Ht cm Wt kg BSA m²

| Date Due | Date Given | Day | CPM mg | TG mg | ARAC mg | IT MTX mg | LCV (DS pts only) mg | Studies |
|---|------------|-----|--|---------|---------|-----------|----------------------|-----------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 29 | _____mg | _____mg | _____mg | _____mg | _____mg | a-e, g |
| | | 30 | | | | | _____mg** | _____mg** |
| | | 31 | | | | | | |
| | | 32 | | | | | | |
| | | 36 | | | _____mg | | | b |
| | | 37 | | | | | | |
| | | 38 | | | | | | |
| | | 39 | | | | | | |
| | | 40 | | | | | | |
| | | 41 | | | | | | |
| | | 42 | | | | | | |
| | | 43 | | | | | | |
| | | 50 | | | | | | |
| | | 56 | | | | | | |
| | | 57 | Begin Interim Maintenance II therapy (Section 4.12) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.11.2 Required Observations in Delayed Intensification – All SR-Avg B-ALL Arm A (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only
- f. ECHO prior to the first dose of DOXOrubicin
- g. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 29.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.11.3 Delayed Intensification Treatment Details - All SR-Avg B-ALL Arm A (including DS patients)

Delayed Intensification is given in 2 parts.

For all SR-Avg B-ALL EOI HTS MRD undetectable patients assigned to Arm A and SR-Avg B-All EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to receive therapy on Control Arm A, begin Delayed Intensification Part 1 on Day 57 of IM I or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2-28 or Days 30-43, but Day 29 does not begin until ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Delayed Intensification Part 1

Dexamethasone: Oral (PO; may give intravenous (IV))

Days 1-7 and 15-21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8 and 15

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal

formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: Intravenous (IV) push/infusion over 1 - 15 minutes

Days: 1, 8, and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pegaspargase: Intravenous (IV) over 1 - 2 hours (may also be given IM.)

Day: 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modification in [Section 5.2](#).

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

Cyclophosphamide: Intravenous (IV) over 30 - 60 minutes

Day: 29

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: Oral (PO)

Days 29-42

Dose: 60 mg/m²/dose* once daily

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

Cytarabine: Intravenous (IV) over 1 - 30 minutes or subcutaneous

Days: 29 - 32 and 36 - 39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)

Day: 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days: 30

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities](#).

Following completion of Delayed Intensification, Interim Maintenance II therapy starts on Day 57 ([Section 4.12](#)) or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.12 All SR-Avg B-ALL Arm A (including DS patients) – Interim Maintenance II EscMTX

| | |
|--|--|
| 4.12.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE II (EscMTX)</u> | Patient COG ID number _____ DOB _____ |
| IM II therapy in this TDM is for all SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to Arm A, or EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ patients randomized to receive therapy on the control Arm A. IM II therapy is 8 weeks (56 days). Begin IM II on Day 57 of DI or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.12.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|---|--------------------|--|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | ____ mg/m ² /dose* | 1, 11, 21, 31 & 41 | *Starting dose for IM II is two-thirds of the maximum tolerated dose attained in IM I. Thereafter, escalate by 50 mg/m²/dose . See Section 4.12.3 for details. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 31 | See Section 4.12.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 & 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.12.3 for administration guidelines. |

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | VCR ____ mg | IV MTX ____ mg (escalating dose) | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | Studies |
|---|------------|-----|--|--|-------------------|--------------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | | a-e |
| | | 2 | | | | ____ mg** ____ mg** | |
| | | 11 | ____ mg | ____ mg | | | a-c |
| | | 21 | ____ mg | ____ mg | | | a-c |
| | | 31 | ____ mg | ____ mg | ____ mg | | a-d |
| | | 32 | | | | ____ mg** ____ mg** | |
| | | 41 | ____ mg | ____ mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Maintenance therapy (Section 4.13 for non-DS SR-Avg and Section 4.14 for DS SR-Avg) on Day 57 of IM II or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.12.2 Required Observations in Interim Maintenance II with EscMTX– All SR-Avg B-ALL (including DS patients) Arm A

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.12.3 Interim Maintenance II with EscMTX Treatment Details – All SR-Avg B-ALL (including DS patients) Arm A

For all SR-Avg B-ALL EOI HTS MRD undetectable patients assigned to Arm A or SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A, IM II therapy starts on Day 57 of DI, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$ resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, hold therapy until counts recover to ANC $> 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$. When ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC $\geq 500/\mu\text{L}$ but $< 750/\mu\text{L}$ and/or platelets $\geq 50,000/\mu\text{L}$ but $< 75,000/\mu\text{L}$, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ escalate MTX by $50 \text{ mg/m}^2/\text{dose}$.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days: 1, 11, 21, 31 and 41

Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two thirds of 200 mg/m² (or 130 mg/m²) IV over 2 - 5 minutes (undiluted) or over 10 – 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (\pm 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: Intrathecal (IT)

Days 1 and 31

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2 & 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of Interim Maintenance II, Maintenance therapy ([Section 4.13](#) for non-DS SR Avg B-ALL and [Section 4.14](#) for DS SR-Avg B-ALL) begins on Day 57 or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.13 Non-DS SR-Avg B-ALL Arm A – Maintenance

4.13.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for non-DS SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to Arm A, or EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A. Begin Maintenance on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all cycles of Maintenance therapy.

Patient COG ID number

DOB

Treatment details and criteria to start are in [Section 4.13.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|--|--|---|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.13.3 for administration guidelines Note age-based dosing |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | *See Section 5.8 for suggested starting dose based on <i>TPMT</i> and <i>NUDT15</i> status See Section 4.13.3 & Appendix III for administration guidelines |
| Oral Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit Day 1 dose as it coincides with IT MTX |

| Enter Cycle #: | | | Ht cm | Wt kg | BSA m ² | | | |
|---|------------|-----|--|--------|--------------------|-------|-----------|----------|
| Date Due | Date Given | Day | VCR mg | DEX mg | IT MTX mg | MP mg | PO MTX mg | Studies |
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 1 | mg | mg | mg | mg | | a-e, g-j |
| | | 2 | | | | | | |
| | | 3 | | | | | | |
| | | 4 | | | | | | |
| | | 5 | | | | | | |
| | | 8 | | | | | mg | |
| | | 15 | | | | | mg | |
| - | | 22 | | | | | mg | |
| | | 29 | | | | | mg | a, b, f |
| | | 36 | | | | | mg | |
| | | 43 | | | | | mg | |
| | | 50 | | | | | mg | |
| | | 57 | | | | | mg | a, b |
| - | | 64 | | | | | mg | |
| | | 71 | | | | | mg | |
| | | 78 | | | | | mg | |
| | | 84 | | | | | | e |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of IM I. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.13.2 Required Observations in Maintenance – Non-DS SR-Avg B-ALL Arm A

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship study anytime **between Day 1 of Cycle 1 and end of Cycle 2**, and at 1st off-therapy visit and 1 year off-therapy visit. Refer to [Section 17.1](#) for additional information.
- f. For patients who consent, complete assessments for the Caregiver Burden study on **Day 29 of Cycle 1**. Refer to [Section 17.1](#) for additional information. May be completed +28 days from Day 29 of Cycle 1.
- g. For patients who consent, send CSF specimens to the ALL Molecular Reference Lab for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.
- h. IgG and IgM **Day 1 of Cycle 1 ONLY**
- i. Absolute CD19 count **Day 1 of Cycle 1 ONLY**
- j. Absolute lymphocyte count **Day 1 of Cycle 1 ONLY**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.13.3 Maintenance – Non-DS SR-Avg B-ALL Arm A

For non-DS SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to- or EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to receive therapy on the control Arm A, Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later. This count recovery applies to the start of Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I with Esc MTX is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day: 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days: 1 - 5 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Mercaptopurine: PO

Days 1 – 84

Dose: 75 mg/m²/dose* once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**

Dose: 20 mg/m²/dose once weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of IM with Esc MTX is reached for both males and females.

4.14 DS SR-Avg B-ALL Arm A – Maintenance

4.14.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for DS SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to Arm A, or EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to receive therapy on the control Arm A. Begin Maintenance on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all cycles of Maintenance therapy.

| |
|-----------------------|
| Patient COG ID number |
| DOB |

Treatment details and criteria to start are in [Section 4.14.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|---|--|---|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.14.3 for administration guidelines Note age-based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.14.3 for administration guidelines. |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | *See Section 5.8 for suggested starting dose based on <i>TPMT</i> and <i>NUDT15</i> status See Section 4.14.3 & Appendix III for administration guidelines |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit Day 1 dose as it coincides with IT MTX |

Enter Cycle #: _____ Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR mg | DEX mg | MP mg | IT MTX mg | LCV mg | PO MTX mg | Studies |
|---|------------|-----|---|----------|----------|-----------|----------|-----------|----------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-e, g-j |
| | | 2 | | | | | _____ mg | _____ mg | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 8 | | | | | _____ mg | | |
| | | 15 | | | | | _____ mg | | |
| | | 22 | | | | | _____ mg | | |
| | | 29 | | | | | _____ mg | | a, b, f |
| | | 36 | | | | | _____ mg | | |
| | | 43 | | | | | _____ mg | | |
| | | 50 | | | | | _____ mg | | |
| | | 57 | | | | | _____ mg | | a, b |
| | | 64 | | | | | _____ mg | | |
| | | 71 | | | | | _____ mg | | |
| | | 78 | | | | | _____ mg | | |
| | | 84 | | | | | | | |
| | | 85 | Regardless of sex, continue Maintenance therapy until 2 years from the start of Interim Maintenance I. | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.14.2 Required Observations in Maintenance – DS SR-Avg B-ALL Arm A

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT,
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG
- f. For patients who consent, complete the assessment for the Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL study on **Day 29 of Cycles 1 and 5, and 1 year after end of therapy**. Refer to [Section 17.2](#) for additional information. Note: flexible time point, must be obtained/administered within ±4 weeks of time point.
- g. For DS patients who consent, collect peripheral blood specimen for Immune Function in DS B-ALL patients on **Day 1 of Cycle 2 ONLY**. Refer to [Section 14.6](#) for additional details.
- h. IgM **Day 1 of Cycle 1 ONLY**
- i. Absolute CD19 count **Day 1 of Cycle 1 ONLY**
- j. Absolute lymphocyte count **Day 1 of Cycle 1 ONLY**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.14.3 Maintenance – DS SR-Avg B-ALL Arm A

For DS SR-Avg B-ALL who are EOI HTS MRD undetectable patients assigned to- or EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to receive therapy on the control Arm A, Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later. This count recovery applies to the start of Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I with Esc MTX is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day; 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days: 1 - 5 (do not taper).

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 – 84

Dose: 75 mg/m²/dose once daily

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV)

Days: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing

schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Methotrexate: PO

Days: 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**

Dose: 20 mg/m²/dose once weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of IM I with Esc MTX is reached for both males and females.

4.15 All SR-Avg B-ALL Arm B (including DS patients) – Blinatumomab Block 1**4.15.1 Therapy Delivery Map – Blinatumomab Block 1**

This TDM is for the first cycle of Blinatumomab therapy for all B-ALL patients who are EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the experimental Arm B. Blinatumomab Block 1 lasts 5 weeks (35 Days). Begin therapy when peripheral counts recover and no more than 7 days after Callback #2.

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.15.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|-------------------------|---|--------------|--|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² (max 20 mg) 30-60 mins prior to the start of BLIN infusion | 1 | Start prior to blinatumomab therapy. |
| Blinatumomab (BLIN) IND# 117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose: 28 micrograms/day Section 4.15.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs) Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | Note age based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.15.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | DEX mg | BLIN mcg | IT MTX mg | LCV (DS pts only) mg mg | Studies |
|---|------------|-------|--|-----------|-----------|-------------------------|--------------|
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | _____ mg | _____ mcg | _____ mg | _____ mg** _____ mg** | a-d, e*, f-h |
| | | 2 | | | | | |
| | | 3 | | | | | |
| | | 4 | | | | | |
| | | 5 | | | | | |
| | | 6 | | | | | |
| | | 7 | | | | | |
| | | 8 | | | | | (b, c)^ |
| | | 9 | | | | | |
| | | 10 | | | | | |
| | | 11 | | | | | |
| | | 12 | | | | | |
| | | 13 | | | | | |
| | | 14 | | | | | |
| | | 15 | | | | | (b, c)^, i |
| | | 16 | | | | | |
| | | 18 | | | | | |
| | | 19 | | | | | |
| | | 20 | | | | | |
| | | 21 | | | | | |
| | | 22 | | | | | (b, c)^ |
| | | 23 | | | | | |
| | | 24 | | | | | |
| | | 25 | | | | | |
| | | 26 | | | | | |
| | | 27 | | | | | |
| | | 28 | | | | | |
| | | 29 | | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | | |
| | | 36 | Begin IM I therapy (Section 4.16) on Day 36 or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

Version Date 11/22/2019

Page 127

4.15.2 Required Observations in Blinatumomab Block 1 – All SR-Avg B-ALL Arm B (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. **^May be completed ±2 days from scheduled assessment days.**
- c. Creatinine, total bilirubin, ALT. **^May be completed ±2 days from scheduled assessment days.**
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG ***Obtain before blinatumomab infusion**
- f. IgM ***Obtain before blinatumomab infusion**
- g. Absolute CD19 count ***Obtain before blinatumomab infusion**
- h. Absolute lymphocyte count ***Obtain before blinatumomab infusion**
- i. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 15.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.15.3 Blinatumomab Block 1 Treatment Details – All SR-Avg B-ALL Arm B (including DS patients)

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED.

FOR PATIENTS RISK ASSIGNED TO ARM B, COMPLETE CALLBACK #2 PRIOR TO BEGINNING BLINATUMOMAB BLOCK 1 THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ on Arm B, Blinatumomab Block 1 therapy starts when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ and **no more than 7 days after Callback #2 is completed**.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 48 hours of Block 1 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 72 hours of Block 1 blinatumomab therapy in patients with flow MRD $\geq 0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle,

which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Dexamethasone: Oral (PO) or Intravenous (IV)

Day 1

Dose Prior to Day 1 therapy

- A single dose of 5 mg/m²/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of blinatumomab infusion in block 1.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Blinatumomab: Intravenous (IV) continuous infusion over 28 days*

Days 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Day: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of the Blinatumomab therapy, Interim Maintenance (IM) I ([Section 4.16](#)) should begin on either Day 36 of Blinatumomab Block 1, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.16 All SR-Avg B-ALL Arm B (including DS patients) – Interim Maintenance I EscMTX

| | |
|--|--|
| 4.16.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE I (IM I EscMTX)</u> | Patient COG ID number _____ DOB _____ |
| IM I therapy in this TDM is for all All SR-Avg B-ALL patients who are EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the experimental Arm B. IM I therapy is 8 weeks (56 days). Begin IM I on Day 35 of Blinatumomab Block 1 or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.16.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|-----------------------|--|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | +Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose 100 mg/m ² & escalate by 50 mg/m ² /dose | 1, 11, 21, 31 & 41 | See Section 4.16.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 31 ONLY | See Section 4.16.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.16.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | IV MTX ____mg (escalating dose) | IT MTX ____mg | LCV (DS pts only) ____mg ____mg | Studies |
|---|------------|-----|---|---------------------------------------|------------------|------------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____mg | ____mg | | | a-c, e |
| | | 11 | ____mg | ____mg | | | a-c |
| | | 21 | ____mg | ____mg | | | a-c |
| | | 31 | ____mg | ____mg | ____mg | | a-d |
| | | 32 | | | | ____mg** ____mg** | |
| | | 41 | ____mg | ____mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Blinatumomab Block 2 on Day 57 (Section 4.17) or when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.16.2 Required Observations in Interim Maintenance I with EscMTX – All SR-Avg B-ALL Arm B (including DS patients)

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.16.3 Interim Maintenance I with EscMTX Treatment Details – All SR-Avg B-ALL Arm B (including DS patients)

For all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ on Arm B, IM I begins on Day 35 of Blinatumomab Block 1 or when peripheral counts recover with an ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$ resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, hold therapy until counts recover to ANC $> 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$. When ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC $\geq 500/\mu\text{L}$ but $< 750/\mu\text{L}$ and/or platelets $\geq 50,000/\mu\text{L}$ but $< 75,000/\mu\text{L}$, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ escalate MTX by $50 \text{ mg/m}^2/\text{dose}$.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41
Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days: 1, 11, 21, 31 and 41
Starting dose of 100 mg/m²/dose; thereafter, escalate by 50 mg/m²/dose

Methotrexate: Intrathecal (IT)

Day: 31 ONLY

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days: 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing

schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Interim Maintenance I, Blinatumomab Block 2 ([Section 4.17](#)) should begin on Day 57 or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.17 All SR-Avg B-ALL Arm B (including DS patients) – Blinatumomab Block 2**4.17.1 Therapy Delivery Map – Blinatumomab Block 2**

This TDM is for the second cycle of Blinatumomab therapy for all SR-Avg B-ALL patients who are EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to the experimental Arm B. Blinatumomab Block 2 lasts 5 weeks (35 Days). Begin Blinatumomab Block 2 therapy on Day 57 of IM I or when criteria to start are met, whichever occurs later.

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.17.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|------------------------|---|--------------|--|
| Blinatumomab (BLIN) IND# 117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day See Section 4.17.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | Note age based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.17.3 for administration guidelines. |

| | | Ht _____ cm | Wt _____ kg | BSA _____ m ² | | |
|---|------------|-------------|---|--------------------------|---------------------------------------|------------|
| Date Due | Date Given | Day | BLIN ____mcg | IT MTX ____mg | LCV (DS pts only) ____mg ____mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | ____mcg | ____mg | | a-e |
| | | 2 | | | ____mg** ____mg** | |
| | | 3 | | | | |
| | | 4 | | | | |
| | | 5 | | | | |
| | | 6 | | | | |
| | | 7 | | | | |
| | | 8 | | | | (b, c)^ |
| | | 9 | | | | |
| | | 10 | | | | |
| | | 11 | | | | |
| | | 12 | | | | |
| | | 13 | | | | |
| | | 14 | | | | |
| | | 15 | | | | (b, c)^, f |
| | | 16 | | | | |
| | | 18 | | | | |
| | | 19 | | | | |
| | | 20 | | | | |
| | | 21 | | | | |
| | | 22 | | | | (b, c)^ |
| | | 23 | | | | |
| | | 24 | | | | |
| | | 25 | | | | |
| | | 26 | | | | |
| | | 27 | | | | |
| | | 28 | | | | |
| | | 29 | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | |
| | | 36 | Begin Delayed Intensification therapy (Section 4.18) on Day 36 of Blinatumomab Block 2 or when blood count parameters are met (whichever occurs later). | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.17.2 Required Observations in Blinatumomab Block 2 – SR-Avg B-ALL Arm B
(including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. [^]May be completed ±2 days from scheduled assessment days.
- c. Creatinine, total bilirubin, ALT. [^]May be completed ±2 days from scheduled assessment days.
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG
- f. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 15.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.17.3 Blinatumomab Block 2 Treatment Details – All SR-Avg B-ALL Arm B (including DS patients)

For all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ patients on Arm B, Blinatumomab Block 2 therapy starts on Day 57 of Interim Maintenance I or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 24 hours of Block 2 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 48 hours of Block 2 blinatumomab therapy in patients with flow MRD $\geq 0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Blinatumomab: Intravenous (IV) continuous infusion over 28 days*

Days: 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: Intrathecal (IT)

Day: 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Day: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose

immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Following completion of the Blinatumomab Block 2, Delayed Intensification ([Section 4.18](#)) should begin on either Day 36 of the Blinatumomab Block 2, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.18 All SR-Avg B-ALL Arm B (including DS patients) – Delayed Intensification

| | |
|--|--|
| 4.18.1 <u>Therapy Delivery Map – Delayed Intensification (DI) Part 1</u> | Patient COG ID number _____ DOB _____ |
| DI therapy in this TDM is for all SR-Avg B-ALL patients who are EOI MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to the experimental Arm B. DI therapy is 8 weeks (56 days). Begin DI Part 1 on Day 36 of Blinatumomab Block 2 or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.18.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|--|---|--|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day. See Section 4.18.3 for administration guidelines. |
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXOrubicin (DOXO) | IV push/infusion over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.18.3 for administration guidelines. *Obtain ECHO (f) prior to the first dose of DOXO. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) 1-1.99 2-2.99 3-8.99 ≥ 9 | Dose 8 mg 10 mg 12 mg 15 mg | 1 See Section 4.18.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.18.3 for administration guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | DEX mg | VCR mg | DOXO mg | IT MTX mg | LCV (DS pts only) mg | PEG-ASP IU | Studies |
|--|------------|-----|-----------|-----------|------------|--------------|-------------------------|---------------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-e, f* |
| | | 2 | | | | | _____ mg** | _____ mg** | |
| | | 4 | | | | | | | IU |
| | | 5 | | | | | | | |
| | | 6 | | | | | | | |
| | | 7 | | | | | | | |
| | | 8 | | _____ mg | _____ mg | | | | b |
| | | 15 | _____ mg | _____ mg | _____ mg | _____ mg | | | b |
| | | 16 | | | | | | | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 19 | | | | | | | |
| | | 20 | | | | | | | |
| | | 21 | | | | | | | |
| | | 22 | | | | | | | |

This Therapy Delivery Map continues on the next page.

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.18.1 Therapy Delivery Map – Delayed Intensification (DI) Part 2

DI therapy in this TDM is for all SR-Avg B-ALL patients who are EOI MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the experimental Arm B. DI therapy is 8 weeks (56 days). Begin DI Part 2 on Day 29 of DI Part 1 or when criteria to start are met (whichever occurs later). **Patients should have ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ to begin Day 29 of DI Part 2.**

Treatment details and criteria to start are in [Section 4.18.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--------------------------|---|---------------|--|
| Cyclophosphamide (CPM) | IV over 30-60 minutes | 1,000 mg/m ² /dose | 29 | See Section 4.18.3 for administration guidelines |
| Thioguanine (TG) | PO | 60 mg/m ² /dose daily | 29-42 | See Section 4.18.3 & Appendix IV for administration guidelines See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/m ² /dose daily | 29-32 & 36-39 | See Section 4.18.3 for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 29 | See Section 4.18.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 30 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.18.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | CPM mg | TG mg | ARAC mg | IT MTX mg | LCV (DS pts only) mg mg | Studies |
|---|------------|-----|---|----------|------------|--------------|----------------------------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 29 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg ** _____ mg ** | a-e |
| | | 30 | | | | | | |
| | | 31 | | | | | | |
| | | 32 | | | | | | |
| | | 36 | | | _____ mg | | | b |
| | | 37 | | | | | | |
| | | 38 | | | | | | |
| | | 39 | | | | | | |
| | | 40 | | | | | | |
| | | 41 | | | | | | |
| | | 42 | | | | | | |
| | | 43 | | | | | | |
| | | 50 | | | | | | |
| | | 56 | | | | | | |
| | | 57 | Begin IM II therapy (Section 4.19) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.18.2 Required Observations in Delayed Intensification – All SR-Avg B-ALL Arm B
(including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG
- f. ECHO **prior to the first dose of DOXOrubicin**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.18.3 Delayed Intensification Treatment Details All SR-Avg B-ALL Arm B (including DS patients)

Delayed Intensification is given in 2 parts.

For all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ on Arm B, Delayed Intensification Part 1 begins on Day 36 of Blinatumomab Block 2 or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2-28 or Days 30-43, but Day 29 does not begin until ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Delayed Intensification Part 1

Dexamethasone: Oral (PO; may give intravenous (IV))

Days: 1-7 and 15-21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8, and 15

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: Intravenous (IV) push/infusion over 1 - 15 minutes

Days: 1, 8, and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Methotrexate: Intrathecal (IT)

Day: 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Day: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pegaspargase: Intravenous (IV) over 1 - 2 hours (may also be given IM)

Day: 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modification in [Section 5.2](#).

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Cyclophosphamide: Intravenous (IV) over 30 - 60 minutes

Day: 29

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: Oral (PO)

Days 29-42

Dose: 60 mg/m²/dose once daily*

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

Cytarabine: Intravenous (IV) over 1 - 30 minutes or subcutaneous

Days: 29-32 and 36-39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)

Day 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Day: 30

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion Delayed Intensification, IM II ([Section 4.19](#)) starts on Day 57 or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.19 All SR-Avg B-ALL Arm B (including DS patients) – Interim Maintenance II EscMTX

| | |
|--|--|
| 4.19.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE II (EscMTX)</u> IM II therapy in this TDM is for all SR-Avg B-ALL patients who are HTS EOI MRD detectable/ineterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to the experimental arm (Arm B). IM II therapy is 8 weeks (56 days). Begin IM II on Day 57 of DI or when criteria to start are met (whichever occurs later). | Patient COG ID number _____ DOB _____ |
|--|--|

Treatment details and criteria to start are in [Section 4.19.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|--|
| VinCRIStine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | ___mg/m ² /dose* | 1, 11, 21, 31 & 41 | *Starting dose for IM II is two-thirds of the maximum tolerated dose attained in IMI. Thereafter, escalate by 50 mg/m²/dose . See Section 4.19.3 for details. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 31 | See Section 4.19.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 and 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.19.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ___mg | IV MTX ___mg (escalating dose) | IT MTX ___mg | LCV (DS pts only) ___mg ___mg | Studies |
|---|------------|-----|---|--------------------------------------|-----------------|----------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ___mg | ___mg | ___mg | | a-e |
| | | 2 | | | | ___mg** ___mg** | |
| | | 11 | ___mg | ___mg | | | a-c |
| | | 21 | ___mg | ___mg | | | a-c |
| | | 31 | ___mg | ___mg | ___mg | | a-e |
| | | 32 | | | | ___mg** ___mg** | |
| | | 41 | ___mg | ___mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Maintenance on Day 57 (Section 4.20 for non-DS SR Avg B-ALL and Section 4.21 for DS SR-Avg B-ALL) when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.19.2 Required Observations in Interim Maintenance II with EscMTX – All SR-Avg B-ALL Arm B (including DS patients)

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.19.3 Interim Maintenance II with EscMTX Treatment Details – All SR-Avg B-ALL Arm B (including DS patients)

For all SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to Arm B, Interim Maintenance II therapy starts on Day 57 of DI, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31). Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$ resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, hold therapy until counts recover to ANC $> 500/\mu\text{L}$ and platelets $> 50,000/\mu\text{L}$. When ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC $\geq 500/\mu\text{L}$ but $< 750/\mu\text{L}$ and/or platelets $\geq 50,000/\mu\text{L}$ but $< 75,000/\mu\text{L}$, give same dose of MTX as previously (i.e., no escalation).
- C) If ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ escalate MTX by $50 \text{ mg/m}^2/\text{dose}$.
- D) Do not escalate MTX dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days: 1, 11, 21, 31 and 41

Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two thirds of 200 mg/m² (or 130 mg/m²) IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (\pm 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: Intrathecal (IT)

Days: 1 & 31

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2 and 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Interim Maintenance II, Maintenance therapy (for non-DS SR-Avg B-ALL and [Section 4.21](#) for DS SR-Avg B-ALL) begins on Day 57, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.20 Non-DS SR-Avg B-ALL Arm B – Maintenance

4.20.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for non-DS SR-Avg B-ALL patients who are EOI HTS MRD detectable/indeterminate/unavailable and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ and randomized to the experimental Arm B. Maintenance therapy is 12 weeks (84 days). Begin Maintenance on Day 57 of IM II or when criteria to start are met. Use a copy of this TDM for all cycles of Maintenance therapy (whichever occurs later).

Patient COG ID number

DOB

Treatment details and criteria to start are in [Section 4.20.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|--|---|---|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily* | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.20.3 & Appendix III for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1^ | See Section 4.20.3 for administration guidelines Note age-based dosing ^ OMIT FINAL 2 CYCLES |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 1 [#] , 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | #Omit Day 1 dose as it coincides with IT MTX, except for final 2 cycles |

Enter Cycle #: _____ Ht _____ cm _____ Wt _____ kg _____ BSA _____ m²

| Date Due | Date Given | Day | VCR mg | DEX mg | MP mg | IT MTX mg | PO MTX mg | Studies |
|---|------------|-----|---|----------|----------|-----------|-----------------------|----------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg^ | _____ mg [#] | a-e, g-k |
| | | 2 | | | | | | |
| | | 3 | | | | | | |
| | | 4 | | | | | | |
| | | 5 | | | | | | |
| | | 8 | | | | _____ mg | | |
| | | 15 | | | | _____ mg | | |
| - | | 22 | | | | _____ mg | | |
| | | 29 | | | | _____ mg | a, b, f, h | |
| | | 36 | | | | _____ mg | | |
| | | 43 | | | | _____ mg | | |
| | | 50 | | | | _____ mg | | |
| | | 57 | | | | _____ mg | a, b, h | |
| | | 64 | | | | _____ mg | | |
| | | 71 | | | | _____ mg | | |
| | | 78 | | | | _____ mg | | |
| | | 84 | | | | | | h |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of Blintumomab Block 1. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.20.2 Required Observations in Maintenance – Non-DS SR-Avg B-ALL Arm B

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship study anytime **between Day 1 of Cycle 1 and end of Cycle 2**, and at 1st off-therapy visit and 1 year off-therapy visit. Refer to [Section 17.1](#) for additional information.
- f. For patients who consent, complete the assessment for the Caregiver Burden study on **Day 29 of Cycle 1**. Refer to [Section 17.1](#) for additional information. May be completed ±28 days from Day 29 of Cycle 1.
- g. For patients who consent, send CSF specimens to the ALL Molecular Reference Lab for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.
- h. IgG Cycle 1 ONLY
- i. IgM Day 1 of Cycle 1 ONLY
- j. Absolute CD19 count Day 1 of Cycle 1 ONLY
- k. Absolute lymphocyte count Day 1 of Cycle 1 ONLY

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.20.3 Maintenance – Non-DS SR-Avg B-ALL Arm B

For non-DS SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $< 0.1\%$ randomized to Arm B, Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/dsc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Day: 1

Dose: $1.5 \text{ mg/m}^2/\text{dose}$ (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days: 1 - 5 (do not taper).

Dose: $3 \text{ mg/m}^2/\text{dose BID}$ (i.e., total daily dose: $6 \text{ mg/m}^2/\text{day}$)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation ($6 \text{ mg/m}^2/\text{day}$, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 - 84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). The liquid or tablet formulation may be used. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details.

Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

Methotrexate: Intrathecal (IT)

Day 1*

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

***OMIT DURING THE FINAL TWO CYCLES**

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PO

Days 1*, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78.

***Omit Day 1 dose as it coincides with IT MTX, except final two cycles.**Dose: 20 mg/m²/dose once weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Blintumomab Block 1 is reached for both males and females.

4.21 DS SR-Avg B-ALL Arm B – Maintenance

| | |
|--|----------------------------------|
| 4.21.1 Therapy Delivery Map – MAINTENANCE | Patient COG ID number DOB |
|--|----------------------------------|

Treatment details and criteria to start are in [Section 4.21.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---------------------------------|--|--|---|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.21.3 & Appendix III for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1^ | See Section 4.21.3 for administration guidelines Note age-based dosing ^ OMIT FINAL 2 CYCLES |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 1#, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | #Omit Day 1 dose as it coincides with IT MTX, except for final 2 cycles |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2^ | 24 & 30 hours after each IT MTX. See Section 4.21.3 for administration guidelines. ^ OMIT FINAL 2 CYCLES |

| Enter Cycle #: | | | Ht | cm | Wt | kg | BSA | m ² | |
|---|------------|-----|--|----------|----------|-----------|------------|----------------|-------------|
| Date Due | Date Given | Day | VCR mg | DEX mg | MP mg | IT MTX mg | PO MTX mg | LCV mg | Studies |
| | | | | | | | | | |
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg^ | _____ mg # | | a-e, g-j |
| | | 2 | | | | | | _____ mg^ | _____ mg^ |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 8 | | | | | _____ mg | | |
| | | 15 | | | | | _____ mg | | |
| - | | 22 | | | | | _____ mg | | |
| | | 29 | | | | | _____ mg | | a, b, f, e* |
| | | 36 | | | | | _____ mg | | |
| | | 43 | | | | | _____ mg | | |
| | | 50 | | | | | _____ mg | | |
| | | 57 | | | | | _____ mg | | a, b, e* |
| - | | 64 | | | | | _____ mg | | |
| | | 71 | | | | | _____ mg | | |
| | | 78 | | | | | _____ mg | | |
| | | 84 | | | | | | | e* |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of Blinatumomab Block 1. | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.21.2 Required Observations in Maintenance – DS SR-Avg B-ALL Arm B

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG ***Day 29, 57, and 84 are done in Cycle 1 only**
- f. For patients who consent, complete the assessment for the Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL study on **Day 29 of Cycles 1 and 5, and 1 year after end of therapy**. Refer to [Section 17.2](#) for additional information. Note: flexible time point, must be obtained/administered within ±4 weeks of time point.
- g. For patients who consent, collect peripheral blood specimen for Immune Function in DS B-ALL patients on **Day 1 of Cycle 2**. Refer to [Section 14.6](#) for additional details.
- h. Absolute CD19 count **Day 1 of Cycle 1 only**
- i. Absolute lymphocyte count **Day 1 of Cycle 1 only**
- j. IgM **Day 1 of Cycle 1 only**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.21.3 Maintenance – DS SR-Avg B-ALL Arm B

For DS SR-Avg B-ALL EOI HTS MRD detectable/indeterminate/unavailable patients and DT patients with EOI BM flow MRD ≥ 0.01 to $<0.1\%$ randomized to Arm B Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRIStine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: $1.5 \text{ mg/m}^2/\text{dose}$ (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days: 1 - 5 (do not taper).

Dose: $3 \text{ mg/m}^2/\text{dose}$ BID (i.e., total daily dose: $6 \text{ mg/m}^2/\text{day}$)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 - 84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: Intrathecal (IT)

Day: 1*

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

***OMIT DURING THE FINAL TWO CYCLES**

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PO

Days 1**, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX, except final two cycles.

Dose: 20 mg/m²/dose once weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

Leucovorin: Oral (PO) or Intravenous (IV)

Days: 2[^]

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

^OMIT DURING THE FINAL TWO CYCLES

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females.

4.22 SR-High B-ALL – Consolidation

4.22.1 Therapy Delivery Map – CONSOLIDATION

Consolidation therapy in this TDM is for SR-High B-ALL patients. Consolidation therapy is 8 weeks (56 days). Begin Consolidation on Day 36 of Induction therapy or when criteria to start are met (whichever occurs later).

Patient COG ID number

DOB

Treatment details and criteria to start are in [Section 4.22.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|--|--------------------------|---|
| Cyclophosphamide (CPM) | IV over 30-60 min | 1,000 mg/m ² /dose | 1 & 29 | See Section 4.22.3 for administration guidelines. Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy. |
| Cytarabine (ARAC) | IV over 1-30 mins or SubQ | 75 mg/m ² /dose daily | 1-4, 8-11, 29-32 & 36-39 | See Section 4.22.3 for administration guidelines. Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy. |
| Mercaptopurine (MP) | PO | 60 mg/m ² /dose* daily | 1-14 & 29-42 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status. See Appendix III for administration guidelines. Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1, 8, 15 & 22 | Note age-based dosing |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 15, 22, 43 & 50 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Pegasparagase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 15 & 43 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

| Date Due | Date Given | Day | Ht cm | Wt kg | BSA m ² | Studies |
|--|------------|-----|---|-------|--------------------|----------------------|
| Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | mg | mg | mg | a- e |
| | | 2 | | | | |
| | | 3 | | | | |
| | | 4 | | | | |
| | | 8 | | mg | | b, d |
| | | 9 | | | | |
| | | 10 | | | | |
| | | 11 | | | | |
| | | ... | | | | |
| | | 14 | | | | |
| | | 15 | | mg | mg | IU b, d |
| | | 22 | | mg | mg | b, d, f |
| | | 29 | mg | mg | | a-c |
| | | 30 | | | | |
| | | 31 | | | | |
| | | 32 | | | | |
| | | 36 | | mg | | b |
| | | 37 | | | | |
| | | 38 | | | | |
| | | 39 | | | | |
| | | 40 | | | | |
| | | 41 | | | | |
| | | 42 | | | | |
| | | 43 | | mg | IU | b |
| | | 50 | | mg | | b |
| | | 56 | | | | b [^] , g-h |
| | | 57 | Begin next course when peripheral counts recover and no more than 7 days after Callback #2. | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.22.2 Required Observations in Consolidation SR-High B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets ^Day 56 CBC is meant to determine count recovery criteria to continue on to the next phase of therapy.
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed +14 days from Day 1.
- f. For patients who consent, send CSF specimens to the ALL Molecular Reference Lab for cell banking at final LP. Refer to [Section 14.7](#) for additional details.
- g. **Required:** For patients with end of Induction MRD $\geq 0.1\%$, collect a bone marrow specimen for assessment of response by morphology (at local institution), flow minimal residual disease (MRD). BM specimen for flow MRD testing should be sent to University of Washington flow MRD laboratory. Refer to [Section 14.4](#) for additional details and requirements for obtaining this sample. For patients with end of Induction MRD 0.01-0.099%, treating clinicians may choose whether or not to perform an EOC BM MRD assessment, in which case this assessment may either be performed on Consolidation day 56 or Day 1 of IM1 or Blinatumomab Block 1 for these patients. EOC BM samples for MRD assessment should be collected using green top sodium heparin tubes.
- h. For patients with EOI flow MRD $\geq 0.1\%$, and SR-High patients with EOI flow MRD 0.01-0.099% whose treating clinician chooses to assess BM MRD at EOC, and who consent, collect bone marrow for optional biobanking of EOC BM. Refer to [Section 14.5](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.22.3 Treatment Details for Consolidation SR-High B-ALL

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For all SR-High B-ALL patients, Consolidation therapy begins on Day 36 of Induction (7 days following Day 29 LP), or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later), after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Interruption and/or Modifications of Therapy

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should not be interrupted for fever, if there are no signs of serious infection. Therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC \geq 75,000/ μ L and platelets \geq 750/ μ L.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes

Days: 1 and 29

Dose: 1,000 mg/m²/dose

Patients should have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L to begin Day 29 therapy.

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV over 1-30 minutes or Subcutaneous

Days: 1-4, 8-11, 29-32 and 36-39

Dose: 75 mg/m²/dose once daily

Patients should have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L to begin Day 29 therapy.

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Mercaptopurine: PO

Days 1-14 and 29-42

Dose: 60 mg/m²/dose once daily*

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy.

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status.

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#))

Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)

Days 1, 8, 15 and 22

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.6](#) for guidelines of administration.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 15, 22, 43 and 50

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours (may also be given IM)

Days 15 and 43

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl

See dose modifications [Section 5.2](#).

BONE MARROW AT END CONSOLIDATION (SEE [Section 14.4](#))

Required for B-ALL with end of Induction BM MRD ≥ 0.1%:

- Following completion of Consolidation, end of consolidation marrow MRD will determine if eligible to continue on protocol therapy and to determine eligibility for randomization for those who remain on protocol therapy (See [Section 8.1](#)).
- The end of Consolidation marrow should occur as close to Day 56 as possible, but should be delayed until counts have recovered with an APC (Absolute Phagocyte Count) ≥ 500/µL and platelets ≥ 50,000/µL. **The end of Consolidation marrow should not be performed prior to Day 56 even if counts have recovered.**
- If on Day 56, the counts have recovered with an APC ≥ 500/µL and platelets ≥ 50,000/µL, the bone marrow for end of Consolidation MRD should be performed on that day. A three-day deviation is allowed, but any deviation that is greater than 3 days after count recovery must be discussed with the study chair.
- If on Day 56, the counts have not recovered (e.g., APC < 500/µL or platelets < 50,000/µL), the bone marrow for end of Consolidation MRD should be delayed until APC ≥ 500/µL and platelets ≥ 50,000/µL. The bone marrow for end of Consolidation MRD should be performed within 3 days of count recovery (APC ≥ 500/µL and platelets ≥ 50,000/µL). Any deviation that is greater than 3 days after count recovery must be discussed with the study chair. If counts have not recovered on Day 56, patients should have a CBC checked every 2-3 days (three times a week) at minimum until count recovery to minimize delay in obtaining the bone marrow.
- Patients who have not had count recovery (e.g., APC ≥ 500/µL and platelets ≥ 50,000/µL) by Day 72 should undergo bone marrow to ensure they are not Consolidation failures.

Following completion of Consolidation therapy, the next course should begin when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL and Callback #2 is completed. **The next phase of therapy (Interim**

Maintenance I or Blinatumomab Block 1) must begin no more than 7 days after Callback #2.

END CONSOLIDATION CALLBACK #2 OCCURS PRIOR TO STARTING POST-CONSOLIDATION THERAPY FOR ALL SR-HIGH B-ALL PATIENTS.

- SR-High B-ALL patients randomized to Arm C refer to Interim Maintenance I in [Section 4.23](#).
- SR-High B-ALL patients randomized to Arm D refer to [Section 4.28](#) for Blinatumomab Block 1 therapy.
- SR-High B-ALL patients with EOC MRD 0.1% - <1% are non-randomly assigned to Arm D (refer to [Section 4.28](#) for Blinatumomab Block 1 therapy).

4.23 SR-High B-ALL Arm C – Interim Maintenance I HDMTX**4.23.1 Therapy Delivery Map – INTERIM MAINTENANCE I (IM I HDMTX)**

IM I therapy in this TDM is for SR-High B-ALL patients randomized to Arm C. IM I therapy is 8 weeks (56 days). Begin IM I when peripheral counts recover and no more than 7 days after Callback #2.

Patient COG ID number DOB

Treatment details and criteria to start are in [Section 4.24.34.23.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|----------------------------|---|-----------------------------|---|
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 15, 29 & 43 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| High Dose Methotrexate (HD MTX) | IV | 5,000 mg/m ² /dose | 1, 15, 29 & 43 | Refer to Section 4.23.3 and Appendix V-A for admin guidelines. |
| Mercaptopurine (MP) | PO | 25 mg/m ² /dose daily | 1-14, 15-28, 29-42, & 43-56 | See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status. See Appendix III for administration guidelines. Must have ANC ≥ 750/µL and platelets ≥ 75,000/µL prior to each fourteen day course. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 29 | Administer on same day as HDMTX infusion. See Section 4.23.3 for admin guidelines . Note age based dosing. |
| Leucovorin (LCV) | PO or IV | 15 mg/m ² /dose x 3 | 3-4, 17-18, 31-32, 45-46 | 42, 48, and 54 hours after the start of HD MTX infusion. |

| | | Ht _____ cm | Wt _____ kg | BSA _____ m ² | | | | | |
|----------|------------|-------------|---|--------------------------|-------------|-----------------|--------------|---------|--|
| Date Due | Date Given | Day | VCR _____ mg | HD MTX _____ mg | MP _____ mg | IT MTX _____ mg | LCV _____ mg | Studies | |
| | | | Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-g | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 14 | | | | | | | |
| | | 15 | _____ mg | _____ mg | _____ mg | | | a-c | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 28 | | | | | | | |
| | | 29 | _____ mg | _____ mg | _____ mg | _____ mg | | a-d, h | |
| | | 31 | | | | | | | |
| | | 32 | | | | | | | |
| | | 42 | | | | | | | |
| | | 43 | _____ mg | _____ mg | _____ mg | _____ mg | | a-c | |
| | | 45 | | | | | | | |
| | | 46 | | | | | | | |
| | | 56 | | | | | | | |
| | | 64 | Begin Delayed Intensification (Section 4.24) on Day 64 or when blood count parameters are met (whichever occurs later). | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.23.2 Required Observations in IM I with HDMTX: SR-High B-ALL Arm C

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG and IgM
- f. Absolute CD19 count
- g. Absolute lymphocyte count
- h. For patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ± 14 days from Day 29.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.23.3 Treatment Details for Interim Maintenance I with HDMTX: SR-High B-ALL Arm C

For SR-High B-ALL patients randomized to Arm C, Interim Maintenance I begins when peripheral counts recover with an ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ and **no more than 7 days after Callback #2 is completed.**

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRIStine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 15, 29, and 43

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

High Dose (HD) Methotrexate: IV over 24 hours

Days 1, 15, 29, and 43

Dose: 5,000 mg/m²/dose (no maximum dose)

ANC must be $\geq 750/\mu\text{L}$ and platelets must be $\geq 75,000/\mu\text{L}$ prior to each dose of High Dose methotrexate. See below for HD methotrexate/leucovorin rescue and infusion guidelines.

Leucovorin: Oral (PO) or Intravenous (IV)

Days 3-4, 17-18, 31-32, and 45-46

Dose: 15 mg/m²/dose

3 doses given at 42, 48 and 54 hours after the start of HD methotrexate infusion. Document the total number of doses given.

Doses > 25 mg should be given IV due to the saturation of absorption.

High dose (HD) methotrexate/leucovorin rescue and infusion guidelines.

When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of high dose methotrexate infusion and for at least 72 hours after the start of the HD methotrexate infusion and until methotrexate level is less than 0.4 μM . *In the presence of delayed clearance, continue to hold these medications until methotrexate level is less than 0.1 μM .*

Recommended Prehydration: D5W 0.2% NaCl + alkalinizer at 750 mL/m² over 1 hour or at 125 mL/m²/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 . Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and alkalinizers to maintain urine specific gravity and pH at above parameters.

Alkalinizers: sodium bicarbonate or sodium acetate, 40 mEq/L.

An acetate or bicarbonate bolus (0.5-1 mEq/kg over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: Methotrexate 500 mg/m² IV infused over 30 minutes. This is followed, immediately, by methotrexate 4500 mg/m² given by continuous IV infusion over 23.5 hours. Be certain that the HD methotrexate infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours, though not encouraged, is acceptable.

Recommended Post-hydration: Continue hydration with D₅W 0.2% NaCl + alkalinizer 40 mEq/L at 125 mL/m²/hr until clearance parameters are met. In patients with delayed methotrexate clearance, continue hydration and leucovorin as instructed (see [Section 5.7](#) and [Appendix V-A](#)) until the plasma methotrexate concentration is below 0.1 μM .

Leucovorin rescue: 15 mg/m²/dose IV/PO every 6 hours starting at Hour 42. If the 42 and 48-hour methotrexate levels are ≤ 1 and 0.4 μM , respectively, give leucovorin at 15 mg/m²/dose IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

For all other levels, adjust dosing per [Section 5.7.2](#) and continue leucovorin until methotrexate level is $< 0.1 \mu\text{M}$.

Hours 24, (36), 42 and 48: Draw methotrexate level and serum creatinine;
NOTE: 36 hour level is only drawn if needed (see [Section 5.7](#) and [Appendix V-A](#))

Mercaptopurine: PO

Days 1-14, 15-28, 29-42, & 43-56

Dose: 25 mg/m²/dose once daily

Note that each HD methotrexate course is to be accompanied by a 14-day course of Mercaptopurine.

- If Day 15, 29, or 43 HD methotrexate is delayed due to myelosuppression (ANC $<750/\mu\text{L}$ or platelets $<75,000/\mu\text{L}$) or hepatotoxicity, hold mercaptopurine and resume when counts are adequate to resume HD methotrexate.

- If Day 15, 29, or 43 HD methotrexate is delayed to accommodate schedule requests or similar logistics, mercaptopurine may be continued without a pause. Note that the total number of mercaptopurine doses should not exceed 56.
- If at any point during this phase of therapy, the ANC is found to be <750/ μ L or platelets <75,000/ μ L, hold mercaptopurine. Start the next 14-day course of mercaptopurine when the next dose of HD methotrexate is administered. Do not make up missed doses (see [Section 5.8](#)).

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)).

If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 175 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)

Days 1 and 29

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

SEE PROTOCOL [Section 5.0](#) FOR DOSE MODIFICATIONS AND TOXICITIES. SEE [APPENDIX IX](#) FOR SUPPORTIVE CARE

Following completion of Interim Maintenance I, Delayed Intensification ([Section 4.24](#)) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.24 SR-High B-ALL Arm C – Delayed Intensification (DI)

4.24.1 Therapy Delivery Map – Delayed Intensification Part 1

Delayed Intensification Part 1 therapy in this TDM is for SR-High B-ALL patients randomized to Arm C. DI therapy is 8 weeks (56 days). Begin DI on Day 64 of IM I or when criteria to start are met (whichever occurs later).

Treatment details and criteria to start are in [Section 4.24.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-----------------------------------|--|-------------|---|
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.24.3 for admin guidelines. Age-based dosing |
| Dexamethasone (DEX) | PO or IV | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day See Section 4.24.3 for admin guidelines. |
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXOrubicin (DOXO) | IV over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.24.3 for admin guidelines. *Obtain ECHO (e) prior to the first dose of DOXO. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hrs (or IM injection) | 2,500 International Units/m ² | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | IT MTX ____ mg | DEX ____ mg | VCR ____ mg | DOXO ____ mg | PEG-ASP ____ IU | Studies |
|--|------------|-----|---|----------------|----------------|-----------------|--------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | ____ mg | | a-e* |
| | | 2 | | ____ mg | | | | |
| | | 3 | | ____ mg | | | | |
| | | 4 | | ____ mg | | | ____ IU | |
| | | 5 | | ____ mg | | | | |
| | | 6 | | ____ mg | | | | |
| | | 7 | | ____ mg | | | | |
| | | 8 | | | ____ mg | ____ mg | | b |
| | | 15 | | ____ mg | ____ mg | ____ mg | | b |
| | | 16 | | ____ mg | ____ mg | | | |
| | | 17 | | ____ mg | ____ mg | | | |
| | | 18 | | ____ mg | ____ mg | | | |
| | | 19 | | ____ mg | ____ mg | | | |
| | | 20 | | ____ mg | ____ mg | | | |
| | | 21 | | ____ mg | ____ mg | | | |
| | | 22 | | | | | | |
| | | 28 | Continue to DI Part 2 (Day 29-49) on the next page. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.24.1 Therapy Delivery Map – Delayed Intensification Part 2

Begin DI Part 2 on Day 29 or when criteria to start are met. Delayed Intensification therapy is a total of 8 weeks (56 days). **Patients should have ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ to begin Day 29 of DI Part 2.**

Patient COG ID number DOB

Treatment details and criteria to start are in [Section 4.24.3](#). This Therapy Delivery Map is three (3) pages.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-----------------------------------|---|---------------|--|
| Cyclophosphamide (CPM) | IV over 30-60 min | 1,000 mg/m ² /dose | 29 | See Section 4.24.3 for admin guidelines. |
| Thioguanine (TG) | PO | 60 mg/m ² /dose daily | 29-42 | See Section 4.24.3 & Appendix IV for administration guidelines See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/m ² /dose daily | 29-32 & 36-39 | See Section 4.24.3 for admin guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 29 & 36 | See Section 4.24.3 for admin guidelines. Note age-based dosing. |
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/ m ² /dose | 43 & 50 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Pegaspargase (PEG-ASP) | IV over 1-2 hrs (or IM injection) | 2,500 International Units/m ² /dose | 43 | Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl |

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | CPM ____ mg | TG ____ mg | ARAC ____ mg | IT MTX ____ mg | VCR ____ mg | PEG-ASP ____ IU | Studies |
|---|------------|-----|---|---------------|-----------------|-------------------|----------------|--------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | | | |
| | | 29 | ____ mg | ____ mg | ____ mg | ____ mg | | | a-d, f |
| | | 30 | | ____ mg | | | | | |
| | | 31 | | ____ mg | | | | | |
| | | 32 | | ____ mg | | | | | |
| | | 36 | | ____ mg | ____ mg | | | | b, d |
| | | 37 | | ____ mg | | | | | |
| | | 38 | | ____ mg | | | | | |
| | | 39 | | ____ mg | | | | | |
| | | 40 | | | | | | | |
| | | 41 | | | | | | | |
| | | 42 | | | | | | | |
| | | 43 | | | | | ____ mg | ____ IU | b |
| | | 50 | | | | | ____ mg | | b |
| | | 57 | Begin IM II therapy (Section 4.26) on Day 57 or when peripheral counts recover (whichever occurs later) | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.24.2 Required Observations in Delayed Intensification: SR-High B-ALL Arm C

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. ECHO **prior to the first dose of DOXOrubicin**
- f. For patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ± 14 days from Day 29.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.24.3 Treatment Details for Delayed Intensification: SR-High B-ALL Arm C

Delayed Intensification is given in 2 parts.

Delayed Intensification Part 1

For all SR-High B-ALL patients randomized to Arm C, Delayed Intensification Part 1 begins on Day 64 of Interim Maintenance I or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2 - 28 or Days 30 - 43, but Day 29 does not begin until ANC \geq 750/ μ L and platelets \geq 75,000/ μ L.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Dexamethasone: PO (may give IV)

Days: 1-7 and 15-21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8, 15

Dose: 1.5 mg/m²/dose (maximum 2 mg)**Special precautions: FOR INTRAVENOUS USE ONLY.**

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: IV push/infusion over 1-15 minutes

Days: 1, 8 and 15.

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Pegaspargase: IV over 1-2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#))

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Cyclophosphamide: IV over 30-60 minutes

Day 29 ONLY

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: PO

Days: 29-42

Dose: 60 mg/m²/dose once daily

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on

alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Cytarabine: IV over 1-30 minutes or subcutaneous

Days: 29-32 and 36-39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)

Days: 29 and 36

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days: 43 and 50

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegaspargase: IV over 1-2 hours (may also be given IM)

Day: 43

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#).

SEE PROTOCOL [Section 5.0](#) FOR DOSE MODIFICATIONS AND TOXICITIES. SEE [APPENDIX IX](#) FOR SUPPORTIVE CARE

Following completion of Delayed Intensification, Interim Maintenance II ([Section 4.25](#)) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.25 SR-High B-ALL Arm C – Interim Maintenance II CMTX**4.25.1 Therapy Delivery Map – INTERIM MAINTENANCE II (IM II CMTX)**

IM II therapy in this TDM is for SR-High B-ALL patients randomized to Arm C. IM II therapy is 8 weeks (56 days). Begin IM II on Day 57 of DI or when criteria to start are met (whichever occurs later).

Patient COG ID number DOB

Treatment details and criteria to start are in [Section 4.25.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|--|
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| Capizzi style Methotrexate (CMTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose is 100 mg/m ² /dose. Escalate by 50 mg/m²/dose | 1, 11, 21, 31 & 41 | Refer to Section 4.25.3 for admin guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 2 & 22 | Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 31 | See Section 4.25.3 for admin guidelines. Note age based dosing. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | CMTX ____mg <i>escalating dose</i> | PEG-ASP ____IU | IT MTX ____mg | Studies |
|---|------------|-----|---|--|-------------------|------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | ____mg | ____mg | | ____mg | a-d |
| | | 2 | | | ____IU | | |
| | | 11 | ____mg | ____mg | | | a-c |
| | | 21 | ____mg | ____mg | | | a-c |
| | | 22 | | | ____IU | | |
| | | 31 | ____mg | ____mg | | ____mg | a-d |
| | | 41 | ____mg | ____mg | | | a-c |
| | | 57 | Begin Maintenance (Section 4.27) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.25.2 Required Observations in IM II with CMTX: SR-High B-ALL Arm C

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.25.3 Treatment Details for Interim Maintenance II with CMTX: SR-High B-ALL Arm C

For SR-High B-ALL patients randomized to Arm C, Interim Maintenance II begins on Day 57 of DI or when peripheral counts recover with an ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31) and pegaspargase (if due). Pegaspargase may be given on the same day as the vinCRISTine dose if the IV methotrexate is omitted. Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of methotrexate as previously (i.e., no escalation).
- C) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate methotrexate by 50 mg/ m^2 /dose.
- D) Do not escalate methotrexate dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2-5 minutes (undiluted) or over 10-15 minutes (diluted)

Days 1, 11, 21, 31, and 41

Dose: Starting dose of 100 mg/m²/dose and then **escalate by 50 mg/m²/dose**

Pegaspargase: IV over 1-2 hours (may also be given IM)

Days 2 & 22

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl

See dose modifications in [Section 5.2](#).

Methotrexate: Intrathecal (IT)

Days 1 and 31

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

SEE PROTOCOL [Section 5.0](#) FOR DOSE MODIFICATIONS AND TOXICITIES. SEE [APPENDIX IX](#) FOR SUPPORTIVE CARE

Following completion of IM II, begin Maintenance ([Section 4.26](#)) on Day 57 or when blood count parameters are met (whichever occurs later).

4.26 SR-High B-ALL Arm C – Maintenance Cycles 1-2

4.26.1 Therapy Delivery Map – Maintenance

Maintenance therapy in this TDM is for SR-High B-ALL patients randomized to Arm C. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance therapy on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for cycles 1 and 2 of Maintenance therapy.

| | |
|-----------------------|-----|
| Patient COG ID number | DOB |
|-----------------------|-----|

Treatment details and criteria to start are in [Section 4.26.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|----------------------|--|--|---|
| VinCRISTine (VCR) | IV over 1 min* | 1.5 mg/m ² /dose | 1 | *Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| PredniSO(LO)NE (PRED) | PO (may be given IV) | 20 mg/m ² /dose BID | 1-5 | Total daily dose: 40 mg/m ² /day, divided BID. Note: IV methylprednisolone may be substituted for predniso(lo)ne at 80% of the oral dose |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily* | 1-84 | Refer to Section 4.26.3 & Appendix III for admin guidelines. *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 29 | Refer to Section 4.26.3 for admin guidelines. Note age-based dosing. |
| Oral Methotrexate (PO MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 36, 43, 50, 57, 64, 71, 78 | Omit when IT MTX is administered. |

| Enter Cycle #: _____ | | | Ht _____ cm | Wt _____ kg | BSA _____ m ² | | | |
|---|------------|-----|---|---------------|--------------------------|-----------------|-----------------|------------|
| Date Due | Date Given | Day | VCR _____ mg | PRED _____ mg | MP _____ mg | IT MTX _____ mg | PO MTX _____ mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg | _____ mg | a-e, g-j |
| | | 5 | | | | | | |
| | | 8 | | | | | | |
| | | 15 | | | | | | |
| | | 22 | | | | | | |
| | | 29 | | | | | | a, b, d, f |
| | | 36 | | | | | | |
| | | 43 | | | | | | |
| | | 50 | | | | | | |
| | | 57 | | | | | | a, b |
| | | 64 | | | | | | |
| | | 71 | | | | | | |
| | | 78 | | | | | | |
| | | 84 | | | | | | |
| | | 85 | After the completion of the first 2 cycles of Maintenance therapy, continue to Maintenance Cycle 3 Section 4.28 . | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.26.2 Required Observations in Maintenance –SR-High B-ALL Arm C

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each cycle of Maintenance.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship study anytime **between Day 1 of Cycle 1 and end of Cycle 2**, and at 1st off-therapy visit and 1 year off-therapy visit. Refer to [Section 17.1](#) for additional information.
- f. For patients who consent, complete the assessment for the Caregiver Burden study on **Day 29 of Cycle 1**. Refer to [Section 17.1](#) for additional information. May be completed ±28 days from Day 29 of Cycle 1.
- g. IgG and IgM **Day 1 of Cycle 1 ONLY**
- h. Absolute CD19 count **Day 1 of Cycle 1 ONLY**
- i. Absolute lymphocyte count **Day 1 of Cycle 1 ONLY**
- j. For patients who consent, send CSF for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.26.3 Treatment Details for Maintenance Cycles 1-2 SR-High B-ALL Arm C

For SR-High B-ALL patients randomized to Arm C, Maintenance therapy starts on Day 57 of Delayed Intensification, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day predniSO(LO)NE is completed for the cycle (i.e., complete all 5 days of predniSO(LO)NE before ending therapy). Otherwise continue current cycle through predniSO(LO)NE administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSO(LO)NE: PO (may give IV^)

Days 1-5

Dose: 20 mg/m²/dose BID (i.e., total daily dose: 40 mg/m²/day)

^Note: If a patient is unable to take predniSONE or prednisoLONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Mercaptopurine: PO

Days 1-84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. A liquid formulation is available (see drug monograph in [Section 6.8](#)). Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: Intrathecal (IT)

Days 1 and 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PO

Days 8, 15, 22, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**

Dose: 20 mg/m²/dose weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.8](#) for dose modifications during Maintenance.

After the completion of the first 2 cycles of Maintenance therapy, continue to Maintenance Cycle 3 [Section 4.27](#).

4.27 SR-High B-ALL Arm C – Maintenance Cycle 3 and Subsequent Cycles

4.27.1 Therapy Delivery Map – Maintenance Cycle 3 and Subsequent Cycles

Begin Maintenance therapy on Day 85 of the previous Maintenance cycle. Maintenance therapy in this TDM is for SR-High B-ALL patients. Each cycle of Maintenance therapy is 12 weeks (84 days). Use a copy of this TDM for all cycles of Maintenance therapy after cycle 2.

Treatment details and criteria to start are in [Section 4.27.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|----------------------|--|--|---|
| VinCRISTine (VCR) | IV over 1 min* | 1.5 mg/m ² /dose | 1 | *Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| PredniSO(LO)NE (PRED) | PO (may be given IV) | 20 mg/m ² /dose BID | 1-5 | Total daily dose: 40 mg/m ² /day, divided BID. Note: IV methylprednisolone may be substituted for predniSO(LO)NE at 80% of the oral dose |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose* daily | 1-84 | Refer to Section 4.27.3 & Appendix III for admin guidelines. *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | Note age-based dosing. |
| Oral Methotrexate (PO MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit when IT MTX is administered. |

| Enter Cycle #: | | Ht cm | Wt kg | BSA m ² | | | | |
|--|------------|-------|--|--------------------|-------|-----------|-----------|---------|
| Date Due | Date Given | Day | VCR mg | PRED mg | MP mg | IT MTX mg | PO MTX mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | | | |
| | | 1 | mg | mg | mg | mg | mg | a-d, f |
| | | 5 | | | | | | |
| | | 8 | | | | | mg | |
| | | 15 | | | | | mg | |
| | | 22 | | | | | mg | |
| | | 29 | | | | | mg | a, b |
| | | 36 | | | | | mg | |
| | | 43 | | | | | mg | |
| | | 50 | | | | | mg | |
| | | 57 | | | | | mg | a, b |
| | | 64 | | | | | mg | |
| | | 71 | | | | | mg | |
| | | 78 | | | | | mg | |
| | | 84 | | | | | | e |
| | | 85 | Regardless of sex, continue cycles of Maintenance therapy until 2 years from the start of Interim Maintenance I. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.27.2 Required Observations in Maintenance Cycle 3 and Subsequent Cycles – SR-High B-ALL Arm C

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship and Neurocognition study **at the end of Maintenance therapy**. Refer to [Section 17.1](#) for additional information.
- f. For patients who consent, send CSF for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.27.3 Treatment Details for Maintenance Cycle 3 and Subsequent Cycles SR-High B-ALL Arm C

For SR-High B-ALL patients on Arm C, begin Maintenance therapy Cycle 3 on Day 85 of the previous Maintenance cycle. Only oral mercaptourine and methotrexate will be interrupted for myelosuppression as outlined in [Section 5.7](#). Intrathecal methotrexate, vinCRISTine and predniSO(LO)ne will be delivered as scheduled, despite myelosuppression.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of Interim Maintenance I is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day predniSO(LO)NE is completed for the cycle (i.e., complete all 5 days of predniSO(LO)NE before ending therapy). Otherwise continue current cycle through predniSO(LO)NE administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSO(LO)NE: PO (may give IV^)

Days 1-5

Dose: 20 mg/m²/dose BID (i.e., total daily dose: 40 mg/m²/day)

^Note: If a patient is unable to take predniSONE or prednisolONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Mercaptopurine: PO

Days 1-84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. A liquid formulation is available (see drug monograph in [Section 6.8](#)). Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details.

Methotrexate: Intrathecal (IT)

Day 1 ONLY

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**

Dose: 20 mg/m²/dose weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.8](#) for dose modifications during Maintenance.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Interim Maintenance I is reached for both males and females.

4.28 SR-High B-ALL Arm D – Blinatumomab Block 1

| | |
|--|--|
| 4.28.1 Therapy Delivery Map – Blinatumomab Block 1 | Patient COG ID number _____ DOB _____ |
|--|--|

This TDM is for the first cycle of Blinatumomab therapy for SR-High B-ALL patients assigned to Arm D. Blinatumomab Block 1 lasts 5 weeks (35 Days). Begin therapy when peripheral counts recover and no more than 7 days after Callback #2.

Treatment details and criteria to start are in [Section 4.28.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|--|-------------------------|--|------|---|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² (max 20 mg) 30-60 mins prior to the start of BLIN infusion | 1 | Start prior to blinatumomab therapy. See Section 4.28.3 for admin guidelines. |
| Blinatumomab (BLIN) IND#117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day See Section 4.28.3 for admin guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.28.3 for admin guidelines. Note age based dosing |

| | Ht cm | Wt kg | BSA m ² | | | |
|---|------------|----------|--|-------------|--------------|--------------|
| Date Due | Date Given | Day | DEX mg | BLIN mcg | IT MTX mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | _____ mg | _____ mcg | _____ mg | a-d, e*, f-h |
| | | 2 | | | | |
| | | 3 | | | | |
| | | 4 | | | | |
| | | 5 | | | | |
| | | 6 | | | | |
| | | 7 | | | | |
| | | 8 | | | | (b, c)^ |
| | | 9 | | | | |
| | | 10 | | | | |
| | | 11 | | | | |
| | | 12 | | | | |
| | | 13 | | | | |
| | | 14 | | | | |
| | | 15 | | | | (b, c)^, i |
| | | 16 | | | | |
| | | 17 | | | | |
| | | 18 | | | | |
| | | 19 | | | | |
| | | 20 | | | | |
| | | 21 | | | | |
| | | 22 | | | | (b, c)^ |
| | | 23 | | | | |
| | | 24 | | | | |
| | | 25 | | | | |
| | | 26 | | | | |
| | | 27 | | | | |
| | | 28 | | | | |
| | | 29 | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | |
| | | 36 | Begin IM I therapy (Section 4.29) on Day 36 or when blood count parameters are met (whichever occurs later). | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.28.2 Required Observations in Blinatumomab Block 1 – SR-High B-ALL Arm D

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. **^May be completed ±2 days from scheduled assessment days.**
- c. Creatinine, total bilirubin, ALT. **^May be completed ±2 days from scheduled assessment days.**
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG ***Obtain before blinatumomab infusion**
- f. IgM ***Obtain before blinatumomab infusion**
- g. Absolute CD19 count ***Obtain before blinatumomab infusion**
- h. Absolute lymphocyte count ***Obtain before blinatumomab infusion**
- i. For patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 15.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.28.3 Blinatumomab Block 1 Treatment Details – SR-High B-ALL Arm D

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED.

FOR PATIENTS RISK ASSIGNED TO ARM D, COMPLETE CALLBACK #2 PRIOR TO BEGINNING BLINATUMOMAB BLOCK 1 THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For all SR-High B-ALL patients assigned to Arm D, Blinatumomab Block 1 therapy starts when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ and **no more than 7 days after Callback #2 is completed**.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 48 hours of Block 1 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 72 hours of Block 1 blinatumomab therapy in patients with flow MRD $\geq 0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met.

The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Dexamethasone: Oral (PO) or Intravenous (IV)

Day 1

Dose Prior to Day 1 therapy

- A single dose of 5 mg/m²/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of blinatumomab infusion in Block 1.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Blinatumomab: Intravenous (IV) continuous infusion over 28 days*

Days 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1 for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours \(7 days\). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.](#)

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of the Blinatumomab Block 1, the next cycle of therapy, IM I ([Section 4.29](#)) should begin on either Day 36 of the Blinatumomab Block 1, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.29 SR-High B-ALL Arm D – Interim Maintenance I HDMTX

| | |
|---|------------------------------|
| 4.29.1 <u>Therapy Delivery Map – INTERIM MAINTENANCE I (IM I HDMTX)</u> | Patient COG ID number DOB |
| IM I therapy in this TDM is for SR-High B-ALL patients assigned to Arm D. IM I therapy is 8 weeks (56 days). Begin IM I on Day 36 of Blinatumomab Block 1 or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.29.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|----------------------------|---|-----------------------------------|---|
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 15, 29 & 43 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| High Dose Methotrexate (HD MTX) | IV | 5,000 mg/m ² /dose | 1, 15, 29 & 43 | Refer to Section 4.29.3 and Appendix V-A for admin guidelines. |
| Mercaptopurine (MP) | PO | 25 mg/m ² /dose daily | 1-14, 15-28, 29-42, & 43-56 | See Section 5.8 for suggested starting dose based on <i>TPMT</i> and <i>NUDT15</i> status. See Appendix III for administration guidelines. Must have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L prior to each fourteen day course. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 29 | Administer on same day as HDMTX infusion. Refer to Section 4.29.3 for admin guidelines. Note age based dosing. |
| Leucovorin (LCV) | PO or IV | 15 mg/m ² /dose x 3 | 3-4, 17-18, 31-32, 45-46 | 42, 48, and 54 hours after the start of HD MTX infusion. |

| | | Ht cm | Wt kg | BSA m ² | | | | |
|---|------------|-------|--|--------------------|---------|-----------|---------|---------|
| Date Due | Date Given | Day | VCR mg | HD MTX mg | MP mg | IT MTX mg | LCV mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | a-e |
| | | 3 | | | | | ____ mg | |
| | | 4 | | | | | ____ mg | |
| | | 14 | | | | | ____ mg | |
| | | 15 | ____ mg | ____ mg | ____ mg | | | a-c |
| | | 17 | | | | ____ mg | ____ mg | |
| | | 18 | | | | | ____ mg | |
| | | 28 | | | | | | |
| | | 29 | ____ mg | ____ mg | ____ mg | ____ mg | | a-e |
| | | 31 | | | | | ____ mg | |
| | | 32 | | | | | ____ mg | |
| | | 42 | | | | | ____ mg | |
| | | 43 | ____ mg | ____ mg | ____ mg | | | a-c |
| | | 45 | | | | ____ mg | | |
| | | 46 | | | | | ____ mg | |
| | | 56 | | | | | | |
| | | 64 | Begin Blinatumomab Block 2 (Section 4.31) on Day 64 or when blood count parameters are met (whichever occurs later). | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.29.2 Required Observations in IM I with HDMTX: SR-High B-ALL Arm D

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.29.3 Treatment Details for Interim Maintenance I with HD MTX: SR-High B-ALL Arm D

For SR-High B-ALL patients assigned to Arm D, IM I begins on Day 36 of Blinatumomab Block 1 or when peripheral counts recover with an ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modification of Therapy

ANC must be \geq 750/ μ L and platelets must be \geq 75,000/ μ L prior to each dose of High Dose methotrexate.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 15, 29, and 43

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

High Dose Methotrexate: IV over 24 hours

Days 1, 15, 29, and 43

Dose: 5,000 mg/m²/dose (no maximum dose)

ANC must be \geq 750/ μ L and platelets must be \geq 75,000/ μ L prior to each dose of High Dose methotrexate. See below for high dose methotrexate/leucovorin rescue and infusion guidelines.

Leucovorin: Oral (PO) or Intravenous (IV)

Days 3-4, 17-18, 31-32, and 45-46

Dose: 15 mg/m²/dose

3 doses given at 42, 48 and 54 hours after the start of HD methotrexate infusion. Document the total number of doses given.

Doses > 25 mg should be given IV due to the saturation of absorption.

High dose (HD) methotrexate/leucovorin rescue and infusion guidelines.

When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of high dose methotrexate infusion and for at least 72 hours after the start of the HD methotrexate infusion and until methotrexate level is less than 0.4 μM . *In the presence of delayed clearance, continue to hold these medications until methotrexate level is less than 0.1 μM .*

Recommended Prehydration: D5W 0.2% NaCl + alkalinizer at 750 mL/m² over 1 hour or at 125 mL/m²/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 . Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and alkalinizers to maintain urine specific gravity and pH at above parameters.

Alkalinizers: sodium bicarbonate or sodium acetate, 40 mEq/L.

An acetate or bicarbonate bolus (0.5-1 mEq/kg over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: Methotrexate 500 mg/m² IV infused over 30 minutes. This is followed, immediately, by methotrexate 4500 mg/m² given by continuous IV infusion over 23.5 hours. Be certain that the HD methotrexate infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours, though not encouraged, is acceptable.

Recommended Post-hydration: Continue hydration with D₅W 0.2% NaCl + alkalinizer 40 mEq/L at 125 mL/m²/hr until clearance parameters are met. In patients with delayed methotrexate clearance, continue hydration and leucovorin as instructed (see [Section 5.7](#) and [Appendix V-A](#)) until the plasma methotrexate concentration is below 0.1 μM .

Leucovorin rescue: 15 mg/m²/dose IV/PO every 6 hours starting at Hour 42. If the 42 and 48-hour methotrexate levels are ≤ 1 and 0.4 μM , respectively, give leucovorin at 15 mg/m²/dose IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

For all other levels, adjust dosing per [Section 5.7](#) and continue leucovorin until methotrexate level is $< 0.1 \mu\text{M}$.

Hours 24, (36), 42 and 48: Draw methotrexate level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see [Section 5.7](#) and [Appendix V-A](#))

Mercaptopurine: PO

Days 1-14, 15-28, 29-42, & 43-56

Dose: 25 mg/m²/dose once daily

Note that each HD methotrexate course is to be accompanied by a 14-day course of Mercaptapurine.

- If day 15, 29, or 43 HD methotrexate is delayed due to myelosuppression (ANC <750/ μ L or platelets <75,000/ μ L) or hepatotoxicity, hold mercaptapurine and resume when counts are adequate to resume HD methotrexate.
- If day 15, 29, or 43 HD methotrexate is delayed to accommodate schedule requests or similar logistics, mercaptapurine may be continued without a pause. Note that the total number of mercaptapurine doses should not exceed 56.
- If at any point during this phase of therapy, the ANC is found to be <750/ μ L or platelets <75,000/ μ L, hold mercaptapurine. Start the next 14-day course of mercaptapurine when the next dose of HD methotrexate is administered. Do not make up missed doses (see [Section 5.8](#)).

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)).

If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 175 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptapurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)

Days 1 and 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

When IT therapy and high dose methotrexate are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

SEE PROTOCOL [Section 5.0](#) FOR DOSE MODIFICATIONS AND TOXICITIES. SEE [APPENDIX IX](#) FOR SUPPORTIVE CARE

Following completion of Interim Maintenance I, Blinatumomab Block 2 ([Section 4.30](#)) starts on Day 64 or when blood count parameters are met (whichever occurs later).

4.30 SR-High B-ALL Arm D – Blinatumomab Block 2

4.30.1 Therapy Delivery Map – Blinatumomab Block 2

This TDM is for Blinatumomab Block 2 for SR-High B-ALL patients assigned to Arm D. Blinatumomab Block 2 lasts 5 weeks (35 Days). Begin Blinatumomab Block 2 therapy on Day 64 of IM I or when criteria to start are met (whichever occurs later).

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.30.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|--|------------------------|---|-----------|---|--------|------|--------|-------|--------|-------|-----|-------|---|--|
| Blinatumomab (BLIN) IND#117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day See Section 4.30.3 for admin guidelines. | | | | | | | | | | |
| Intrathecal Methotrexate (IT MTX) | IT | <table border="1"> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>≥ 9</td> <td>15 mg</td> </tr> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | ≥ 9 | 15 mg | 1 | See Section 4.30.3 for admin guidelines. Note age based dosing |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| ≥ 9 | 15 mg | | | | | | | | | | | | | |

| Date Due | Date Given | Day | BLIN mcg | IT MTX mg | Studies |
|---|------------|-------|---|--------------|------------|
| Enter calculated dose above and actual dose administered below | | | | | |
| | | 1 | mcg | mg | a-e |
| | | 2 | | | |
| | | 3 | | | |
| | | 4 | | | |
| | | 5 | | | |
| | | 6 | | | |
| | | 7 | | | |
| | | 8 | | | (b, c)^ |
| | | 9 | | | |
| | | 10 | | | |
| | | 11 | | | |
| | | 12 | | | |
| | | 13 | | | |
| | | 14 | | | |
| | | 15 | | | (b, c)^, f |
| | | 16 | | | |
| | | 17 | | | |
| | | 18 | | | |
| | | 19 | | | |
| | | 20 | | | |
| | | 21 | | | |
| | | 22 | | | (b, c)^ |
| | | 23 | | | |
| | | 24 | | | |
| | | 25 | | | |
| | | 26 | | | |
| | | 27 | | | |
| | | 28 | | | |
| | | 29 | | | (b, c)^ |
| | | 30-35 | Rest Period | | |
| | | 36 | Begin Delayed Intensification therapy (Section 4.32) on Day 36 of Blinatumomab Block 2 or when blood count parameters are met (whichever occurs later). | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.30.2 Required Observations in Blinatumomab Block 2 – SR-High B-ALL Arm D

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. [^]May be completed ±2 days from scheduled assessment days.
- c. Creatinine, total bilirubin, ALT. [^]May be completed ±2 days from scheduled assessment days.
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG
- f. For non-DS patients who consent, complete assessments for the Caregiver Burden study. Refer to [Section 17.1](#) for additional information. May be completed ±14 days from Day 15.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.30.3 Blinatumomab Block 2 Treatment Details – SR-High B-ALL Arm D

For all SR-High B-ALL patients assigned to Arm D, Blinatumomab Block 2 starts on Day 64 of Interim Maintenance I or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 24 hours of Block 2 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 48 hours of Block 2 blinatumomab therapy in patients with flow MRD $\geq0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible. Every interruption longer than 5 minutes should be documented clearly in the medical record and CRFs. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Blinatumomab: Intravenous (IV) continuous infusion over 28 days*

Days 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of the Blinatumomab Block 2, Delayed Intensification ([Section 4.31](#)) should begin on either Day 36 of the Blinatumomab Block 2, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

4.31 SR-High B-ALL Arm D – Delayed Intensification (DI)

4.31.1 Therapy Delivery Map – Delayed Intensification Part 1

Delayed Intensification therapy in this TDM is for SR-High B-ALL patients assigned to Arm D. DI therapy is 8 weeks (56 days). Begin DI on Day 36 of Blinatumomab Block 2 or when criteria to start are met (whichever occurs later).

Patient COG ID number DOB

Treatment details and criteria to start are in [Section 4.31.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-----------------------------------|---|-------------|---|
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.31.3 for admin guidelines. Note age-based dosing |
| Dexamethasone (DEX) | PO or IV | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day |
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXORubicin (DOXO) | IV over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.31.3 for admin guidelines. *Obtain ECHO (e) prior to the first dose of DOXO. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hrs (or IM injection) | 2,500 IU/m ² | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm

Wt _____ kg

BSA _____ m²

| Date Due | Date Given | Day | IT MTX ____ mg | DEX ____ mg ____ mg | VCR ____ mg | DOXO ____ mg | PEG-ASP ____ IU | Studies |
|--|------------|-----|---|---------------------------|----------------|-----------------|--------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | | |
| | | 1 | ____ mg | ____ mg ____ mg | ____ mg | ____ mg | | a-e*, f |
| | | 2 | | | | | | |
| | | 3 | | | | | | |
| | | 4 | | | | | ____ IU | |
| | | 5 | | | | | | |
| | | 6 | | | | | | |
| | | 7 | | | | | | |
| | | 8 | | | ____ mg | ____ mg | | b |
| | | 15 | | ____ mg ____ mg | ____ mg | ____ mg | | b |
| | | 16 | | | | | | |
| | | 17 | | | | | | |
| | | 18 | | | | | | |
| | | 19 | | | | | | |
| | | 20 | | | | | | |
| | | 21 | | | | | | |
| | | 22 | | | | | | |
| | | 28 | Continue to DI Part 2 (Day 29-49) on the next page. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

| | | |
|--|-----------------------|-----|
| 4.31.1 Therapy Delivery Map – Delayed Intensification Part 2 | Patient COG ID number | DOB |
| Begin DI Part 2 on Day 29 or when criteria to start are met. Delayed Intensification therapy is a total of 8 weeks (56 days). Patients should have ANC \geq 750/μL and platelets \geq 75,000/μL to begin Day 29 of DI Part 2. | | |

Treatment details and criteria to start are in [Section 4.31.3](#). This Therapy Delivery Map is three (3) pages.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|----------------------------|---|------------------|--|
| Cyclophosphamide (CPM) | IV over 30-60 min | 1,000 mg/m ² /dose | 29 | See Section 4.31.3 for admin guidelines. |
| Thioguanine (TG) | PO | 60 mg/m ² /dose daily | 29-42 | See Section 4.31.3 & Appendix IV for administration guidelines See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/m ² /dose daily | 29-32 & 36-39 | See Section 4.31.3 for admin guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg \geq 9 15 mg | 29 & 36 | See Section 4.31.3 for admin guidelines. Note age-based dosing. |
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/ m ² /dose | 43 & 50 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Pegaspargase (PEG-ASP) | IV over 1-2 hrs (or IM) | 2,500 IU/m ² /dose | 43 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | CPM ____mg | TG ____mg | ARAC ____mg | IT MTX ____mg | VCR ____mg | PEG-ASP ____IU | Studies | |
|--|------------|-----|---|--------------|----------------|------------------|---------------|-------------------|---------|------|
| Enter calculated dose above and actual dose administered below | | | | | | | | | | |
| | | 29 | ____mg | ↓ | ____mg | ____mg | | | a-d, f | |
| | | 30 | | | ____mg | | | | | |
| | | 31 | | | ____mg | | | | | |
| | | 32 | | | ____mg | | | | | |
| | | 36 | | | ____mg | ____mg | | | | b, d |
| | | 37 | | | ____mg | | | | | |
| | | 38 | | | ____mg | | | | | |
| | | 39 | | | ____mg | | | | | |
| | | 40 | | | | | | | | |
| | | 41 | | | | | | | | |
| | | 42 | | | | | | | | |
| | | 43 | | | | | ____mg | ____IU | b | |
| | | 50 | | | | | ____mg | | b | |
| | | 57 | Begin IM II therapy (Section 4.33) on Day 57 or when peripheral counts recover (whichever occurs later) | | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.31.2 Required Observations in Delayed Intensification: SR-High B-ALL Arm D

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytospin (obtain with each IT administration)
- e. ECHO *prior to the first dose of DOXOrubicin
- f. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.31.3 Treatment Details for Delayed Intensification: SR-High B-ALL Arm D

Delayed Intensification is given in 2 parts.

For all SR-High B-ALL patients assigned to Arm D, Delayed Intensification Part 1 begins on Day 36 of Blinatumomab Block 2 or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2 - 28 or Days 30 - 43, but Day 29 does not begin until ANC \geq 750/ μ L and platelets \geq 75,000/ μ L.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAGs) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusions. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

Delayed Intensification Part 1

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Dexamethasone: PO (may give IV)

Days: 1-7 and 15-21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8, and 15

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: IV push/infusion over 1-15 minutes

Days: 1, 8 and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Pegasparagase: IV over 1-2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modification in [Section 5.2](#).

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

Cyclophosphamide: IV over 30-60 minutes

Day: 29 ONLY

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: PO

Days: 29-42

Dose: 60 mg/m²/dose once daily

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Cytarabine: IV over 1-30 minutes or subcutaneous

Days: 29-32 and 36-39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: Intrathecal (IT)

Days: 29 and 36

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days: 43 and 50

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLAStine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Pegasparagase: IV over 1-2 hours (may also be given IM)

Day 43

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#).

SEE PROTOCOL [Section 5.0](#) FOR DOSE MODIFICATIONS AND TOXICITIES. SEE [APPENDIX IX](#) FOR SUPPORTIVE CARE

Following completion of Delayed Intensification, the next phase of therapy ([Section 4.32](#)) starts on Day 57 or when blood count parameters are met (whichever occurs later).

4.32 SR-High B-ALL Arm D – Interim Maintenance II CMTX

| | |
|---|------------------------------|
| 4.32.1 Therapy Delivery Map – INTERIM MAINTENANCE II (CMTX) | Patient COG ID number DOB |
| IM II therapy in this TDM is for SR-High B-ALL patients assigned Arm D. IM II therapy is 8 weeks (56 days). Begin IM II on Day 57 of DI or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.32.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|---|---|--------------------|--|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Capizzi style Methotrexate (CMTX) | IV push over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose is 100 mg/m ² . Escalate by 50 mg/m²/dose | 1, 11, 21, 31 & 41 | See Section 4.32.3 for details. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | <u>2,500 International Units/m²/dose</u> | 2 & 22 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 & 31 | See Section 4.32.3 for administration guidelines Note age-based dosing |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | CMTX ____mg (escalating dose) | IT MTX ____mg | PEG-ASP ____IU | Studies |
|---|------------|-----|---|-------------------------------------|------------------|-------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____mg | ____mg | ____mg | ____IU | a-e |
| | | 2 | | | | | |
| | | 11 | ____mg | ____mg | | | a-c |
| | | 21 | ____mg | ____mg | | | a-c |
| | | 22 | | | | ____IU | |
| | | 31 | ____mg | ____mg | ____mg | | a-e |
| | | 41 | ____mg | ____mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Maintenance on Day 57 (Section 4.35) when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.32.2 Required Observations in Interim Maintenance II with CMTX – SR-High B-ALL
Arm D

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.32.3 Interim Maintenance II with CMTX Treatment Details – SR-High B-ALL Arm D

For all SR-High B-ALL patients assigned to Arm D, Interim Maintenance II therapy starts on Day 57 of DI, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

A) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.

1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.

2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31) and pegaspargase (if due). Pegaspargase may be given on the same day as the vinCRISTine dose if the IV methotrexate is omitted. Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. DO NOT make up omitted dose of methotrexate.

- a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.

- b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.

B) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of methotrexate as previously (i.e., no escalation).

C) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate methotrexate by 50 mg/m²/dose.

D) Do not escalate methotrexate dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only – Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinCRIStine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: Intravenous (IV) over 2 – 5 minutes (undiluted) or over 10 – 15 minutes (diluted)

Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m² and then **escalate by 50 mg/m²/dose**

Pegaspargase: IV over 1-2 hours (may also be given IM)

Days 2 & 22

Dose: 2,500 International Units/m²/dose

Administer through the tubing of a freely infusing solution of D₅W or 0.9% NaCl

See dose modification in [Section 5.2](#).

Methotrexate: Intrathecal (IT)

Day: 1 and 31

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Interim Maintenance II, Maintenance therapy ([Section 4.33](#)) begins on Day 57, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.33 SR-High B-ALL Arm D – Maintenance Cycles

4.33.1 Therapy Delivery Map – Maintenance

Maintenance therapy in this TDM is for SR-High B-ALL patients assigned to Arm D. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance therapy on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all cycles of Maintenance therapy.

| | |
|-----------------------|-----|
| Patient COG ID number | DOB |
|-----------------------|-----|

Treatment details and criteria to start are in [Section 4.33.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|-----------------------------------|----------------------------|--|--|--|--------|------|--------|-------|--------|-------|-----|-------|---|---|
| Intrathecal Methotrexate (IT MTX) | IT | <table> <thead> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>≥ 9</td> <td>15 mg</td> </tr> </tbody> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | ≥ 9 | 15 mg | 1 | <p>Refer to Section 4.33.3 for admin guidelines.</p> <p>Note age-based dosing.</p> |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| ≥ 9 | 15 mg | | | | | | | | | | | | | |
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | <p>⁺Or infusion via minibag as per institutional policy</p> <p>Maximum dose: 2 mg</p> | | | | | | | | | | |
| PredniSO(LO)NE (PRED) | PO (may be given IV) | 20 mg/m ² /dose BID | 1-5 | <p>Total daily dose: 40 mg/ m²/day, divided BID.</p> <p>[^]Note: IV methylprednisolone may be substituted for predniSO(LO)NE at 80% of the oral dose</p> | | | | | | | | | | |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily* | 1-84 | <p>Refer to Section 4.33.3 & Appendix III for admin guidelines.</p> <p>*See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status.</p> | | | | | | | | | | |
| Oral Methotrexate (PO MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit when IT MTX is administered. | | | | | | | | | | |

| Enter Cycle # | | | Ht cm | Wt kg | BSA m ² | | | | | |
|---------------|------------|-----|--|--------|--------------------|-------|-----------|------------|--|--|
| Date Due | Date Given | Day | IT MTX mg | VCR mg | PRED mg | MP mg | PO MTX mg | Studies | | |
| | | | Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | mg | mg | mg | mg | mg | a-e, g-k | | |
| | | 5 | | | | mg | | | | |
| | | 8 | | | | mg | | | | |
| | | 15 | | | | mg | | | | |
| | | 22 | | | | mg | | | | |
| | | 29 | | | | mg | | a, b, f, h | | |
| | | 36 | | | | mg | | | | |
| | | 43 | | | | mg | | | | |
| | | 50 | | | | mg | | | | |
| | | 57 | | | | mg | | a, b, h | | |
| | | 64 | | | | mg | | | | |
| | | 71 | | | | mg | | | | |
| | | 78 | | | | mg | | | | |
| | | 84 | | | | | | h | | |
| | | 85 | Continue Maintenance cycles until 2 years from the start of Blinatumomab Block 1, regardless of sex. | | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.33.2 Required Observations in Maintenance – SR-High B-ALL Arm D

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of each course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. For patients who consent, complete the assessment for the Household Material Hardship study anytime **between Day 1 of Cycle 1 and end of Cycle 2**, and at 1st off-therapy visit and 1 year off-therapy visit. Refer to [Section 17.1](#) for additional information.
- f. For patients who consent, complete the assessment for the Caregiver Burden study on **Day 29 of Cycle 1**. Refer to [Section 17.1](#) for additional information. May be completed ±28 days from Day 29 of Cycle 1.
- g. For patients who consent, send CSF for cell banking at **Day 1 LP of Cycle 1 and the final LP of the final cycle**. Refer to [Section 14.7](#) for additional details.
- h. IgG **Cycle 1 ONLY**
- i. IgM **Day 1 of Cycle 1 ONLY**
- j. Absolute CD19 count **Day 1 of Cycle 1 ONLY**
- k. Absolute lymphocyte count **Day 1 of Cycle 1 ONLY**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

(Include any held doses, or dose modifications)

4.33.3 Treatment Details for Maintenance - SR-High B-ALL Arm D

For SR-High B-ALL patients assigned to Arm D Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day predniSO(LO)NE is completed for the cycle (i.e., complete all 5 days of predniSO(LO)NE before ending therapy). Otherwise continue current cycle through predniSO(LO)NE administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLAStine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSO(LO)NE: PO (may give IV^)

Days 1-5

Dose: 20 mg/m²/dose BID (i.e., total daily dose: 40 mg/m²/day divided BID)

^Note: If a patient is unable to take predniSONE or prednisoLONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Mercaptopurine: PO

Days 1-84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. A liquid formulation is available (see drug monograph in [Section 6.8](#)). Tablets are scored and doses can be rounded to half tablet. If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit on days when IT MTX is given.**

Dose: 20 mg/m²/dose weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.8](#) for dose modifications during Maintenance.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females.

4.34 All DS B-ALL Patients – Induction

| | |
|--|-------------------|
| <p>4.34.1 Therapy Delivery Map – INDUCTION All DS B-ALL</p> <p>Induction therapy in Section 4.36.1 is for all DS B-ALL patients. Induction therapy is 5 weeks (35 days). Refer to Section 4.2 for Non-DS SR B-ALL therapy, and Section 4.44 and Section 4.45 for B-Lly Induction therapy.</p> | <hr/> <hr/> <hr/> |
|--|-------------------|

Treatment details and criteria to start are in [Section 4.34.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|-------------------------------------|---|---|---|
| Intrathecal Cytarabine (IT ARAC) | IT | <u>Age (yrs) Dose</u> 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg | Given at time of diagnostic LP OR Day 1 | See Section 4.34.3 for administration guidelines. Note age-based dosing. |
| Intrathecal Cytarabine (IT ARAC) | IT | <u>Age (yrs) Dose</u> 1-1.99 20 mg 2-2.99 30 mg ≥ 3 40 mg | CNS2: twice weekly [†] | [†] The initial dose is followed by twice weekly IT ARAC except during weeks when Days 8 & 29 IT MTX is administered Note: IT therapy is administered until 3 consecutive CSF samples are clear of blasts. |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 8, 15 &22 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| Dexamethasone (DEX) For patients < 10 years ONLY | PO (may be given IV) | 3 mg/m ² /dose BID | 1-28 (do not taper) | Total daily dose: 6 mg/m ² /day, divided BID See Section 4.34.3 for administration guidelines. |
| PredniSO(LO)NE (PRED) For patients ≥ 10 years ONLY | PO (may be given IV) | 30 mg/m ² /dose BID | 1-28 (do not taper) | Total daily dose: 60 mg/m ² /day, divided BID Note: IV methylprednisolone may be substituted for predniSO(LO)NE at 80% of the dose. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Note: pegaspargase should be administered on Day 4. Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs) Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 8 and 29 *CNS3 also on Days 15 & 22 | See Section 4.34.3 for administration guidelines. Note age-based dosing Note: All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation. |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 9 & 30 *CNS3 also on Days 16 & 23 | 24 & 30 hours after each IT MTX. This is not required after IT ARAC. See Section 4.34.3 for administration guidelines. |

Continue to the next page for the therapy log.

| 4.34.1 Therapy Delivery Map – INDUCTION All DS B-ALL | | | | | | Patient COG ID number _____ DOB _____ | | | | | | |
|--|------------|-----------------|---|-------------------------------|--------------------------|--|---|--------------------|-------------------|------------------------|----------------|--|
| Induction therapy in Section 4.36.1 is for all DS B-ALL patients. Induction therapy is 5 weeks (35 days). Refer to Section 4.2 for Non-DS SR B-ALL therapy and Sections 4.44 and Section 4.45 for B-Lly Induction therapy. | | | | | | | | | | | | |
| | | | Ht _____ cm | Wt _____ kg | BSA _____ m ² | | | | | | | |
| Date Due | Date Given | Day | IT ARAC ____ mg | IT ARAC if CNS2 ____ mg | VCR ____ mg | DEX (< 10 yrs old) ____ mg ____ mg | PRED (≥ 10 yrs old) ____ mg ____ mg | PEG-ASP ____ IU | IT MTX ____ mg | LCV ____ mg ____ mg | Studies | |
| Enter calculated dose above and actual dose administered below | | | | | | | | | | | | |
| | | -2/-1/0/LP | ____ mg | | | ____ mg | ____ mg | | | | a-g, k | |
| | | 1 | | | | ____ mg | ____ mg | | | | | |
| | | 4 [†] | | ____ mg [†] | | | | ____ IU | | | f [†] | |
| | | 8 | | | | ____ mg | | | ____ mg | | f, h | |
| | | 9 | | | | | | | ____ mg | ____ mg | | |
| | | 10 | | | | | | | | | | |
| | | 11 [†] | | ____ mg [†] | | | | | | | f [†] | |
| | | 15 | | | | ____ mg | | | ____ mg* | | f* | |
| | | 16 | | | | | | | ____ mg* | ____ mg | | |
| | | 22 | | | | ____ mg | | ____ mg* | | | f* | |
| | | 23 | | | | | | | ____ mg* | ____ mg | | |
| | | 28 | | | | | | | | | | |
| | | 29 | | | | | | | ____ mg | | f, i, j | |
| | | 30 | | | | | | | | ____ mg | | |
| | | 35 | Begin Consolidation therapy on Day 36 or when blood count criteria have been met (whichever occurs later). DS SR-Fav B-ALL patients refer to Section 4.3 . DS SR-Avg B-ALL patients refer to Section 4.9 . DS-High B-ALL patients refer to Section 4.37 . | | | | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.34.2 Required Observations in Induction – All DS B-ALL

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine
- d. Total bilirubin, ALT
- e. IgG
- f. CSF cell count and cytopsin (obtain with each IT administration)
- g. *TPMT* and *NUDT15* genotype (*TPMT* highly recommended for all subjects; *NUDT15* is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).
- h. **Required** peripheral blood for **NCI SR DS patients only**. Send Day 8 PB sample to COG-Approved ALL Flow Cytometry Lab for MRD. This sample should be drawn prior to day 8 IT MTX or VCR. This sample should be drawn no more than one day early or late. **If Day 8 PB sample is not obtained and shipped to COG-approved Flow lab for MRD testing, then NCI SR DS patients will not be eligible to continue on a COG ALL trial following completion of Induction therapy. This sample is absolutely essential.** See [Section 14.1](#).
- i. **Required** bone marrow evaluation to assess response by morphology (at local institution), flow minimal residual disease (MRD), and high-throughput sequencing (HTS) MRD. BM specimen for flow MRD testing should be sent to a COG-approved flow MRD laboratory (See [Section 14.1](#) for a list of labs). BM specimen for HTS MRD should be sent for NCI SR DS patients to the COG ALL Molecular Reference Lab (See [Section 14.2](#) for additional details). This sample should be drawn no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level. **If Day 29 BM sample is not obtained and shipped to a COG-approved flow lab for MRD testing and the COG ALL Molecular Reference lab then the patient will not be eligible to continue on a COG ALL trial following completion of Induction therapy. These samples are absolutely essential.**
- j. For patients who consent, send Day 29 PB and BM samples to ALL Molecular Reference Lab for cell banking. Done through APEC14B1. Refer to the APEC14B1 protocol for additional details.
- k. For patients who consent, collect peripheral blood specimen for optional Immune Function in DS B-ALL patients at pretreatment/diagnosis. Refer to [Section 14.6](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.34.3 Induction Treatment Details – All DS B-ALL

All DS B-ALL patients will receive common Induction therapy. For non-DS B-ALL patients, refer to [Section 4.2](#) For DS B-LLy patients, refer to [Section 4.45](#).

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: IT

All patients: Day 1 or at the time of diagnostic LP

May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing for Day 1/diagnostic LP:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1-1.99 | 30 mg |
| 2-2.99 | 50 mg |
| ≥ 3 | 70 mg |

B-ALL CNS2 patients ONLY: In addition to the initial dose (above), patients will receive additional IT Cytarabine on either Day 4, 5 or 6 during Induction, IT Methotrexate on Day 8, and then receive IT Cytarabine on Days 11 or 12. If the CSF at all three of these time points is negative for blasts, patients will receive their next IT therapy on Day 29 with methotrexate. If the CSF remains positive after the initial LP, patients will continue IT Cytarabine twice weekly during Induction until the CSF is clear for three consecutive LPs. All patients will receive IT therapy with methotrexate on Day 8 and 29 of Induction regardless of CSF evaluations.

Age-based dosing for additional IT Cytarabine for **B-ALL CNS2 patients ONLY (Days 4, 5 or 6 and Days 11 or 12) and additional IT Cytarabine until clear for three consecutive LPs:**

Age-based dosing for CNS2 additional doses:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 20 mg |
| 2 – 2.99 | 30 mg |
| ≥ 3 | 40 mg |

Use preservative free formulation. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.4](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRIStine: Intravenous (IV) push over 1 minute or infusion via minibag as per institutional policy

Days: 1, 8, 15 and 22

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY

Days: 1 - 28 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

PredniSO(LO)NE: PO (may be given IV^) – Patients ≥ 10 years ONLY

Days 1 - 28 (do not taper)

Dose: 30 mg/m²/dose BID (i.e., total daily dose: 60 mg/m²/day, divided BID)

^Note: If a patient is unable to take predniSONE and prednisolone by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Pegaspargase: IV over 1 - 2 hours (may also be given IM)

Day: 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

PLEASE NOTE: FOR B-ALL PATIENTS, DUE TO THE IMPORTANCE OF DAY 8 EARLY RESPONSE ASSESSMENT, PEGASPARGASE SHOULD BE ADMINISTERED ON DAY 4. Deviation from Day 4 administration may adversely impact risk categorization.

See dose modifications in [Section 5.2](#).

Methotrexate: IT

Days 8 and 29. Also Days 15 and 22 for CNS3 patients.

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV

Days 9 and 30. Also Days 16 and 23 for CNS3 patients.

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities](#).

Following completion of Induction, begin Consolidation therapy on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). DS SR-Fav patients refer to [Section 4.3](#). DS SR-Avg B-ALL patients refer to [Section 4.9](#). DS-High B-ALL patients refer to [Section 4.35](#). Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

4.35 DS-HIGH B-ALL – Consolidation

| | |
|--|---|
| <p>4.35.1 Therapy Delivery Map – CONSOLIDATION</p> <p>Consolidation therapy in this TDM is for DS-High B-ALL patients. Consolidation therapy is 8 weeks (56 days). Begin Consolidation on Day 36 of Induction or when peripheral counts recover with ANC \geq 750/μL & platelets \geq 75,000/μL (whichever occurs later).</p> | <p>Patient COG ID number _____</p> <p>DOB _____</p> |
|--|---|

Treatment details and criteria to start are in [Section 4.35.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|-----------------------------------|-------------------------------------|---|---|--|--------|------|--------|-------|--------|-------|----------|-------|---|--|
| Cyclophosphamide (CPM) | IV over 30-60 min | 1,000 mg/m ² /dose | 1 & 29 | See Section 4.35.3 for admin guidelines Patients should have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L to begin Day 29 therapy | | | | | | | | | | |
| Cytarabine (ARAC) | IV over 1-30 mins or SubQ | 75 mg/m ² /dose daily | 1-4, 8-11, 29-32, & 36-39 | Patients should have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L to begin Day 29 therapy | | | | | | | | | | |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 15, 22, 43, & 50 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg | | | | | | | | | | |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 15 & 43 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl | | | | | | | | | | |
| Mercaptopurine (MP) | PO | 60 mg/m ² /dose daily | 1-14 & 29-42 | See Section 4.35.3 and Appendix III for admin guidelines See Section 5.8 for suggested dose based on TPMT and NUDT15 status. Patients should have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L to begin Day 29 therapy | | | | | | | | | | |
| Intrathecal Methotrexate (IT MTX) | IT | <table style="margin-left: auto; margin-right: auto;"> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>\geq 9</td> <td>15 mg</td> </tr> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | \geq 9 | 15 mg | 1, 8, 15, & 22 *Omit Days 15 & 22 for CNS3 pts only | See Section 4.35.3 for administration guidelines Note age-based dosing |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| \geq 9 | 15 mg | | | | | | | | | | | | | |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2, 9, 16 & 23 **Omit Days 16 and 23 for CNS3 pts only | 24 & 30 hours after each IT MTX. See Section 4.35.3 for administration guidelines. | | | | | | | | | | |

Patients with testicular disease at diagnosis & continued clinical evidence of testicular disease at end-Induction will receive testicular xRT. See [Section 4.35.3](#) for additional details.

Continue to the next page for the therapy log.

| 4.35.1 Therapy Delivery Map – CONSOLIDATION | | | | | | | | | | | |
|---|------------|-----|---|---------------|--------------|--------------------------|--|-----------------|--------------|------------|--|
| Consolidation therapy in this TDM is for all DS-High B-ALL patients. Start Consolidation on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC \geq 750/ μ L & platelets \geq 75,000/ μ L (whichever occurs later). | | | | | | | Patient COG ID number _____ DOB _____ | | | | |
| Treatment details and criteria to start are in Section 4.35.3 . This Therapy Delivery Map is three (3) pages in length. | | | | | | | | | | | |
| Ht _____ cm | | | Wt _____ kg | | | BSA _____ m ² | | | | | |
| Date Due | Date Given | Day | CPM _____ mg | ARAC _____ mg | VCR _____ mg | PEG-ASP _____ IU | MP _____ mg | IT MTX _____ mg | LCV _____ mg | Studies | |
| Enter calculated dose above and actual dose administered below | | | | | | | | | | | |
| | | 1 | _____ mg | _____ mg | | | _____ mg | _____ mg | | a-e | |
| | | 2 | | | | | | | _____ mg | _____ mg | |
| | | 3 | | | | | | | | | |
| | | 4 | | | | | | | | | |
| | | 8 | | _____ mg | | | | _____ mg | | b, d | |
| | | 9 | | | | | | | _____ mg | _____ mg | |
| | | 10 | | | | | | | | | |
| | | 11 | | | | | | | | | |
| | | 14 | | | | | | | | | |
| | | 15 | | | _____ mg | _____ IU | | _____ mg* | | b, d | |
| | | 16 | | | | | | | _____ mg** | _____ mg** | |
| | | 22 | | | _____ mg | | | _____ mg* | | b, d | |
| | | 23 | | | | | | | _____ mg** | _____ mg** | |
| | | 29 | _____ mg | _____ mg | | | _____ mg | | | a-c | |
| | | 30 | | | | | | | | | |
| | | 31 | | | | | | | | | |
| | | 32 | | | | | | | | | |
| | | 36 | | _____ mg | | | | | | b | |
| | | 37 | | | | | | | | | |
| | | 38 | | | | | | | | | |
| | | 39 | | | | | | | | | |
| | | 40 | | | | | | | | | |
| | | 41 | | | | | | | | | |
| | | 42 | | | | | | | | | |
| | | 43 | | | _____ mg | _____ IU | | | | b | |
| | | 50 | | | _____ mg | | | | | b | |
| | | 56 | | | | | | | | f | |
| | | 57 | Begin next course (Section 4.38) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.35.2 Required Observations in Consolidation –DS-HIGH B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG
- f. **Required:** For NCI HR DS B-ALL patients with end of Induction MRD $\geq 0.01\%$ and NCI SR DS with EOI MRD $\geq 0.1\%$, collect a bone marrow specimen for assessment of response by morphology (at local institution), flow minimal residual disease (MRD). BM specimen for flow MRD testing should be sent to University of Washington flow MRD laboratory. Refer to [Section 14.4](#) for additional details and requirements for obtaining these samples. For NCI SR DS patients with end of Induction MRD 0.01-0.099%, treating clinicians may choose whether or not to perform an EOC BM MRD assessment, in which case this assessment may either be performed on Consolidation day 56 or Day 1 of IM1 or Blinatumomab Block 1 for these patients. EOC BM samples for MRD assessment should be collected using green top sodium heparin tubes.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.35.3 Consolidation Treatment Details – DS-HIGH B-ALL

CONSENT TO POST-INDUCTION THERAPY MUST TAKE PLACE BEFORE STARTING CONSOLIDATION THERAPY AFTER THE END INDUCTION RISK ASSIGNMENT HAS BEEN COMPLETED. DO CALLBACK #1 PRIOR TO BEGINNING CONSOLIDATION THERAPY FOR ALL PATIENTS WHO HAVE SIGNED CONSENT FOR POST-INDUCTION THERAPY. PATIENTS WHO ELECT NOT TO CONSENT TO THIS THERAPY ARE OFF-PROTOCOL THERAPY.

For DS-HIGH B-ALL and SR DS B-ALL patients with high risk features, Consolidation therapy begins on Day 36 of Induction (7 days following Day 29 LP) or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later) after the post-Induction risk assignment has been completed. Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Interruption and/or Modifications of Therapy

Therapy should be interrupted for patients with suspected or proven serious infection and resumed when the signs of infection have abated. Therapy should NOT be interrupted for fever, if there are no signs of serious infection. Therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$.

Testicular Radiation Therapy

Patients with Down syndrome and testicular leukemia at diagnosis, as determined by ultrasound and physical examination, and continued clinical evidence of testicular leukemia at the end of Induction should receive radiation to the testes during Consolidation. A testicular biopsy should be performed if the clinical findings are equivocal. Testicular radiation therapy will be given at 2400 cGy in 12 once-daily fractions of 200 cGy (see [Section 16.2](#)). Testicular radiation must be started during Consolidation and should be completed before the end of this phase of therapy. **Patients with testicular leukemia at diagnosis that resolves completely by end-Induction, and those that have a negative testicular biopsy at end-Induction will NOT receive testicular irradiation.**

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/dsc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Cyclophosphamide: IV over 30-60 minutes

Days 1 and 29

Dose: 1,000 mg/m²/dose

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy.

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Cytarabine: IV over 1-30 minutes or Subcutaneous

Days 1-4, 8-11, 29-32 and 36-39

Dose: 75 mg/m²/dose once daily

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy.

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 15, 22, 43, and 50

Dose: 1.5 mg/m²/dose (maximum 2 mg)**Special precautions: FOR INTRAVENOUS USE ONLY.**

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.**Pegaspargase: IV over 1-2 hour (may also be given IM)**

Days 15 and 43

Dose: 2,500 International Units/m²/doseAdminister through the tubing of a freely infusing solution of D₅W or 0.9% NaClSee dose modifications in [Section 5.2](#).**Mercaptopurine: PO**

Days 1 – 14 and 29-42

Dose: 60 mg/m²/dose once daily

Patients should have ANC ≥ 750/µL and platelets ≥ 75,000/µL to begin Day 29 therapy.

See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate dose based on blood counts during this cycle (see [Section 5.8](#)).

Methotrexate: IT

Days 1, 8, 15, and 22 (**Omit Days 15 and 22 for CNS3 patients**)

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV

Days 2, 9, 16 and 23 (**Omit Days 16 and 23 for CNS3 patients**)

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

BONE MARROW AT END CONSOLIDATION (SEE [Section 14.4](#))

Required for NCI HR DS B-ALL with EOI BM MRD $\geq 0.01\%$ and NCI SR DS with EOI MRD $\geq 0.1\%$:

- Following completion of Consolidation, end of consolidation marrow MRD will determine if eligible to continue on protocol therapy (See [Section 8.1](#)).
- The end of Consolidation marrow should occur as close to Day 56 as possible, but should be delayed until counts have recovered with an ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$. The end of Consolidation marrow should not be performed prior to Day 56 even if counts have recovered.
- If on Day 56, the counts have recovered with an ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, the bone marrow for end of Consolidation MRD should be performed on that day. A one day deviation is allowed, but any deviation that is greater than 1 day after count recovery must be discussed with the study chair.
- If on Day 56, the counts have not recovered (e.g., ANC $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$), the bone marrow for end of Consolidation MRD should be delayed until ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$. The bone marrow for end of Consolidation MRD should be performed within 2 days of count recovery (ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$). Any deviation that is greater than 3 days after count recovery must be discussed with the study chair. If counts have not recovered on Day 56, patients should have a CBC checked every 2-3 days (three times a week) at minimum until count recovery to minimize delay in obtaining the bone marrow.
- Patients who have not had count recovery (e.g., ANC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$) by Day 72 should undergo bone marrow to ensure they are not Consolidation failures.

Following completion of Consolidation therapy, Blinatumomab Block 1 ([Section 4.36](#)), should begin on Day 57 or when peripheral counts recover (whichever occurs later).

4.36 DS-HIGH B-ALL – Blinatumomab Block 1**4.36.1 Therapy Delivery Map – Blinatumomab Block 1**

This TDM is for Blinatumomab Block 1 for DS-HIGH B-ALL patients. Blinatumomab Block 1 lasts 5 weeks (35 Days). Begin therapy on Consolidation Day 57 or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.36.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|------------------------|--|-------------|---|
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² (max 20 mg) 30-60 mins prior to the start of BLIN infusion | 1 | Section 4.36.3 for administration guidelines. Start prior to blinatumomab therapy. |
| Blinatumomab (BLIN) IND# 117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day Section 4.36.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | Note age based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.36.3 for administration guidelines. |

| | | Ht cm | Wt kg | BSA m ² | | | |
|---|------------|-------|---|--------------------|-----------|-----------|---------|
| Date Due | Date Given | Day | DEX mg | BLIN mcg | IT MTX mg | LCV mg mg | Studies |
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | mg | mcg | mg | | a-h |
| | | 2 | | | | mg mg | |
| | | 3 | | | | | |
| | | 4 | | | | | |
| | | 5 | | | | | |
| | | 6 | | | | | |
| | | 7 | | | | | |
| | | 8 | | | | | (b, c)^ |
| | | 9 | | | | | |
| | | 10 | | | | | |
| | | 11 | | | | | |
| | | 12 | | | | | |
| | | 13 | | | | | |
| | | 14 | | | | | |
| | | 15 | | | | | (b, c)^ |
| | | 16 | | | | | |
| | | 17 | | | | | |
| | | 18 | | | | | |
| | | 19 | | | | | |
| | | 20 | | | | | |
| | | 21 | | | | | |
| | | 22 | | | | | (b, c)^ |
| | | 23 | | | | | |
| | | 24 | | | | | |
| | | 25 | | | | | |
| | | 26 | | | | | |
| | | 27 | | | | | |
| | | 28 | | | | | |
| | | 29 | | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | | |
| | | 36 | Begin IM with intermediate dose methotrexate (ID MTX) therapy (Section 4.39) on Day 36 or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.36.2 Required Observations in Blinatumomab Block 1 – DS-High B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. [^]May be completed ±2 days from scheduled assessment days.
- c. Creatinine, total bilirubin, ALT. [^]May be completed ±2 days from scheduled assessment days.
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG *Obtain before blinatumomab infusion
- f. IgM *Obtain before blinatumomab infusion
- g. Absolute CD19 count *Obtain before blinatumomab infusion
- h. Absolute lymphocyte count *Obtain before blinatumomab infusion

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.36.3 Blinatumomab Block 1 Treatment Details – DS-High B-ALL

For DS-High B-ALL, Blinatumomab Block 1 starts on Day 57 of Consolidation or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 48 hours of Block 1 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 72 hours of Block 1 blinatumomab therapy in patients with flow MRD $\geq 0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Dexamethasone: PO or IV

Day 1

Dose Prior to Day 1 therapy

- A single dose of 5 mg/m²/dose (maximum 20 mg/dose) will be administered 30 to 60 minutes prior to the start of blinatumomab infusion in block 1.

If using tablets, adjust dose upward to the nearest 0.25 mg. Oral solutions are acceptable and intravenous preparations may be used on a temporary basis, if needed.

Blinatumomab: IV continuous infusion over 28 days*

Days 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: IT

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV

Days 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Following completion of the Blinatumomab Block 1, Interim Maintenance with ID MTX ([Section 4.37](#)) should begin on either Day 36 of Blinatumomab Block 1, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.37 DS-HIGH B-ALL – Interim Maintenance with ID MTX

| | |
|--|--|
| 4.37.1 Therapy Delivery Map – INTERIM MAINTENANCE with Intermediate Dose Methotrexate (IM ID MTX) | Patient COG ID number _____ DOB _____ |
| IM with ID MTX therapy in this TDM is for DS-High B-ALL patients. IM with ID MTX therapy is 9 weeks (63 days). Begin IM with ID MTX on Day 36 of Blinatumomab Block 1 or when peripheral blood count criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.37.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|------------------------------------|---|-----------------------------|--|
| VinCRIStine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 15, 29 & 43 | +Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Intermediate-Dose Methotrexate (ID MTX) | IV over 24 hours | 2,000 mg/m ² /dose | 1, 15, 29 & 43 | See Section 4.37.3 and Appendix V-B for administration guidelines. |
| Leucovorin (LCV) | PO or IV | 15 mg/m ² /dose q6hr | 2-4, 16-18, 30-32 & 44-46 | 30, 36, 42, 48 & 54 hours after each ID MTX. If tolerated, subsequent courses should be administered 36, 42, 48, and 54 hours after the start of ID MTX infusion. See Section 4.37.3 for administration guidelines. |
| Mercaptopurine (6-MP) | PO | 25 mg/m ² /dose daily | 1-14, 15-28, 29-42, & 43-56 | See Section 4.37.3 for administration guidelines. Must have ANC \geq 750/ μ L and platelets \geq 75,000/ μ L prior to each fourteen day course. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg \geq 9 15 mg | 1 & 29 | See Section 4.37.3 for administration guidelines Note age-based dosing |

| Ht cm | Wt kg | BSA m ² | |
|---|--|--------------------|--|
| Date Due | Date Given | Day | VCR mg ID MTX mg LCV mg MP mg IT MTX mg Studies |
| Enter calculated dose above and actual dose administered below | | | |
| 1 | _____ mg | _____ mg | _____ mg _____ mg a-e |
| 2 | | | _____ mg _____ mg |
| 3 | | | _____ mg _____ mg |
| 4 | | | _____ mg |
| 14 | | | |
| 15 | _____ mg | _____ mg | _____ mg _____ mg a-c |
| 16 | | | _____ mg _____ mg |
| 17 | | | _____ mg _____ mg |
| 18 | | | _____ mg |
| 28 | | | |
| 29 | _____ mg | _____ mg | _____ mg _____ mg a-e |
| 30 | | | _____ mg _____ mg |
| 31 | | | _____ mg _____ mg |
| 32 | | | _____ mg |
| 42 | | | |
| 43 | _____ mg | _____ mg | _____ mg _____ mg a-c |
| 44 | | | _____ mg _____ mg |
| 45 | | | _____ mg _____ mg |
| 46 | | | _____ mg |
| 56 | | | |
| 64 | Begin next course (Blinatumomab Block 2, Section 4.40) on Day 64 or when blood count parameters are met (whichever occurs later). | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.37.2 Required Observations in Interim Maintenance with ID MTX – DS-HIGH B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.37.3 Interim Maintenance with ID MTX Treatment Details – DS-HIGH B-ALL

For DS-HIGH B-ALL, IM with ID methotrexate begins on Day 36 of Blinatumomab Block 1 or when peripheral counts recover with an ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRIStine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 15, 29, and 43

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Intermediate Dose (ID) Methotrexate: IV over 24 hours

Days 1, 15, 29, and 43

Dose: 2,000 mg/m²/dose

ANC must be \geq 750/ μ L and platelets must be \geq 75,000/ μ L prior to each dose of ID methotrexate. See below for ID Methotrexate/Leucovorin rescue and infusion guidelines.

Leucovorin: PO or IV

Days: 2-4, 16-18, 30-32, and 44-46

Dose: 15 mg/m²/dose q6h for a minimum of 5 doses given at 30, 36, 42, 48 and 54 hours after the start of ID methotrexate infusion, if 48 hour plasma methotrexate level is < 0.2 μ M.

If tolerated (see below), subsequent cycles of ID methotrexate should be followed by leucovorin 15 mg/m²/dose q6h x minimum 4 doses given at 36, 42, 48 and 54 hours after the start of ID methotrexate infusion. Document the total number of doses given.

Doses > 25 mg should be given IV due to the saturation of absorption.

Intermediate dose (ID) methotrexate/leucovorin rescue and infusion guidelines.

When IT therapy and intermediate dose methotrexate are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

Hold trimethoprim/sulfamethoxazole (TMP-SMX), any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of high dose methotrexate infusion and for at least 72 hours after the start of the ID methotrexate infusion and until methotrexate level is less than 0.2 µM. *In the presence of delayed clearance, continue to hold these medications until methotrexate level is less than 0.1 µM.*

Recommended Prehydration: D5W 0.2% NaCl + alkalinizer at 750 mL/m² over 1 hour or at 125 mL/m²/hour until urine specific gravity is \leq 1.010 and pH is \geq 7.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and alkalinizers to maintain urine specific gravity and pH at above parameters.

Alkalinizers: sodium bicarbonate or sodium acetate, 40 mEq/L. Continue hydration with D5W 0.2% NaCl + alkalinizer 40 mEq/L at 100 mL/m²/hr until serum methotrexate level is less than 0.2 µM for patients who meet expected clearance parameters. In patients with delayed methotrexate clearance, continue hydration and leucovorin as instructed (see [Section 5.7](#) and [Appendix V-B](#)) until the plasma methotrexate concentration is below 0.1 µM.

An acetate or bicarbonate bolus (0.5-1 mEq/kg over 15 min) may be given to raise the urine pH relatively quickly; a normal saline bolus may also be helpful in facilitating hydration.

Hour 0: Methotrexate 200 mg/m² IV infused over 30 minutes. This is followed, immediately, by methotrexate 1800 mg/m² given by continuous IV infusion over 23.5 hours. Be certain that the ID methotrexate infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours, though not encouraged, is acceptable.

Recommended Post-hydration: Continue hydration and alkalinization as above until plasma methotrexate levels are < 0.2 µM for patients who meet expected clearance parameters. For patients with delayed clearance see [Section 5.7](#).

Hours 24, (36), 42 and 48: Draw methotrexate level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see [Section 5.7](#) and [Appendix V-B](#))

Leucovorin rescue: 15 mg/m²/dose PO/IV q6h beginning **30 hr** after the start of ID methotrexate infusion for a minimum of 5 doses (hours 30, 36, 42, 48, and 54) if 48 hr plasma methotrexate level is < 0.2 µM.

- If the first cycle of ID methotrexate is tolerated, defined as no delayed clearance, no treatment delay due to myelosuppression, no mucositis of Grade 2 or higher, and no nephrotoxicity (pre-treatment serum creatinine >1.5 x baseline or GFR creatinine clearance < 65 mL/minute/1.73 m²), subsequent cycles of ID methotrexate should be followed by leucovorin 15 mg/m² PO/IV q6h beginning **36 hrs** after the start of the infusion for a minimum of 4 doses (hours 36, 42, 48, and 54) if 48 hour plasma MTX is < 0.2 µM.
- **If the 42 and 48 hour levels are ≤ 1 and 0.2 µM, respectively,** continue Leucovorin at 15 mg/m² IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose (see above for initial leucovorin guidelines). No additional levels are needed, nor is additional leucovorin. If levels exceed these values, see [Section 5.7.1](#).

Mercaptopurine: PO

Days: 1-14, 15-28, 29-42, & 43-56

Dose: 25 mg/m²/dose once daily

Note that each HD methotrexate course is to be accompanied by a 14-day course of Mercaptopurine.

- If Day 15, 29, or 43 HD methotrexate is delayed due to myelosuppression (ANC <750/µL or platelets <75,000/µL) or hepatotoxicity, hold mercaptopurine and resume when counts are adequate to resume HD methotrexate.
- If Day 15, 29, or 43 HD methotrexate is delayed to accommodate schedule requests or similar logistics, mercaptopurine may be continued without a pause. Note that the total number of mercaptopurine doses should not exceed 56.
- If at any point during this phase of therapy, the ANC is found to be <750/µL or platelets <75,000/µL, hold mercaptopurine. Start the next 14-day course of mercaptopurine when the next dose of HD methotrexate is administered. Do not make up missed doses (see [Section 5.8](#)).

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)).

If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 175 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate or reduce dose based on blood counts during this cycle.

Methotrexate: Intrathecal (IT)

Days 1 and 29

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

When IT therapy and ID MTX are scheduled for the same day, deliver the IT therapy within 24 hours of the beginning of the IV methotrexate infusion (should be administered on same day as methotrexate bolus).

For IT administration, use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining lying down after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Interim Maintenance with ID MTX, Blinatumomab Block 2 ([Section 4.38](#)) should begin on Day 64 of IM or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

4.38 DS-HIGH B-ALL – Blinatumomab Block 2

4.38.1 Therapy Delivery Map – Blinatumomab Block 2

This TDM is for Blinatumomab Block 2 for DS-HIGH B-ALL patients. Blinatumomab Block 2 lasts 5 weeks (35 Days). Begin Blinatumomab Block 2 therapy on Day 64 of IM or when criteria to start are met (whichever occurs later).

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.38.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|------------------------|--|------|--|
| Blinatumomab (BLIN) IND# 117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day See Section 4.38.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.38.3 for administration guidelines. Note age based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.38.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | BLIN ____ mcg | IT MTX ____ mg | LCV (DS pts only) ____ mg ____ mg | Studies |
|---|------------|-------|--|-------------------|--------------------------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | ____ mcg | ____ mg | | a-d, e |
| | | 2 | | | ____ mg ____ mg | |
| | | 3 | | | | |
| | | 4 | | | | |
| | | 5 | | | | |
| | | 6 | | | | |
| | | 7 | | | | |
| | | 8 | | | | (b, c)^ |
| | | 9 | | | | |
| | | 10 | | | | |
| | | 11 | | | | |
| | | 12 | | | | |
| | | 13 | | | | |
| | | 14 | | | | |
| | | 15 | | | | (b, c)^ |
| | | 16 | | | | |
| | | 17 | | | | |
| | | 18 | | | | |
| | | 19 | | | | |
| | | 20 | | | | |
| | | 21 | | | | |
| | | 22 | | | | (b, c)^ |
| | | 23 | | | | |
| | | 24 | | | | |
| | | 25 | | | | |
| | | 26 | | | | |
| | | 27 | | | | |
| | | 28 | | | | |
| | | 29 | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | |
| | | 36 | Begin DI therapy (Section 4.41) on Day 36 of Blinatumomab Block 2 or when blood count parameters are met (whichever occurs later). | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.38.2 Required Observations in Blinatumomab Block 2 – DS-HIGH B-LL

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets. **^May be completed ±2 days from scheduled assessment days.**
- c. Creatinine, total bilirubin, ALT. **^May be completed ±2 days from scheduled assessment days.**
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.38.3 Blinatumomab Block 2 Treatment Details – DS-HIGH B-ALL

For DS-HIGH B-ALL patients, Blinatumomab therapy starts on Day 64 of Interim Maintenance with ID MTX or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 24 hours of Block 2 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction in patients with flow MRD $<0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab, and for the first 48 hours of Block 2 blinatumomab therapy in patients with flow MRD $\geq 0.01\%$ at the last bone marrow assessment prior to receiving blinatumomab. Manifestations of cytokine release syndrome include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, increased total bilirubin, and disseminated intravascular coagulation (DIC). Administer corticosteroids for severe or life-threatening cytokine release syndrome. See [Section 5.1](#) for additional details on how to manage CRS and other possible blinatumomab toxicities.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reason(e.g. routine PORT needle changes, procedural sedation, the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Blinatumomab: Intravenous (IV) continuous infusion over 28 days*

Days: 1-28

Dose: 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV)

Day: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0**](#) for Dose Modifications based on Toxicities.

Following completion of the Blinatumomab Block 2, Delayed Intensification ([**Section 4.39**](#)) should begin on either Day 36 of the Blinatumomab Block 2, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.39 DS-HIGH B-ALL – Delayed Intensification

4.39.1 Therapy Delivery Map – Delayed Intensification (DI)

Delayed Intensification therapy in this TDM is for DS-HIGH B-ALL patients. DI therapy is 4 weeks (28 days). Begin DI on Day 36 of Blinatumomab Block 2 or when criteria to start are met (whichever occurs later).

Patient COG ID number _____
DOB _____

Treatment details and criteria to start are in [Section 4.39.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|--|-------------|--|
| VinCRISTine (VCR) | IV over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or per via minibag per institutional policy Maximum dose: 2mg |
| DOXOrubicin (DOXO) | IV push/infusion over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.39.3 for administration guidelines. *Obtain ECHO (f) prior to the first dose of DOXO. |
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day. See Section 4.39.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.39.3 for administration guidelines Note age-based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.39.3 for administration guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____ mg | DOXO ____ mg | DEX ____ mg | IT MTX ____ mg | LCV mg ____ mg | PEG-ASP ____ IU | Studies |
|--|------------|-----|--|-----------------|----------------|-------------------|----------------------|--------------------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | ____ mg | ____ mg | ____ mg | ____ mg | ____ mg | | a-e, f* |
| | | 2 | | | | | ____ mg | ____ mg | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | ____ IU | |
| | | 5 | | | | | | | |
| | | 6 | | | | | | | |
| | | 7 | | | | | | | |
| | | 8 | ____ mg | ____ mg | | | | | b |
| | | 15 | ____ mg | ____ mg | ____ mg | ____ mg | | | b |
| | | 16 | | | | | | | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 19 | | | | | | | |
| | | 20 | | | | | | | |
| | | 21 | | | | | | | |
| | | 22 | | | | | | | |
| | | 29 | Begin Blinatumomab Block 3 (Section 4.42) on Day 29 or when blood count parameters are met (whichever occurs later). | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.39.2 Required Observations in Delayed Intensification – DS-HIGH B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG
- f. ECHO prior to the first dose of DOXOrubicin

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.39.3 Delayed Intensification Treatment Details – DS-HIGH B-ALL

For DS-HIGH B-ALL, Delayed Intensification begins on Day 36 of Blinatumomab Block 2 or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2 – 28.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdmin_Guidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8 and 15

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: IV push/infusion over 1 - 15 minutes

Days 1, 8 and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Dexamethasone: PO (may give IV)

Days 1 - 7 and 15 - 21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (10 mg/m²/day, divided BID) may be used temporarily as needed.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV)

Days: 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pegaspargase: Intravenous (IV) over 1 - 2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#).

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Delayed Intensification, Blinatumomab Block 3 ([Section 4.40](#)) starts on Day 29 or when peripheral counts recover to ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

4.40 DS-HIGH B-ALL – Blinatumomab Block 3

4.40.1 Therapy Delivery Map – Blinatumomab Block 3

This TDM is for Blinatumomab Block 3 for DS-HIGH B-ALL patients. Blinatumomab Block 3 lasts 5 weeks (35 Days). Begin Blinatumomab Block 3 on Day 29 of DI or when criteria to start are met (whichever occurs later).

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.40.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|------------------------|--|------|--|
| Blinatumomab (BLIN) IND# 117467 Do not use commercial supply | IV continuous infusion | 15 micrograms/m ² /day | 1-28 | Max dose 28 micrograms/day See Section 4.40.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | See Section 4.40.3 for administration guidelines. Note age based dosing |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | 24 & 30 hours after each IT MTX. See Section 4.40.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | BLIN ____ mcg | IT MTX ____ mg | LCV ____ mg ____ mg | Studies |
|---|------------|-------|---|-------------------|------------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | |
| | | 1 | ____ mcg | ____ mg | | a-d, e |
| | | 2 | | | ____ mg ____ mg | |
| | | 3 | | | | |
| | | 4 | | | | |
| | | 5 | | | | |
| | | 6 | | | | |
| | | 7 | | | | |
| | | 8 | | | | (b, c)^ |
| | | 9 | | | | |
| | | 10 | | | | |
| | | 11 | | | | |
| | | 12 | | | | |
| | | 13 | | | | |
| | | 14 | | | | |
| | | 15 | | | | (b, c)^ |
| | | 16 | | | | |
| | | 17 | | | | |
| | | 18 | | | | |
| | | 19 | | | | |
| | | 20 | | | | |
| | | 21 | | | | |
| | | 22 | | | | (b, c)^ |
| | | 23 | | | | |
| | | 24 | | | | |
| | | 25 | | | | |
| | | 26 | | | | |
| | | 27 | | | | |
| | | 28 | | | | |
| | | 29 | | | | (b, c)^ |
| | | 30-35 | Rest Period | | | |
| | | 36 | Begin Maintenance therapy (Section 4.43) on Day 36 of Blinatumomab Block 3 or when blood count parameters are met (whichever occurs later). | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.40.2 Required Observations in Blinatumomab Block 3 – DS-HIGH B-ALL

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets. [^]May be completed ±2 days from scheduled assessment days.
- c. Creatinine, total bilirubin, ALT. [^]May be completed ±2 days from scheduled assessment days.
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.40.3 Blinatumomab Block 3 Treatment Details – DS-HIGH B-ALL

For DS-HIGH B-ALL patients, Blinatumomab Block 3 therapy starts on Day 29 of Delayed Intensification or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

NOTE: Close medical monitoring in an in-patient medical facility is STRONGLY recommended for the first 24 hours of Block 3 blinatumomab therapy to monitor for cytokine release syndrome or neurologic toxicity reaction.

Blinatumomab infusion interruptions for technical reasons:

Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reason(e.g. routine PORT needle changes, procedural sedation, the interruption should be as short as possible and the infusion restarted as soon as possible. For guidance on how to minimize interruptions in various clinical situations, see the Frequently Asked Questions sections pertaining to blinatumomab.

For interruptions lasting longer than four (4) hours, it is STRONGLY recommended that re-initiation of the infusion be in a medical facility with close monitoring for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects.

When the cumulative interruption time over 28 days is greater than 24 hours, missed hours of blinatumomab may be added to the infusion time. Whether or not to make up missed infusion time is ultimately the decision of the treating physician, and it is strongly recommended that every attempt should be made to adhere to the 28 day infusion within 28-29 days. Of note, do not exceed the maximum time allowed from the beginning to the end of a blinatumomab cycle, which is 35 days, assuming count criteria to start the subsequent cycle are met. The total dose of blinatumomab delivered in each cycle should be documented clearly in the CRF.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

See [Appendix X-A](#) and [Appendix X-B](#) for the management options of blinatumomab in the outpatient setting.

Dosing should be based on actual BSA obtained within 2 weeks prior to the start of the infusion.

Blinatumomab: IV continuous infusion over 28 days*

Days 1-28

Dose 15 micrograms/m²/day (max dose 28 micrograms/day)

Avoid flushing of the line during Blinatumomab infusion, particularly in the first week of each cycle. Unavoidable flushes of the line will occur at the time of PORT needle changes, when lines are used for procedural sedation, as well as at the completion of the 28 day cycle. In these cases, the volume of the flush should be minimized. For additional guidance, see the Frequently Asked Questions sections pertaining to blinatumomab.

Please see [Section 6.1](#) for infusion bag change timing details. For patients ≥ 22 kg, IV bag can be changed every 24, 48, 72, 96 or 168 hours (7 days). For patients < 22 kg, IV bag can be changed every 24, 48, 72, or 96 hours. For guidance on how the timing of bag changes and tubing changes may be coordinated, see the Frequently Asked Questions sections pertaining to blinatumomab.

Methotrexate: IT

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Leucovorin: PO or IV

Day: 2

Dose: $5 \text{ mg/m}^2/\text{dose} \times 2$ doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Following completion of the Blinatumomab Block 3, Maintenance ([Section 4.41](#)) should begin on either Day 36 of the Blinatumomab Block 3, or when peripheral counts recover to ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$, whichever occurs later.

4.41 DS-HIGH B-ALL – Maintenance

4.41.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for DS-High B-ALL patients. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance cycle 1 on Day 36 of Blinatumomab Block 3 or when blood count criteria to start are met (whichever occurs later). Use this TDM for all cycles of Maintenance.

Patient COG ID number _____

Treatment details and criteria to start are in [Section 4.41.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--------------------------------------|--|---|---|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| PredniSO(LO)NE (PRED) | PO [^] (may be given IV) | 20 mg/m ² /dose BID | 1-5 | Total daily dose: 40 mg/m ² /day See Section 4.41.3 for administration guidelines ^IV methylprednisolone may be substituted for predniSO(LO)NE at 80% of the oral dose |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily* | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.41.3 & Appendix III for administration guidelines |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1 | *Also on Day 29 of Cycles 1-3, for patients who did NOT receive CXRT. See Section 4.41.3 for administration guidelines Note age-based dosing |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29#, 36, 43, 50, 57, 64, 71, 78 | #Omit Day 29 for first 3 cycles for patients who do NOT receive CXRT, as it coincides with IT MTX. |
| Leucovorin (LCV) | PO | 5 mg/m ² /dose q6hr x 2 | 2 & 30** | 24 & 30 hours after each IT MTX. See Section 4.41.3 for administration guidelines. **Day 30 dose is for first 3 cycles and for patients who do NOT receive CXRT. |

Patients with CNS3 disease receive cranial XRT during the first 4 weeks of Maintenance Cycle 1. Begin CXRT after Day 1 IT MTX.

See [Section 4.41.3](#) and [Section 16.1](#) for details.

| Enter Cycle #: | | Ht cm | Wt kg | BSA m ² | | | | | |
|----------------|------------|-------|---------|--|---------|-----------|-----------|---------|-------------|
| Date Due | Date Given | Day | VCR mg | PRED mg | MP mg | IT MTX mg | PO MTX mg | LCV mg | Studies |
| | | | | | | | | | |
| | | 1 | _____mg | _____mg | _____mg | _____mg | _____mg | _____mg | a-j |
| | | 2 | | | | | | mg** | mg** |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 8 | | | | | _____mg | | |
| | | 15 | | | | | _____mg | | |
| | | 22 | | | | | _____mg | | |
| | | 29 | | | | | mg* | mg# | a, b, e@, f |
| | | 30 | | | | | | | mg** mg** |
| | | 36 | | | | | _____mg | | |
| | | 43 | | | | | _____mg | | |
| | | 50 | | | | | _____mg | | |
| | | 57 | | | | | _____mg | | a, b, e@ |
| | | 64 | | | | | _____mg | | |
| | | 71 | | | | | _____mg | | |
| | | 78 | | | | | _____mg | | |
| | | 84 | | | | | | | e@ |
| | | 85 | | Continue Maintenance cycles until 2 years from the start of Blinatumomab Block 1, regardless of sex. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.41.2 Required Observations in Maintenance – DS-HIGH B-ALL

- a. Hx/PE/Wt/Ht/BSA. Note: Height is only required at the beginning of this course.
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG **@Day 29, 57, and 84 are done in Cycle 1 only**
- f. For patients who consent, complete the assessment for the Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS B-ALL study on **Day 29 of Cycles 1 and 5, and 1 year after end of therapy**. Refer to [Section 17.2](#) for additional information. Note: flexible time point, must be obtained/administered within ±4 weeks of time point.
- g. For DS patients who consent, collect peripheral blood specimen for Immune Function in DS B-ALL patients on **Day 1 of Cycle 2**. Refer to [Section 14.6](#) for additional details.
- h. IgM **Day 1 of Cycle 1 only**
- i. Absolute CD19 count **Day 1 of Cycle 1 only**
- j. Absolute lymphocyte count **Day 1 of Cycle 1 only**

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.41.3 Maintenance Treatment Details – DS-HIGH B-ALL

For DS-HIGH B-ALL patients, Maintenance therapy starts on Day 36 of Blinatumomab Block 3, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Cranial Radiation Therapy

Patients with Down syndrome and CNS3 disease at diagnosis should receive cranial radiation during the first cycle of Maintenance. Cranial radiation therapy will be given at 1800 cGy in 10 once-daily fractions of 180 cGy. See [Section 16.0](#) for details. Cranial radiation must be started after Day 1 MTX during the first 4 weeks of Maintenance for Cycle 1 only, and should be completed before the end Day 29 of Maintenance therapy.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day predniSO(LO)NE is completed for the cycle (i.e., complete all 5 days of predniSO(LO)NE before ending therapy). Otherwise continue current cycle through predniSO(LO)NE administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRIStine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdmin_Guidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

PredniSO(LO)NE: PO (may be given ^ IV)

Days 1-5

Dose: 20 mg/m²/dose BID (i.e., total daily dose: 40 mg/m²/day)[^]**Note:** If a patient is unable to take predniSONE or prednisoLONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.**Mercaptopurine: PO**

Days 1 - 84

Dose: 75 mg/m²/dose once dailySee [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details. Do not escalate dose based on blood counts during this cycle (see [Section 5.8](#)).

Methotrexate: Intrathecal (IT)

Day 1, *Also on Day 29 of Cycles 1-3, for patients who did NOT receive CXRT.

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Methotrexate: PODays 8, 15, 22, 29[#], 36, 43, 50, 57, 64, 71 and 78.[#]**Omit Day 29 for first 3 cycles for patients who do NOT receive CXRT, as it coincides with IT MTX.**Dose: 20 mg/m²/dose weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

Leucovorin: Oral (PO) or Intravenous (IV)

Days 2 and 30**

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

****Day 30 dose is for first 3 cycles for patients who do NOT receive CXRT.**

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Blinatumomab Block 1 is reached for both males and females.

4.42 Non-DS B-Lly – Induction

| | |
|--|----------------------------------|
| 4.42.1 <u>Therapy Delivery Map – INDUCTION non-DS B-Lly</u> Induction therapy in Section 4.44.1 is for B-Lly patients without DS. Induction therapy is 5 weeks (35 days). | Patient COG ID number DOB |
|--|----------------------------------|

Treatment details and criteria to start are in [Section 4.42.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|---|--|--|
| Intrathecal Cytarabine (IT ARAC) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg | Given at time of diagnostic LP <u>OR</u> Day 1* | See Section 4.42.3 for administration guidelines. Note age-based dosing. |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 8, 15 & 22 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| Dexamethasone (DEX) | PO (may be given IV) | 3 mg/m ² /dose BID | 1-28 (do not taper) | Total daily dose: 6 mg/m ² /day See Section 4.42.3 for administration guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Note: pegaspargase should be administered on Day 4. Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 8 and 29 | See Section 4.42.3 for administration guidelines. Note age-based dosing Note: All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation. |

Continue to the next page for the therapy log.

| 4.42.1 Therapy Delivery Map – INDUCTION B-LLy without DS Induction therapy in Section 4.41 is for B-LLy patients without DS. Induction therapy is 5 weeks (35 days). | | | | | | | Patient COG ID number DOB | |
|---|------------|-------------|--|----------|-----------------------|----------|----------------------------------|---------------|
| Date Due | Date Given | Day | Ht cm | Wt kg | BSA m ² | Studies | | |
| Enter calculated dose above and actual administered dose below | | | | | | | | |
| | | -2/-1/0/LP* | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a-h, j |
| | | 1 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b, d |
| | | 4 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b |
| | | 8 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b, d |
| | | 10 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b |
| | | 11 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b |
| | | 15 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b |
| | | 22 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b |
| | | 28 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b, d, g, i |
| | | 29 | _____ mg | _____ mg | _____ mg _____ mg | _____ IU | _____ mg | a, b, d, g, i |
| | | 35 | Begin Consolidation therapy (Section 4.46) on Day 36 or when blood count parameters are met (whichever occurs later). Patients who have progressive disease go off-protocol therapy. | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.42.2 Required Observations in Induction – Non-DS B-LLy

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Hx/PE/Wt/Ht/BSA (Note: Height is only required at the beginning of this course.)
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopspin
- e. Bilateral Bone Marrow Aspirate and Biopsy at diagnosis
- f. *TPMT* and *NUDT15* genotype (*TPMT* highly recommended for all subjects; *NUDT15* is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).
- g. CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement and no PET obtained), and repeat CT of involved areas at EOI.
- h. Diagnostic biopsy/cytology
- i. For patients who consent, submit specimens for Biobanking for Future Research for B-LLy patients. Refer to [Section 14.8](#) for additional details.
- j. For patients who consent, submit bone marrow for Minimal Marrow Disease study. Refer to [Section 14.9](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.42.3 Induction Treatment Details – Non-DS B-LLy

Non-DS B-LLy patients will receive common Induction therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)

Days: Day 1 or at the time of diagnostic LP

May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1-1.99 | 30 mg |
| 2-2.99 | 50 mg |
| ≥ 3 | 70 mg |

Use preservative free formulation. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.4](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8, 15 and 22

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV)

Days 1 - 28 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Pegaspargase: IV over 1 - 2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#).

Methotrexate: IT

Days 8 and 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

For B-LILY patients, following completion of Induction, begin Consolidation therapy ([Section 4.43](#)) on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later). Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician. Patients with Progressive Disease are off-protocol therapy.

4.43 DS B-LL_y – Induction

| | |
|---|---------------------------------------|
| 4.43.1 Therapy Delivery Map – INDUCTION DS B-LL _y Induction therapy in Section 4.45.1 is for DS B-LL _y patients. Induction therapy is 5 weeks (35 days). | Patient COG ID number <hr/> DOB |
|---|---------------------------------------|

Treatment details and criteria to start are in [Section 4.43.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|-------------------------------------|--|--|--|
| Intrathecal Cytarabine (IT ARAC) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg | Given at time of diagnostic LP <u>OR</u> Day 1* | See Section 4.43.3 for administration guidelines. Note age-based dosing. |
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 8, 15 & 22 | ⁺ Or infusion via minibag as per institutional policy. Maximum dose: 2 mg |
| Dexamethasone (DEX) For patients < 10 years ONLY | PO (may be given IV) | 3 mg/m ² /dose BID | 1-28 (do not taper) | Total daily dose: 6 mg/m ² /day See Section 4.43.3 for administration guidelines. |
| PredniSO(LO)NE (PRED) For patients ≥ 10 years ONLY | PO (may be given IV) | 30 mg/m ² /dose BID | 1-28 (do not taper) | Total daily dose: 60 mg/m ² /day Note: IV methylprednisolone may be substituted for predniSO(LO)NE at 80% of the dose. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Note: pegaspargase should be administered on Day 4. Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |
| Intrathecal Methotrexate (IT MTX) | IT | <u>Age (yrs)</u> <u>Dose</u> 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 8 and 29 | See Section 4.43.3 for administration guidelines. Note age-based dosing Note: All patients receive Day 8 and 29 IT MTX regardless of CSF evaluation. |
| Leucovorin (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 9 & 30 | 24 & 30 hours after each IT MTX. See Section 4.43.3 for administration guidelines. |

Continue to the next page for the therapy log.

| 4.43.1 Therapy Delivery Map – INDUCTION DS B-LLy Induction therapy in Section 4.45.1 is for DS B-LLy patients. Induction therapy is 5 weeks (35 days). | | | | | | | | Patient COG ID number <hr/> DOB | |
|---|------------|-----------------------------|--|---------------|-----------------------|--------------|---------|---------------------------------------|---------------|
| Date Due | Date Given | Day | Ht cm | Wt kg | BSA m ² | | | | |
| IT ARAC mg | VCR mg | DEX (< 10 yrs old) mg mg | PRED (\geq 10 yrs old) mg mg | PEG-ASP IU | IT MTX mg | LCV mg mg | Studies | | |
| Enter calculated dose above and actual dose administered below | | | | | | | | | |
| -2/-1/0/LP* mg mg | | | | | | | | | |
| 1 | | | mg mg | mg mg | | | | | a-i, k |
| 4 | | | | | IU | | | | |
| 8 | | | | | | mg | | | a, b, d |
| 9 | | | | | | | mg mg | | |
| 15 | | | | | | | | | a, b |
| 22 | | | | | | | | | a, b |
| 28 | | | | | | | | | |
| 29 | | | | | | mg | | | a, b, d, h, j |
| 30 | | | | | | | mg mg | | |
| 35 | | | Begin Consolidation therapy (Section 4.46) on Day 36 or when blood count criteria have been met (whichever occurs later). Patients who have progressive disease go off-protocol therapy. | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.43.2 Required Observations in Induction – DS B-LLy

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

- a. Hx/PE/Wt/Ht/BSA (Note: Height is only required at the beginning of this course.)
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopspin
- e. IgG
- f. Bilateral Bone Marrow Aspirate and Biopsy at diagnosis
- g. *TPMT* and *NUDT15* genotype (*TPMT* highly recommended for all subjects; *NUDT15* is highly recommended for subjects of Hispanic/Native American or East Asian ancestry, and optional for all other subjects).
- h. CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement and no PET obtained), repeat CT of involved areas at EOI.
- i. Diagnostic biopsy/cytology
- j. For patients who consent, submit specimens for Biobanking for Future Research for B-LLy patients. Refer to [Section 14.8](#) for additional details.
- k. For patients who consent, submit bone marrow for Minimal Marrow Disease study. Refer to [Section 14.9](#) for additional details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.43.3 Induction Treatment Details – DS B-LLy

DS B-LLy patients will receive common Induction therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Cytarabine: Intrathecal (IT)

Days: Day 1 or at the time of diagnostic LP

May be given up to 72 hours prior to the start of protocol therapy for patient convenience.

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1-1.99 | 30 mg |
| 2-2.99 | 50 mg |
| ≥ 3 | 70 mg |

Use preservative free formulation. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.4](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8, 15 and 22

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO (may be given IV) – Patients < 10 years ONLY

Days: 1 - 28 (do not taper)

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

PredniSO(LO)NE: PO (may be given IV^) – Patients ≥ 10 years ONLY

Days 1 - 28 (do not taper)

Dose: 30 mg/m²/dose BID (i.e., total daily dose: 60 mg/m²/day, divided BID)

^Note: If a patient is unable to take predniSONE or prednisoLONE by mouth, IV methylprednisolone may be given at 80% of the oral dose.

Pegaspargase: IV over 1 - 2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modifications in [Section 5.2](#)).

Methotrexate: IT

Days 8 and 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV

Days 9 and 30

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

For DS B-LLY patients, following completion of Induction, begin Consolidation therapy ([Section 4.44](#)) on Day 36 (7 days following Day 29 LP) or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later). Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician. Patients with Progressive Disease are off-protocol therapy.

4.44 All B-LLY (including DS patients) – Consolidation

| | |
|---|--------------------------------|
| 4.44.1 Therapy Delivery Map – CONSOLIDATION | Patient COG ID number _____ |
| Consolidation therapy in this TDM is for all B-LLY patients. Consolidation therapy is 4 weeks (28 days). Begin Consolidation on Day 36 of Induction therapy or when criteria to start are met (whichever occurs later). | DOB _____ |

Treatment details and criteria to start are in [Section 4.44.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|------------------------------------|---|-----------|---|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1 ONLY | + Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily | 1-28 | See Section 4.44.3 and Appendix III for administration guidelines. See Section 5.8 for suggested dose based on <i>TPMT</i> and <i>NUDT15</i> status. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 1, 8 & 15 | See Section 4.44.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2, 9 & 16 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.44.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR mg | MP mg | IT MTX mg | LCV (DS pts only) mg mg | Studies |
|--|------------|-----|--|----------|--------------|---------------------------------|---------|
| Enter calculated dose above and actual dose administered below | | | | | | | |
| | | 1 | _____ mg | _____ mg | _____ mg | _____ mg _____ mg | a-d, f |
| | | 2 | | | | _____ mg** _____ mg** | |
| | | 8 | | | _____ mg | _____ mg _____ mg | d |
| | | 9 | | | | _____ mg** _____ mg** | |
| | | 15 | | | _____ mg | _____ mg | d |
| | | 16 | | | | _____ mg** _____ mg** | |
| | | 22 | | | | | |
| | | 28 | | | | | e |
| | | 29 | Begin IM I (Section 4.47) on Day 29 or when blood count parameters are met (whichever occurs later). | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.44.2 Required Observations in Consolidation – All B-LLy (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. For those positive at the end of Induction: CT (neck, chest, abdomen & pelvis), CXR, PET, bone scan (if bone involvement and no PET obtained)
- f. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.44.3 Consolidation Treatment Details – All B-Lly (including DS patients)

For all B-Lly patients, Consolidation therapy begins on Day 36 of Induction (7 days following Day 29 LP) or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later). Patients with severe systemic illness, who will not tolerate initiation of Consolidation on Day 1 or without count recovery, should begin this phase of therapy when appropriate in the judgment of the treating physician.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Day 1 ONLY

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Mercaptopurine: PO

Days 1 - 28

Dose: 75 mg/m²/dose once daily

See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation). Do not escalate dose based on blood counts during this cycle (see [Section 5.8](#)).

Methotrexate: Intrathecal (IT)

Days 1, 8 & 15

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: Oral (PO) or Intravenous (IV) FOR DOWN SYNDROME PATIENTS ONLY

Days 2, 9 and 16

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [Section 5.0](#) for Dose Modifications based on Toxicities.

Following completion of Consolidation therapy, the next course, Interim Maintenance I ([Section 4.45](#)), should begin on Day 29 or when peripheral counts recover with an ANC ≥ 750/µL and platelets ≥ 75,000/µL (whichever occurs later).

Note: Following completion of Consolidation, B-LLy patients who fail to achieve CR (see [Section 18.0](#) for definitions) are off-protocol therapy with the exception of B-LLy patients with bone primaries who will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation.

4.45 All B-LLy (including DS patients) – Interim Maintenance I EscMTX

| | | |
|--|--|--------------------------------|
| 4.45.1 Therapy Delivery Map – INTERIM MAINTENANCE I (IM I EscMTX) | | Patient COG ID number _____ |
| IM I therapy in this TDM is for all B-LLy patients. IM I therapy is 8 weeks (56 days). Begin IM I on Day 29 of Consolidation or when criteria to start are met (whichever occurs later). | | DOB _____ |

Treatment details and criteria to start are in [Section 4.45.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--|--|--------------------|--|
| VinCRIStine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | Starting dose 100 mg/m ² & escalate by 50 mg/m ² /dose | 1, 11, 21, 31 & 41 | See Section 4.45.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) Dose 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥ 9 15 mg | 31 ONLY | See Section 4.45.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.45.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ____mg | IV MTX ____mg (escalating dose) | IT MTX ____mg | LCV (DS pts only) ____mg ____mg | Studies |
|---|------------|-----|--|---------------------------------------|------------------|------------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ____mg | ____mg | | | a-c, e |
| | | 11 | ____mg | ____mg | | | a-c |
| | | 21 | ____mg | ____mg | | | a-c |
| | | 31 | ____mg | ____mg | ____mg | | a-d |
| | | 32 | | | | ____mg** ____mg** | |
| | | 41 | ____mg | ____mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Delayed Intensification (Section 4.48) on Day 57 or when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

**4.45.2 Required Observations in Interim Maintenance I with EscMTX – All B-LLy
(including DS patients)**

- a. Hx/PE/Wt/Ht/BSA (Note: Height is only required at the beginning of this course.)
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopspin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.45.3 Interim Maintenance I with EscMTX Treatment Details – All B-LLY (including DS patients)

For all B-LLY patients, IM I begins on Day 29 of Consolidation or when peripheral counts recover with an ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- E) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.
1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRIStine. Proceed to subsequent methotrexate and vinCRIStine doses in 10 days.
 2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give vinCRIStine (and IT methotrexate if day 31) and pegaspargase (if due). Pegaspargase may be given on the same day as the vinCRIStine dose if the IV methotrexate is omitted. Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRIStine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRIStine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled vinCRIStine. For subsequent doses, resume standard methotrexate escalation.
- F) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of methotrexate as previously (i.e., no escalation).
- G) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate methotrexate by 50 mg/m²/dose.
- H) Do not escalate methotrexate dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRIStine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days 1, 11, 21, 31 and 41

Starting dose of 100 mg/m²/dose; thereafter, escalate by 50 mg/m²/dose

Methotrexate: IT

Day 31 ONLY

Age-based dosing:

| <u>Age (yrs)</u> | <u>Dose</u> |
|------------------|-------------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY

Days 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by

timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Interim Maintenance I, Delayed Intensification ([**Section 4.46**](#)) should begin on Day 57 of Interim Maintenance I or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.46 All B-LLy (including DS patients) – Delayed Intensification

| | |
|--|--|
| 4.46.1 <u>Therapy Delivery Map – Delayed Intensification (DI) Part 1</u> | Patient COG ID number _____ DOB _____ |
|--|--|

Treatment details and criteria to start are in [Section 4.46.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|-------------------------------------|--|---|--|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1, 8 & 15 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg |
| DOXOrubicin (DOXO) | IV push/infusion over 1-15 min | 25 mg/m ² /dose | 1, 8 & 15 | See Section 4.46.3 for administration guidelines. *Obtain ECHO (e) prior to the first dose of DOXO. |
| Dexamethasone (DEX) | PO (may be given IV) | 5 mg/m ² /dose BID | 1-7 & 15-21 | Total daily dose: 10 mg/m ² /day See Section 4.46.3 for administration guidelines. |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) 1-1.99 2-2.99 3-8.99 ≥ 9 | Dose 8 mg 10 mg 12 mg 15 mg | 1 See Section 4.46.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.46.3 for administration guidelines. |
| Pegaspargase (PEG-ASP) | IV over 1-2 hours (or IM injection) | 2,500 International Units/m ² /dose | 4 | Administer through the tubing of a freely infusing solution of D ₅ W or 0.9% NaCl |

| | | Ht cm | Wt kg | BSA m ² | | | | | |
|---|------------|-------|--------|--------------------|--------|-----------|------------|-------------------------|---------|
| Date Due | Date Given | Day | VCR mg | DOXO mg | DEX mg | IT MTX mg | PEG-ASP IU | LCV (DS pts only) mg mg | Studies |
| Enter calculated dose above and actual dose administered below. | | | | | | | | | |
| | | 1 | ___ mg | ___ mg | ___ mg | ___ mg | ___ mg | ___ mg ___ mg | a-f* |
| | | 2 | | | | | | | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 6 | | | | | | | |
| | | 7 | | | | | | | |
| | | 8 | ___ mg | ___ mg | | | | | b |
| | | 15 | ___ mg | ___ mg | ___ mg | ___ mg | ___ IU | ___ mg ___ mg | b |
| | | 16 | | | | | | | |
| | | 17 | | | | | | | |
| | | 18 | | | | | | | |
| | | 19 | | | | | | | |
| | | 20 | | | | | | | |
| | | 21 | | | | | | | |
| | | 22 | | | | | | | |

This Therapy Delivery Map continues on the next page.

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.46.1 Therapy Delivery Map – Delayed Intensification (DI) Part 2

DI therapy in this TDM is for all B-LLy patients. DI therapy is 8 weeks (56 days). Begin DI Part 2 on Day 29 of DI Part 1 or when criteria to start are met (whichever occurs later). **Patients should have ANC ≥ 750/ μ L and platelets ≥ 75,000/ μ L to begin Day 29 of DI.**

Patient COG ID number _____

DOB _____

Treatment details and criteria to start are in [Section 4.46.3](#). This Therapy Delivery Map is three (3) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|-----------------------------------|--------------------------|--|---|--|
| Cyclophosphamide (CPM) | IV over 30-60 minutes | 1,000 mg/ m^2 /dose | 29 | See Section 4.46.3 for administration guidelines |
| Thioguanine (TG) | PO | 60 mg/ m^2 /dose daily | 29-42 | See Section 4.46.3 & Appendix IV for administration guidelines See Section 5.10 for suggested dose based on TPMT and NUDT15 status. |
| Cytarabine (ARAC) | IV over 1-30 min or SubQ | 75 mg/ m^2 /dose daily | 29-32 & 36-39 | |
| Intrathecal Methotrexate (IT MTX) | IT | Age (yrs) 1-1.99 2-2.99 3-8.99 ≥ 9 | Dose 8 mg 10 mg 12 mg 15 mg | 29 See Section 4.46.3 for administration guidelines Note age-based dosing |
| Leucovorin** (LCV) | PO or IV | 5 mg/ m^2 /dose q6hr x 2 | 30 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.46.3 for administration guidelines. |

Ht _____ cm Wt _____ kg BSA _____ m^2

| Date Due | Date Given | Day | CPM ____mg | TG ____mg | ARAC ____mg | IT MTX ____mg | LCV (DS pts only) ____mg | Studies |
|--|------------|-----|--|--------------|----------------|------------------|--------------------------------|---------|
| Enter calculated dose above and actual dose administered below. | | | | | | | | |
| | | 29 | ____mg | ____mg | ____mg | ____mg | | a-d, f |
| | | 30 | | | | | ____mg** ____mg** | |
| | | 31 | | | | | | |
| | | 32 | | | | | | |
| | | 36 | | | | ____mg | | b |
| | | 37 | | | | | | |
| | | 38 | | | | | | |
| | | 39 | | | | | | |
| | | 40 | | | | | | |
| | | 41 | | | | | | |
| | | 42 | | | | | | |
| | | 43 | | | | | | |
| | | 50 | | | | | | |
| | | 56 | | | | | | |
| | | 57 | Begin Interim Maintenance II therapy (Section 4.49) on Day 57 or when blood count parameters are met (whichever occurs later). | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) for Supportive Care Guidelines

All B-LLy – Delayed Intensification

4.46.2 Required Observations in Delayed Intensification – All B-Lly (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. Echocardiogram **prior to the first dose of DOXOrubicin**
- f. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.46.3 Delayed Intensification Treatment Details – All B-Lly (including DS)

Delayed Intensification is given in 2 parts.

For all B-Lly patients (including DS), Delayed Intensification Part 1 begins on Day 57 of Interim Maintenance I or when peripheral counts recover with ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

Interruption and/or Modifications of Therapy

All therapy should be interrupted for presumed or proven serious infection. Myelosuppression alone does not delay therapy on Days 2 - 28 or Days 30 - 43, but Day 29 does not begin until ANC \geq 750/ μ L and platelets \geq 75,000/ μ L.

Dosing should be based on actual BSA. There is a maximum dose of:

- vinCRISTine, which is capped at a maximum dose of 2 mg

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

Delayed Intensification Part 1

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 8 and 15

Dose: 1.5 mg/m²/dose (maximum dose: 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

DOXOrubicin: IV push/infusion over 1 - 15 minutes

Days 1, 8 and 15

Dose: 25 mg/m²/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl and that it is infused into a large vein.

Dexamethasone: PO (may give intravenous IV)

Days 1 - 7 and 15 - 21

Dose: 5 mg/m²/dose BID (i.e., total daily dose: 10 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Methotrexate: Intrathecal (IT)

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY

Days 2

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Pegaspargase: IV over 1 - 2 hours (may also be given IM)

Day 4

Dose: 2,500 International Units/m²/dose

Administer over 1-2 hours through the tubing of a freely infusing solution of D₅W or 0.9% NaCl.

See dose modification in [Section 5.2](#).

Delayed Intensification Part 2

Begin Delayed Intensification Part 2 on Day 29 or when peripheral counts recover with ANC $\geq 750/\mu\text{L}$ and platelets $\geq 75,000/\mu\text{L}$ (whichever occurs later).

Cyclophosphamide: IV over 30 - 60 minutes

Day 29

Dose: 1,000 mg/m²/dose

Mesna is not required for this dose of cyclophosphamide, but may be administered at institutional discretion.

Thioguanine: PO

Days 29 - 42

Dose: 60 mg/m²/dose/once daily*

*See [Section 5.10](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. Adjust dose using $\frac{1}{2}$ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m²/week as possible. See [Appendix IV](#) for details.

Cytarabine: IV over 1 - 30 minutes or subcutaneous

Days 29 - 32 and 36 - 39

Dose: 75 mg/m²/dose once daily

When given subcutaneously, reconstitute to a concentration not to exceed 100 mg/mL. Rotate injection sites to thigh, abdomen, and flank regions. Avoid repeated administration to a single site. Aspirate prior to injection to avoid injection into a blood vessel.

Methotrexate: IT

Day 29

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY

Day: 30

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Delayed Intensification, Interim Maintenance II therapy ([**Section 4.47**](#)) starts on Day 57 or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L (whichever occurs later).

4.47 All B-LLy (including DS patients) – Interim Maintenance II EscMTX

| | |
|---|--|
| 4.47.1 Therapy Delivery Map – INTERIM MAINTENANCE II | Patient COG ID number _____ DOB _____ |
| IM II therapy in this TDM is for all B-LLy patients. IM II therapy is 8 weeks (56 days). Begin IM II on Day 57 of Delayed Intensification or when criteria to start are met (whichever occurs later). | |

Treatment details and criteria to start are in [Section 4.47.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|-----------------------------------|--|--|--------------------|--|--------|------|--------|-------|--------|-------|-----|-------|--------|--|
| VinCRISTine (VCR) | IV push over 1 minute ⁺ | 1.5 mg/m ² /dose | 1, 11, 21, 31 & 41 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg | | | | | | | | | | |
| Methotrexate (MTX) | IV over 2-5 min (undiluted) or 10-15 min (diluted) | ___mg/m ² /dose | 1, 11, 21, 31 & 41 | Starting dose for IM II is two-thirds of the maximum tolerated dose attained in IM I. Thereafter, escalate by 50 mg/m²/dose . See Section 4.47.3 for details. | | | | | | | | | | |
| Intrathecal Methotrexate (IT MTX) | IT | <table> <thead> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>≥ 9</td> <td>15 mg</td> </tr> </tbody> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | ≥ 9 | 15 mg | 1 & 31 | See Section 4.47.3 for administration guidelines Note age-based dosing |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| ≥ 9 | 15 mg | | | | | | | | | | | | | |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 & 32 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.47.3 for administration guidelines. | | | | | | | | | | |

Enter Cycle #: _____ Ht _____ cm Wt _____ kg BSA _____ m²

| Date Due | Date Given | Day | VCR ___mg | IV MTX ___mg (escalating dose) | IT MTX ___mg | LCV (DS pts only) ___mg ___mg | Studies |
|---|------------|-----|---|--------------------------------------|-----------------|----------------------------------|---------|
| Enter calculated dose above and actual administered dose below | | | | | | | |
| | | 1 | ___mg | ___mg | ___mg | | a-e |
| | | 2 | | | | ___mg** ___mg** | |
| | | 11 | ___mg | ___mg | | | a-c |
| | | 21 | ___mg | ___mg | | | a-c |
| | | 31 | ___mg | ___mg | ___mg | | a-e |
| | | 32 | | | | ___mg** ___mg** | |
| | | 41 | ___mg | ___mg | | | a-c |
| | | 56 | | | | | |
| | | 57 | Begin Maintenance on Day 57 (Section 4.50) when blood count parameters are met (whichever occurs later) | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

**4.47.2 Required Observations in Interim Maintenance II with EscMTX – All B-LLy
(including DS patients)**

- a. Hx/PE/Wt/Ht/BSA
- b. CBC/diff/platelets
- c. Creatinine, total bilirubin, ALT
- d. CSF cell count and cytopsin (obtain with each IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.47.3 Interim Maintenance II with EscMTX Treatment Details – All B-LLy (including DS patients)

For all B-LLy patients (including DS), Interim Maintenance II therapy starts on Day 57 of Delayed Intensification, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

Interruption and/or Modification of Therapy

All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts prior to each dose of methotrexate.

- A) If ANC is $<$ 500/ μ L or platelets $<$ 50,000/ μ L, hold all chemotherapy and repeat blood counts in 4 days.
 1. In 4 days, if ANC \geq 500/ μ L AND platelets \geq 50,000/ μ L, give same dose of methotrexate as previously (no escalation) with scheduled vinCRIStine. Proceed to subsequent methotrexate and vinCRIStine doses in 10 days.
 2. In 4 days, if ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, omit methotrexate dose. Give vinCRIStine (and IT methotrexate if day 31) and pegaspargase (if due). Pegaspargase may be given on the same day as the vinCRIStine dose if the IV methotrexate is omitted. Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRIStine doses. DO NOT make up omitted dose of methotrexate.
 - a) If after 7 days, ANC \geq 500/ μ L and platelets \geq 50,000/ μ L resume methotrexate at 80% of the final administrated dose and administer scheduled vinCRIStine. For subsequent doses, resume standard methotrexate escalation.
 - b) If after 7 days ANC is still $<$ 500/ μ L OR platelets $<$ 50,000/ μ L, hold therapy until counts recover to ANC $>$ 500/ μ L and platelets $>$ 50,000/ μ L. When ANC \geq 500/ μ L and platelets \geq 50,000/ μ L, resume at 80% of the final administered dose and administer scheduled vinCRIStine. For subsequent doses, resume standard methotrexate escalation.
- B) If ANC \geq 500/ μ L but $<$ 750/ μ L and/or platelets \geq 50,000/ μ L but $<$ 75,000/ μ L, give same dose of methotrexate as previously (i.e., no escalation).
- C) If ANC \geq 750/ μ L and platelets \geq 75,000/ μ L escalate methotrexate by 50 mg/m²/dose.
- D) Do not escalate methotrexate dose and resume at 80% of final dose if it had been delayed secondary to myelosuppression and/or Grade 3 mucositis. For subsequent doses, resume standard escalation.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRIStine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1, 11, 21, 31, and 41

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRIStine and vinBLASTine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Methotrexate: IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted)

Days 1, 11, 21, 31 and 41

Starting dose is two-thirds of the maximum tolerated dose attained in Interim Maintenance I. For example, if a patient has toxicity at 250 mg/m² on Interim Maintenance I, the starting dose for Interim Maintenance II will be two thirds of 200 mg/m² (or 130 mg/m²) IV over 2 - 5 minutes (undiluted) or over 10 - 15 minutes (diluted). Subsequent doses will be escalated by 50 mg/m² every 10 days (\pm 2 days) for 4 doses, to toxicity Days 11, 21, 31 and 41.

Methotrexate: IT

Days 1 and 31

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| \geq 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV FOR DOWN SYNDROME PATIENTS ONLY

Days 2 & 32

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

See [**Section 5.0 for Dose Modifications based on Toxicities.**](#)

Following completion of Interim Maintenance II, Maintenance therapy ([**Section 4.48**](#)) begins on Day 57, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later.

4.48 All B-LLy (including DS patients) – Maintenance

4.48.1 Therapy Delivery Map – MAINTENANCE

Maintenance therapy in this TDM is for all B-LLy patients. Each cycle of Maintenance therapy is 12 weeks (84 days). Begin Maintenance therapy on Day 57 of IM II or when criteria to start are met (whichever occurs later). Use a copy of this TDM for all Maintenance cycles.

Patient COG ID number _____
DOB _____

Treatment details and criteria to start are in [Section 4.48.3](#). This Therapy Delivery Map is two (2) pages in length.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | | | | | | | | | | |
|-----------------------------------|---------------------------------|---|--|---|--------|------|--------|-------|--------|-------|-----|-------|---|--|
| VinCRISTine (VCR) | IV push over 1 min ⁺ | 1.5 mg/m ² /dose | 1 | ⁺ Or infusion via minibag as per institutional policy Maximum dose: 2 mg | | | | | | | | | | |
| Dexamethasone (DEX) | PO | 3 mg/m ² /dose BID | 1-5 | Total daily dose: 6 mg/m ² /day | | | | | | | | | | |
| Mercaptopurine (MP) | PO | 75 mg/m ² /dose daily* | 1-84 | *See Section 5.8 for suggested starting dose based on TPMT and NUDT15 status See Section 4.48.3 & Appendix III for administration guidelines | | | | | | | | | | |
| Intrathecal Methotrexate (IT MTX) | IT | <table border="0"> <tr> <th>Age (yrs)</th> <th>Dose</th> </tr> <tr> <td>1-1.99</td> <td>8 mg</td> </tr> <tr> <td>2-2.99</td> <td>10 mg</td> </tr> <tr> <td>3-8.99</td> <td>12 mg</td> </tr> <tr> <td>≥ 9</td> <td>15 mg</td> </tr> </table> | Age (yrs) | Dose | 1-1.99 | 8 mg | 2-2.99 | 10 mg | 3-8.99 | 12 mg | ≥ 9 | 15 mg | 1 | See Section 4.48.3 for administration guidelines Note age-based dosing |
| Age (yrs) | Dose | | | | | | | | | | | | | |
| 1-1.99 | 8 mg | | | | | | | | | | | | | |
| 2-2.99 | 10 mg | | | | | | | | | | | | | |
| 3-8.99 | 12 mg | | | | | | | | | | | | | |
| ≥ 9 | 15 mg | | | | | | | | | | | | | |
| Leucovorin** (LCV) | PO or IV | 5 mg/m ² /dose q6hr x 2 | 2 | **Down-syndrome patients only. 24 & 30 hours after each IT MTX. See Section 4.48.3 for administration guidelines. | | | | | | | | | | |
| Methotrexate (MTX) | PO | 20 mg/m ² /dose | Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 | Omit Day 1 dose as it coincides with IT MTX | | | | | | | | | | |

| Enter Cycle #: | | | Ht | cm | Wt | kg | BSA | m ² | |
|----------------|------------|-----|--|-----------|-------|-----------|-----------|----------------|---------|
| Date Due | Date Given | Day | VCR mg | DEX mg mg | MP mg | IT MTX mg | LCV mg mg | PO MTX mg | Studies |
| | | 1 | mg | mg# mg# | mg | mg | mg** mg** | | a-e |
| | | 2 | | | | | | | |
| | | 3 | | | | | | | |
| | | 4 | | | | | | | |
| | | 5 | | | | | | | |
| | | 8 | | | | | mg | | |
| | | 15 | | | | | mg | | |
| | | 22 | | | | | mg | | |
| | | 29 | | | | | mg | a, b, e | |
| | | 36 | | | | | mg | | |
| | | 43 | | | | | mg | | |
| | | 50 | | | | | mg | | |
| | | 57 | | | | | mg | a, b, e | |
| | | 64 | | | | | mg | | |
| | | 71 | | | | | mg | | |
| | | 78 | | | | | mg | | |
| | | 84 | | | | | | | |
| | | 85 | Continue Maintenance cycles until 2 years from the start of Interim Maintenance I, regardless of sex | | | | | | |

See [Section 5.0](#) for Dose Modifications for Toxicities and [Appendix IX](#) Supportive Care Guidelines.

4.48.2 Required Observations in Maintenance – All B-LLy (including DS patients)

- a. Hx/PE/Wt/Ht/BSA
- b. CBC with diff/platelets
- c. Creatinine, total bilirubin & ALT
- d. CSF cell count and cytopsin (obtain with IT administration)
- e. IgG for Down-syndrome patients only

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments

4.48.3 Maintenance Treatment Details—All B-LLy (including DS patients)

For all B-LLy patients (including DS), Maintenance therapy starts on Day 57 of IM II, or when peripheral counts recover to ANC \geq 750/ μ L and platelets \geq 75,000/ μ L, whichever occurs later. This count recovery applies to Maintenance Cycle 1 only.

Maintenance consists of 12 week cycles repeated until total duration of therapy of 2 years from the start of IM I with Esc MTX is reached for both males and females. Therapy may be stopped on anniversary date if the 5 day dexamethasone is completed for the cycle (i.e., complete all 5 days of dexamethasone before ending therapy). Otherwise continue current cycle through dexamethasone administration.

The administration schedule below describes one 12 week cycle of Maintenance therapy.

Dosing should be based on actual BSA. There is a maximum dose of:

- **vinCRISTine, which is capped at a maximum dose of 2 mg**

See the Chemotherapy Administration Guidelines (CAG) for children on the COG website at:

https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy

Days 1

Dose: 1.5 mg/m²/dose (maximum 2 mg)

Special precautions: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes.”

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine. VinCRISTine is available in a liposomal formulation (vinCRISTine sulfate liposomal injection, VSLI, Marqibo®). The conventional and liposomal formulations are NOT interchangeable; use of the liposomal formulation is not permitted in this trial.

Dexamethasone: PO

Days 1 – 5 (do not taper).

Dose: 3 mg/m²/dose BID (i.e., total daily dose: 6 mg/m²/day)

Each dose may be adjusted upward to the nearest 0.25 mg as necessary for tablet size. Liquid preparations are also acceptable. Intravenous preparation (6 mg/m²/day, divided BID) may be used temporarily as needed.

Mercaptopurine: PO

Days 1 - 84

Dose: 75 mg/m²/dose once daily*

*See [Section 5.8](#) for suggested starting dose based on *TPMT* and *NUDT15* status (if status is known)

Administer at the same time every day. Tablets are scored and doses can be rounded to half tablet. A liquid formulation is available (see drug monograph in [Section 6.8](#)). If using tablets, adjust dose using ½ tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 525 mg/m²/week as possible. See [Appendix III](#) for details (Note: The mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation).

Methotrexate: IT

Day 1

Age-based dosing:

| Age (yrs) | Dose |
|-----------|-------|
| 1 – 1.99 | 8 mg |
| 2 – 2.99 | 10 mg |
| 3 – 8.99 | 12 mg |
| ≥ 9 | 15 mg |

Use preservative free formulation. The volume to be given IT should be in the range of 5-10 mL. The volume of CSF removed should be equal to at least half the volume delivered (see drug monograph in [Section 6.9](#)).

Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Leucovorin: PO or IV

Days: 2**

Dose: 5 mg/m²/dose x 2 doses given 24 and 30 hours after IT methotrexate

****FOR DOWN SYNDROME PATIENTS ONLY**

Leucovorin rescue will be given after intrathecal methotrexate for patients with Down syndrome during ALL applicable phases of therapy. The first dose to be given 24 hours after the lumbar puncture and the second dose to be given approximately 30 hours after the lumbar puncture.

Administer with or without food. Administer doses on schedule as determined by timing of methotrexate administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing

schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed.

Methotrexate: PO

Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78. **Omit Day 1 dose as it coincides with IT MTX.**

Dose: 20 mg/m²/dose weekly

Oral bioavailability is highly variable and dose-dependent; decreased absorption occurs at higher doses (pediatric patients: >40 mg/m²; adult patients: >80 mg/m²) possibly due to saturation effect.

See [Section 5.0 for Dose Modifications based on Toxicities.](#)

Maintenance consists of 12 week cycles until a total duration of therapy of 2 years from the start of Interim Maintenance I is reached for both males and females.

5 DOSE MODIFICATIONS FOR TOXICITIES

Notify the Study Chairs at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order with IND agent listed first.

5.1 Blinatumomab

The most frequent serious adverse events noted in patients treated with blinatumomab to date are disorders of the nervous system, both peripheral and central, and systemic cytokine release syndrome (CRS), though both are less likely to occur in patients with lower burden of disease at the time of administration. Both categories of events are more likely to occur within the first week of treatment with blinatumomab, and both categories of events are usually reversible and manageable with attentive supportive care.

AEs related to blinatumomab that require treatment interruption (according to table below) and do not resolve to CTCAE \leq Grade 1 within 14 days will require permanent discontinuation of blinatumomab treatment. The exception to this is Grade 3 neurologic AEs, which if not resolved within 7 days, also require permanent discontinuation of blinatumomab. If the patient is otherwise eligible to continue protocol therapy (standard chemotherapy), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy.

NOTE: Blinatumomab must be permanently discontinued for Grade 4 Central Nervous System/Psychiatric, Grade 4 thromboembolic, or Grade 4 CRS AEs. Blinatumomab may be resumed at a reduced dose (**5 mcg/m²/day, max 9 mcg/day**) to complete the 28 day course (not counting the duration of treatment interruption) with dexamethasone premedication (Section 4.0) for other AE(s) that **DO resolve within 14 days**.

For patients who experience a seizure, **dose escalation beyond 5 mcg/m²/day (max 9 mcg/day) will NOT be permitted** for subsequent cycles. For patients who experienced other AEs related to blinatumomab, subsequent cycles will begin at the reduced dose of **5 mcg/m²/day (max 9 mcg/day)**, **but the infusion may be increased to 15 mcg/m²/day (max 28 mcg/day)** after 7 days if there are no additional significant blinatumomab-related AEs.

A second occurrence of the same AE that requires interruption **will require permanent discontinuation** of blinatumomab. If the patient is otherwise eligible to continue protocol therapy (standard chemotherapy), then the patient may, at the discretion of the investigator and family, continue to receive protocol therapy.

The resumption of the infusion at the reduced dose should be accompanied by **dexamethasone premedication** as indicated in the relevant subsection of [Section 4.0](#), and should be performed in the hospital under supervision of the investigator. Patients should be observed for at least 72 hours after the start of the infusion at the reduced dose before considering discharge to the outpatient setting.

Table: Dose modifications for Adverse Events (AE) Possibly, Probably or Definitely Related to Blinatumomab:

| Category: AE (CTCAE v5.0) | AE Grade | Stop Infusion? | Supportive Care (in addition to institutional guidelines)* | Restart allowed (with dex premed) if Gr 1 within 14 days? | Restarting dose (5 mcg/m ² /day) Max: 9 mcg/day | Escalation to 15 mcg/m ² /day after 7 days (with dex premed) in subsequent cycle allowed? Max: 28 mcg/day |
|---|------------|---|---|---|---|---|
| Central Nervous system: Psychiatric ¹ (Confusion, Hallucination, Delirium, Psychosis), Dysarthria, Tremor | 1 | N | CNS | - | - | - |
| | 2 | N | CNS | - | - | - |
| | 3 | Y | CNS, DEX | Y | 5 | Y |
| | 4 | Y | CNS, DEX | N | - | - |
| Central Nervous system: Seizure | 1, 2, 3 | Y | SZ, CNS, DEX | Y | 5 | N |
| | 4 | Y | SZ, CNS, DEX | N | | |
| Immune system: Cytokine release syndrome – NOTE that it is NOT recommended to use the CTCAE grading ³ | 1 | N | | - | - | - |
| | 2 | N, unless patient is unable to tolerate symptoms (e.g., due to other comorbidities) | TOCI, DEX only if patient is unable to tolerate symptoms (e.g., due to other comorbidities) | Y | 5 | Y |
| | 3 | Y | TOCI, DEX | Y | 5 | Y |
| | 4 | Y | TOCI, DEX | N | - | - |
| Blood and lymphatic system ⁴ : Disseminated intravascular coagulation, hemolysis, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura | 1, 2 | N | | - | - | - |
| | 3, 4 | Y | | Y | 5 | Y |
| Blood and lymphatic system ⁵ : All others (lymphopenia, neutropenia, anemia, thrombocytopenia, etc.) | 1, 2, 3, 4 | N | | - | - | - |
| Vascular: Thromboembolic event | 1 | N | | - | - | - |
| | 2, 3 | Y | | Y | 5 | Y |
| | 4 | Y | | N | - | - |
| Investigations ^{6,7} , Metabolism and Nutrition: All | 1, 2, 3, 4 | N | | - | - | - |

| | | | | | | |
|---|-----|---|--|---|---|---|
| (if not considered clinically relevant or responding to routine medical management) | | | | | | |
| Investigations ^{6,7} , Metabolism and Nutrition: All (if clinically relevant and not responding to routine medical management) | 1,2 | N | | - | - | - |
| | 3,4 | Y | | Y | 5 | Y |
| All other AE | 1,2 | N | | - | - | - |
| | 3,4 | Y | | Y | 5 | Y |

Table Footnotes:

¹ Most neurologic AEs associated with blinatumomab are central in nature (e.g., dysarthria, encephalopathy, tremor). Peripheral neurologic AEs are very unlikely to be secondary to blinatumomab, and are far more likely to be secondary to other causes such as vinCRISTine. Discontinuation of blinatumomab secondary to peripheral neurologic AEs should be avoided when possible. Most AEs in the psychiatric disorders category are unlikely to be caused by blinatumomab and generally require supportive care rather than dose modification or discontinuation of blinatumomab (e.g., Insomnia, Depression, Anxiety). Psychiatric AEs that may reflect underlying central nervous system toxicity (e.g., Confusion, Delirium, Hallucinations, Psychosis) are of greater interest, particularly if accompanied by other AEs in the nervous system disorders category.

² Close monitoring of fluid status by intake and output should be undertaken for the first 48 hours of blinatumomab infusion. Efforts to keep patients balanced between intake and output should be maintained, even if diuretic therapy (furosemide or similar) is needed to do this. Careful attention to fluid status may prevent deterioration from capillary leak, however even with meticulous attention some patients may experience pulmonary edema and require more aggressive respiratory support. Treating physicians should use their clinical judgment and institutional standards for whatever supportive care measures are needed during this period of time.

³ Grading of cytokine release syndrome (CRS) severity should be performed according to that of Lee et al. below, which is similar but not identical to that of CTCAE v5.0. As many of the symptoms of CRS overlap with those of other medical complications such as infection, attribution should be carefully considered. Accurate application of this grading system requires clinical judgment to confirm that the symptoms are most likely due to CRS rather than to another medical condition. In all grades of CRS, aggressive supportive care is required. In grade 2 or 3 CRS, careful monitoring of cardiac function is strongly suggested.

| | |
|---------|--|
| Grade 1 | Symptoms are not life threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache) |
| Grade 2 | Symptoms require and respond to moderate intervention Oxygen requirement <40%, or Hypotension responsive to fluids or Grade 2 organ toxicity |
| Grade 3 | Symptoms require and respond to aggressive intervention Oxygen requirement ≥40%, or Hypotension requiring one vasopressor, or Grade 3 organ toxicity or grade 4 transaminitis |
| Grade 4 | Life-threatening symptoms Requirement for urgent intervention, ventilator support, or Grade 4 organ toxicity (excluding transaminitis) |

⁴ In the first days of treatment, transient DIC-like pictures may develop. Because patients are at risk for capillary leak syndrome and cytokine release syndrome, appropriate supportive care with dexamethasone (described above), blood products and factors (packed red cells, platelets, cryoprecipitate, fresh frozen plasma), vitamin K, and/or albumin should be considered according to institutional standards of care. Particularly in the first week of infusion, when the risk of capillary leak and cytokine release is more prominent, appropriate use of blood products and factors is preferred

if laboratory indications suggest the need for replacement, as large volumes of crystalloid fluids tend to exacerbate the capillary leak.

- ⁵ In the first days of treatment, a rapid transient drop in platelets, neutrophils and/or hemoglobin may be observed. These effects are not necessarily cytokine-mediated. Counts typically recover to baseline during treatment, and usually within two weeks of starting blinatumomab. Transfusion of blood and platelets should be performed according to appropriate institutional standards.
- ⁶ In the first days of treatment, transient increases in transaminases up to over 1,000 U/L may develop. These have generally returned to baseline in the 1st week of treatment.
- ⁷ Decrease in serum immunoglobulins have been observed in patients treated with blinatumomab. Intravenous immunoglobulin should be administered according to institutional standards, but is recommended for any patient with a total IgG level below 400. Immunoglobulin must not be administered through the line through which blinatumomab is actively being infused.

* Definitions of supportive care abbreviations:

DEX: Given its potential to interfere with the efficacy of blinatumomab, the use of dexamethasone should be reserved for serious side effects that are unresponsive to other treatments (supportive care, discontinuation of blinatumomab infusion, tocilizumab) and for clinically significant neurologic toxicity. If required, dexamethasone should be administered at a total daily dose of at least 0.2 - 0.4 mg/kg/day (maximum 24 mg per day) administered preferably intravenous divided 3 - 4 times daily for at least 1 day but no more than 4 days. The dose should then be stopped or tapered as clinically indicated.

SZ: Appropriate imaging should be performed to evaluate for possible hemorrhage or thrombosis, and other diagnostic procedures should be performed as clinically appropriate. Prophylactic anticonvulsant treatment with a therapeutic dose of institutional standard agents (e.g., lorazepam, phenytoin, levetiracetam) should be administered if seizures develop, and continued throughout the blinatumomab infusion. Anti-convulsant therapy should be considered starting at least 24 - 48 hours prior to any subsequent blinatumomab infusions, and continuing for the remainder of those treatment cycles. Diagnostic measures to exclude potential infectious causes should be conducted once the patient has stabilized (i.e., a lumbar puncture to evaluate for bacterial, viral or fungal sources should be performed). Any identified pathology should be treated as clinically appropriate.

CNS: A daily finger-nose-finger or writing sample test is recommended according to age-appropriate activities for patients. In adults treated with blinatumomab, it has been found that a daily handwriting sample can often predict future nervous system toxicity before the clinical toxicity develops. Dexamethasone should be used for clinically significant neurologic toxicity. Patients who experience nervous system toxicity in the first cycle typically do not experience it again in subsequent cycles, although it is possible.

TOCI: In patients with CRS who respond to tocilizumab, fever and hypotension often resolve within 6 hours, and pressors and other supportive care measures can be weaned quickly thereafter. In some cases, however, symptoms may not completely resolve, and continued aggressive support may be necessary for several days. If the patient's condition does not improve or stabilize within 24 hours of the tocilizumab dose, administration of a second dose of tocilizumab and/or a second immunosuppressive agent, such as dexamethasone, should be considered. Tocilizumab is generally not used in the management of CNS symptoms without significant hemodynamic instability or other life-threatening symptomatology.

TOCI Suggested Dosing:

- <30 kg: 12 mg/kg
- ≥30 kg: 8 mg/kg (max: 800 mg/dose)

5.2 Asparaginase [Erwinia or Pegaspargase (PEG-Asparaginase)]

Systemic Allergic Reactions/Anaphylaxis:

For severe allergic reaction, discontinue pegaspargase and substitute asparaginase *Erwinia*. Asparaginase *Erwinia* therapy should begin within 72 hours of the pegaspargase reaction or sooner if possible. Asparaginase *Erwinia* dosing: 25,000 international units (IU)/m² IM/IV M-W-F for six doses substituted for each dose of pegaspargase. If asparaginase *Erwinia* is given IV it should be given as a 1-2 hour infusion.

For mild-moderate reversible reaction:

1. If the infusion was completed, consider sending an asparaginase activity level. Note that an asparaginase level of at least 0.1 IU/mL 14 days after administration is considered therapeutic. There are several reports that suggest different thresholds for switching to asparaginase *Erwinia*. The following guidelines are recommendations for switching to asparaginase *Erwinia*, but decisions are ultimately up to the treating clinician.

| Time point after completion of pegaspargase infusion | Asparaginase activity level | Action |
|--|-----------------------------|--|
| 1 hour – 1 day | < 0.5 IU/mL | Substitute asparaginase <i>Erwinia</i> |
| 7 days | < 0.3 IU/mL | Substitute asparaginase <i>Erwinia</i> |
| 14 days | < 0.1 IU/mL | Substitute asparaginase <i>Erwinia</i> |

2. If the infusion was discontinued early, consider re-challenging with pegaspargase after premedication and send asparaginase levels as above.

Premedication with antihistamines in the absence of prior hypersensitivity has been discouraged in the past since antihistamine use may mask the appearance of systemic allergy and fail to alert the provider of the presence of asparaginase neutralizing antibodies. The use of asparaginase activity assays, as described above, are now commercially available and may help determine if neutralizing antibodies are present, thus the use of premedications is left to the discretion of the provider.

If there is a question of silent inactivation, check levels as described above between 1 hour and 7 days after the dose. Subsequent doses of asparaginase should be changed to asparaginase *Erwinia* based on the activity levels described above. Whether the dose after which levels were checked should be substituted with asparaginase *Erwinia* will depend on when the results are received, the patient's clinical status, and what other therapy is being administered, and is ultimately left to the discretion of the treating physician. Of note, asparaginase *Erwinia* is recommended only for pegaspargase hypersensitivity reactions and/or in the presence of silent antibody. It is not recommended as a substitute for pancreatitis, transaminitis, hyperbilirubinemia, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase.

Patients with allergy/anaphylaxis to pegaspargase or silent inactivation of pegaspargase may be eligible to receive recombinant Cristantaspase *Pseudomonas fluorescens* (RC-P), a recombinant *Erwinia chrysanthemi* asparaginase expressed in *Pseudomonas fluorescens*, on COG AALL1931 (JZP458-201) at doses prescribed on that protocol. Patients who have previously received *Erwinia* asparaginase are not eligible for AALL1931.

Coagulopathy/bleeding: If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

Hyperbilirubinemia: Asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. No specific dose adjustment guidelines are provided in the manufacturer's labeling. Below are proposed dose adjustment guidelines from published literature: ⁶⁴

| Direct Bilirubin | Dose Modification |
|------------------|---|
| ≤ 3.0 mg/dl | Full dose |
| 3.1 – 5.0 mg/dl | Hold pegasparagase and resume when direct bilirubin is < 2 mg/dl |
| >5.0 mg/dl | Hold the dose of pegasparagase; do not substitute other asparaginase products; do not make up the missed dose |

Hyperglycemia: Do not modify dose. Treat hyperglycemia as medically indicated.

Hyperlipidemia: Do not modify dose. Treat hyperlipidemia as medically indicated.

Ketoacidosis: Hold asparaginase until blood glucose can be regulated with insulin.

Pancreatitis: Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiographic findings only), asparaginase should be held until amylase/lipase levels return to normal and/or other signs subside, and then resumed.

Thrombosis (including CNS and non-CNS events): Withhold asparaginase until acute symptoms resolve and treat with appropriate antithrombotic therapy and consider repletion of AT-III, as indicated. Upon resolution of symptoms, consider resuming asparaginase while continuing low molecular weight heparin (LMWH) or antithrombotic therapy. Consider measurement and repletion of AT-III during subsequent courses of asparaginase if unable to achieve therapeutic Anti-Xa levels. For significant thrombosis (not catheter-related) consider evaluation for inherited predisposition to thrombosis.

5.3 Cyclophosphamide

Gross Hematuria: Omit in the presence of macroscopic hematuria.

Microscopic hematuria: Begin pre-hydration as in the treatment section of the protocol. Increasing the rate and duration of post-hydration should be considered (eg., 200 mL/m²/hr x 12-24 hours). Give IV mesna at a total dose that is 100% of the cyclophosphamide dose divided into 5 doses. Give the first mesna dose 15 minutes before or at the same time as the cyclophosphamide dose and repeat at Hours 3, 6, 9 and 12 after the start of cyclophosphamide. This total daily dose of mesna can also be administered as IV continuous infusion. The continuous infusion should be started 15 - 30 minutes before or at the same time as cyclophosphamide and finished no sooner than 12 hours after the start of cyclophosphamide infusion. If the child develops gross hematuria, continue mesna infusion for 24 hours from the start of the cyclophosphamide infusion.

Renal Dysfunction: If creatinine clearance or radioisotope GFR is < 10 mL/min/1.73 m², reduce dose of cyclophosphamide by 25%. Prior to dose adjustment of cyclophosphamide, the creatinine clearance should be repeated with good hydration.

5.4 Cytarabine (ARAC)

Cytarabine Syndrome: Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. Obtain blood cultures and consider antibiotics per institutional guidelines.

For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis.

Myelosuppression: Once Consolidation (C) or Delayed Intensification (DI) has started, do not interrupt for uncomplicated myelosuppression unless otherwise specified per protocol; do hold for proven or presumed serious infection. Do make up missed doses unless otherwise specified in the clinical trial.

Neurotoxicity: Discontinue cytarabine immediately for \geq Grade 2 CNS toxicity (e.g., ataxia, nystagmus, dysarthria, dysmetria, seizures and/or encephalopathy).

5.4.1 IT Cytarabine

Dose modifications following an episode of acute neurotoxicity:

Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.⁶⁵⁻⁶⁷

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.⁶⁸

Complete clinical evaluation including imaging of the brain is strongly recommended. For patients who return to their baseline pre-event neurological status, clinicians may:

1. Hold the next dose planned dose of IT therapy, or
2. Hold the next planned dose of IT therapy and space LPs to weekly

If the event does not recur, resumption of standard therapy should be considered for subsequent intrathecal therapy.

For patients who do not return to their baseline pre-event neurological status or for those with recurrent events, or evidence of progressive encephalopathy, additional evaluations may be warranted and the treating physician may consider a more prolonged or definitive change in therapy upon discussion with the Study Chair.

Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture:

Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow is a contraindication to intrathecal and/or intraventricular therapy.

Viral, bacterial, or fungal meningitis: Omit until resolved.

5.5 DOXOrubicin (Anthracyclines)

Consider Dexrazoxane prior to each dose for patients with:

- Anticipated cumulative anthracycline dose $\geq 250 \text{ mg/m}^2$ of DOXOrubicin equivalent.

Anthracycline Dose Conversion:

| |
|---|
| DOXOrubicin: Multiply total dose x 1 |
| DAUNOrubicin: Multiply total dose x 0.5 |
| EpiRUBicin: Multiply total dose x 0.67 |
| IDArubicin: Multiply total dose x 5 |
| MitoXANTRONE: Multiply total dose x 4 |

- Past or anticipated radiation with potential impact to the heart (radiation to chest, abdomen, spine or TBI).
- Recommended dose of dexrazoxane is 10 x the DOXOrubicin dose or 40 x the mitoXANtrone dose, given over 5-15 minutes immediately before the chemotherapeutic agent.

Monitoring Cardiac Echocardiogram:

At baseline and then recommended after cumulative dose of 175, 300, 375, and 450 mg/m². Please see COG Long Term Follow Up Guidelines for additional monitoring recommendations at http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf

Dose modification for cardiac toxicity:

If left ventricular ejection fraction (EF) < 50% (as determined by the Biplane Simpson method), or if EF inevaluable shortening fraction (SF) < 24%, hold the anthracycline or anthracenedione and repeat the echocardiogram in one week. If EF remains < 50% (or if EF inevaluable, SF < 24%), discontinue the anthracycline or anthracenedione as per the protocol or provider decision. Resuming cardiotoxic therapy depends on the cause of the cardiac dysfunction and the results of further cardiac evaluation.

Myelosuppression (beyond Induction):

If patient has severe infection or severe mucositis, consider modifying or omitting anthracycline.

Hyperbilirubinemia:

| Direct Bilirubin | Dose Adjustment |
|------------------|---|
| ≤ 3.0 mg/dl | Full dose |
| 3.1 – 5.0 mg/dl | Administer 50% of calculated dose |
| 5.1 – 6.0 mg/dl | Administer 25% of calculated dose |
| > 6.0 mg/dl | Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses. |

Extravasation:

In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also, see https://cogmembers.org/_files/disc/pharmacy/ExtravasationReference.pdf for COG reference.

5.6 IT Methotrexate

Systemic toxicity: The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m²/dose IV/PO every 6 hours x 2 doses, beginning 24 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/ μ L) or mucositis. Do not administer leucovorin solely to prevent myelosuppression. For patients with Down syndrome, leucovorin should be administered after every dose of IT methotrexate during ALL phases of therapy.

Dose modifications following an episode of acute neurotoxicity:

Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.⁶⁵⁻⁶⁷

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others. Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.⁶⁸

Complete clinical evaluation including imaging of the brain is strongly recommended.

For patients who return to their baseline pre-event neurological status, clinicians may:

1. Hold the next dose planned dose of IT therapy, or
2. Substitute IT cytarabine or IT cytarabine/hydrocortisone for 1 dose of IT methotrexate or
3. Proceed with IT methotrexate and include leucovorin rescue at a dose of 5 mg/m² IV/PO q 6 hrs x 2 doses beginning 24 hours after the LP.

If the event does not recur, resumption of standard therapy should be considered for subsequent intrathecal therapy.

For patients who do not return to their pre-event baseline neurological status or for those with recurrent events, or evidence of progressive encephalopathy, additional evaluations may be warranted and the treating physician may consider a more prolonged or definitive change in therapy upon discussion with the Study Chair.

Leucovorin rescue of IT MTX without acute neurotoxicity

Prevention of neurotoxicity by using leucovorin after IT MTX has not been studied in a randomized fashion. Neither the BFM, DFCI, nor COG have routinely introduced leucovorin rescue to prevent acute neurotoxicity, however SJCRH protocols use leucovorin rescue during remission Induction and Consolidation phases. The cumulative incidence of all neurotoxicities among non-DS patients enrolled on AALL0932 and AALL1131 indicate a less than 1% incidence of acute neurotoxicity during Induction. For non-DS patients enrolled on AALL0932, the incidence during Consolidation was 0.3%. For non-DS patients receiving Consolidation therapy on AALL1131, the incidence was 3.3%.

For the reasons above, it is permissible for patients receiving augmented Consolidation, such as that prescribed for NCI SR-High (AALL1731) patients, to receive leucovorin during Consolidation therapy after the 4 doses of weekly IT MTX on the following schedule:

- Leucovorin, 5 mg/m² IV/PO at hours 24 and 30 after IT MTX.

It is not known if providing leucovorin rescue after IT MTX during Consolidation as a measure to reduce acute neurotoxicity will reduce therapeutic efficacy in the context of COG protocols.

Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture:

Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based doses** that would be given by LP. NOTE: Obstruction to CSF flow is a contraindication to intrathecal and/or intraventricular therapy.

Viral, bacterial, or fungal meningitis: Omit until resolved.

5.7 IV Methotrexate

5.7.1 Intermediate-dose (ID) Methotrexate (2 g/m^2 over 24 hours) and leucovorin rescue (for patients with Down syndrome)

See protocol treatment delivery sections for hydration and standard leucovorin guidelines

- Methotrexate level and creatinine monitoring:
 - Draw methotrexate level and serum creatinine at Hours 24, (36), 42 and 48. NOTE: 36 hour level is only drawn if needed (see below).
 - If the 24 hour level is $< 60 \mu\text{M}$ draw the next level at hour 42 and refer to table below.
 - If 24 hour level is $\geq 60 \mu\text{M}$ and/or creatinine $> 1.5 \times$ above baseline, repeat level if methotrexate contamination is possible. If the methotrexate level is not the result of contamination, increase post-hydration with alkalinization to $200 \text{ mL/m}^2/\text{hr}$ and repeat the methotrexate level with a serum creatinine at hour 36.
 - If 36 hour level is $\leq 2 \mu\text{M}$, resume standard post-hydration and draw next level at hour 42.
 - If 36 hour level is $> 2 \mu\text{M}$, continue increased post-hydration and draw next level at hour 42. If the patient "catches up" and the level falls to the expected values of ≤ 1 and/or $\leq 0.2 \mu\text{M}$ at hours 42 and 48, respectively, resume standard leucovorin and post-hydration as long as urine output remains satisfactory. On days 2-3, 17-18, 31-32, and 45-46:
 - Dose: 15 mg/m^2 for a minimum of 5 doses given at 30, 36, 42, 48 and 54 hours after the start of ID MTX infusion.
 - If tolerated, subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m^2 for a minimum of 4 doses given at 36, 42, 48 and 54 hours after the start of ID MTX infusion.
 - If 36 hour level is $\geq 30 \mu\text{M}$, continue increased post-hydration and consider glucarpidase regardless of urine output.
 - For 42 and 48 hour methotrexate levels, refer to table below for leucovorin modifications
 - If 42 hour level is $\geq 10 \mu\text{M}$, consider glucarpidase regardless of urine output.
 - If 48 hour level is $\geq 5 \mu\text{M}$, consider glucarpidase regardless of urine output.

| (36 hr MTX level) | 42 hr MTX level | 48 hr MTX level | Leucovorin Rescue |
|--|---------------------------|---------------------------|---|
| Only required if 24 hr level is $\geq 60 \mu\text{M}^{**}$ | 1.01 to $9.9 \mu\text{M}$ | 0.21 to $4.9 \mu\text{M}$ | Continue 15 mg/m^2 q6h until MTX level $< 0.1 \mu\text{M}$ (draw q12-24h). |
| | 10 to $19.9 \mu\text{M}$ | 5 to $9.9 \mu\text{M}$ | Increase to 15 mg/m^2 q3h until MTX level $< 0.1 \mu\text{M}$ (draw q6-24 h). Consider glucarpidase. |
| | 20 to $200 \mu\text{M}$ | 10 to $100 \mu\text{M}$ | Increase to 100 mg/m^2 q6h until MTX level $< 0.1 \mu\text{M}$ (draw q6-24 h). Consider glucarpidase. |
| | $> 200 \mu\text{M}$ | $> 100 \mu\text{M}$ | Increase to $1,000 \text{ mg/m}^2$ q6h until MTX level $< 0.1 \mu\text{M}$ (draw q6-24 h). Consider glucarpidase. |

** If the 36 hour level exceeds $2 \mu\text{M}$, increase hydration to $200 \text{ mL/m}^2/\text{hr}$, monitor urine pH to assure a value > 7.0 and monitor urine output to determine if volume is $> 80\%$ of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase if 36 hour MTX level exceeds $30 \mu\text{M}$ (see above).

Dose modifications for toxicity

1. Nephrotoxicity:
 - a. Postpone course if pre-treatment (methotrexate) serum creatinine is $> 1.5 \times$ baseline or GFR creatinine clearance $< 65 \text{ mL/minute}/1.73\text{m}^2$. If renal function does not recover, omit methotrexate. Do not give HD methotrexate to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase.
 - b. For patients who have markedly delayed methotrexate clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G₂, Voraxaze™).^{69,70} Patients requiring glucarpidase rescue may continue to receive subsequent scheduled doses of HD methotrexate and remain on study.
2. Liver dysfunction:
 - a. Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous methotrexate. Blood samples for ALT should not be drawn following the start of methotrexate infusions as methotrexate causes significant short term elevation in ALT levels. (See Table in Capizzi methotrexate section)
 - b. Hyperbilirubinemia: Hold IV methotrexate for direct hyperbilirubinemia of $> 2.0 \text{ mg/dL}$.
3. Mucositis or Delayed Clearance (level $>0.2 \mu\text{M}$ at 48 hours after start of MTX infusion) in DS patients:
 - a. For Grade 2 mucositis, continue MTX at $2,000 \text{ mg/m}^2$ and leucovorin rescue starting at **30 hours** after the start of MTX.
 - b. For Grade 3-4 mucositis, withhold IV MTX until resolved.
 - c. For Grade 3-4 mucositis or delayed clearance (level $>0.2 \mu\text{M}$ at 48 hours after start of MTX infusion), decrease IV methotrexate to $1,500 \text{ mg/m}^2$ (i.e., a 25% reduction of total dose) for subsequent doses. Increase hydration to 200 mL/m^2 until level $<0.1 \mu\text{M}$ and start leucovorin rescue ($15 \text{ mg/m}^2 \text{ IV/PO every 6 hours}$) at **Hour 30** for a minimum of 7 doses.
 - i. If subsequent course with the dose reduction is not associated with Grade 3-4 mucositis or delayed clearance, continue with IV methotrexate $1,500 \text{ mg/m}^2$, post-hydration at $200 \text{ mL/m}^2/\text{hr}$ until level $<0.1 \mu\text{M}$ for remaining courses, and start leucovorin ($15 \text{ mg/m}^2 \text{ IV/PO every 6 hours}$) at **Hour 30**.
 - ii. If Grade 3-4 mucositis or delayed clearance recurs despite these interventions, decrease the subsequent methotrexate dose to $1,000 \text{ mg/m}^2$ (i.e., a 50% reduction of total dose) and as above, continue post-hydration at $200 \text{ mL/m}^2/\text{hr}$ until level $<0.1 \mu\text{M}$, and start leucovorin ($15 \text{ mg/m}^2 \text{ IV/PO every 6 hours}$) at **Hour 30** for a minimum of 7 doses. Should subsequent courses be well tolerated, continue with these interventions, but do not attempt to resume standard approach to drug delivery.
 - d. Consider culturing lesions for herpes simplex if mucositis persists or recurs.
4. Myelosuppression: All chemotherapy should be held for ANC $< 750/\mu\text{L}$ and platelets $< 75,000/\mu\text{L}$.

5.7.2 High-dose (HD) Methotrexate (5 g/m^2 over 24 hours) and leucovorin rescue

See protocol treatment delivery sections for hydration and standard leucovorin guidelines

- Methotrexate level and creatinine monitoring:
 - General guidelines
 - For methotrexate levels that exceed the expected values modify the leucovorin rescue regimen as noted in table below and increase post-hydration to $200 \text{ mL/m}^2/\text{hr}$, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is $\geq 80\%$ of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide.

- For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m²/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.
 - If serum creatinine rises significantly (>1.5 x above baseline), at any time point, assure appropriate urine pH and urine volume as above. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G2) (see below).
 - Glucarpidase: For methotrexate levels greater than 30 µM at hour 36, 10 µM at hour 42 and 5 µM at hour 48 and/or in the presence of deteriorating renal function, consider glucarpidase. Note that if indicated, glucarpidase therapy should be initiated within 48-60 hours of the start of the methotrexate infusion since beyond this window, life-threatening toxicity may not be preventable. For details relevant to glucarpidase administration and associated components of management, see the “Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance” By Ramsey LB et al at <http://theoncologist.alphamedpress.org/content/23/1/52.full.pdf+html>.
- Draw methotrexate level and serum creatinine at Hours 24, (36), 42 and 48. NOTE: 36 hour level is only drawn if needed (see below).
 - If the 24 hour level is < 120 µM draw the next level at hour 42 and refer to table below.
 - If 24 hour level is ≥ 120 µM and/or creatinine > 1.5 x above baseline, repeat level if methotrexate contamination is possible. If the methotrexate level is not the result of contamination, increase post-hydration with alkalinization to 200 mL/m²/hr and repeat the methotrexate level with a serum creatinine at hour 36.
 - If 36 hour level is ≤ 3 µM, resume standard post-hydration and draw next level at hour 42.
 - If 36 hour level is > 3 µM, continue increased post-hydration and draw next level at hour 42. If the patient “catches up” and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and post-hydration as long as urine output remains satisfactory.
 - If 36 hour level is ≥ 30 µM, continue increased post-hydration and consider glucarpidase regardless of urine output.
 - For 42 and 48 hour methotrexate levels, refer to table below for leucovorin modifications
 - If 42 hour level is ≥ 10 µM, consider glucarpidase regardless of urine output.
 - If 48 hour level is ≥ 5 µM, consider glucarpidase regardless of urine output.

| (36 hr MTX level) | 42 hr MTX level | 48 hr MTX level | Leucovorin Rescue |
|---|-----------------|-----------------|---|
| Only required if 24 hr level is ≥ 120 µM.** | 1.01 to 9.9 µM | 0.41 to 4.9 µM | Continue 15 mg/m ² q6h until MTX level < 0.1 µM (draw q12-24h). |
| | 10 to 19.9 µM | 5 to 9.9 µM | Increase to 15 mg/m ² q3h until MTX level < 0.1 µM (draw q6-24 h). Consider glucarpidase. |
| | 20 to 200 µM | 10 to 100 µM | Increase to 100 mg/m ² q6h until MTX level < 0.1 µM (draw q6-24 h). Consider glucarpidase. |
| | > 200 µM | > 100 µM | Increase to 1,000 mg/m ² q6h until MTX level < 0.1 µM (draw q6-24 h). Consider glucarpidase. |

** If the 36 hour level exceeds 3 μM , increase hydration to 200 mL/m²/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is $\geq 80\%$ of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase if 36 hour MTX level exceeds 30 μM (see above).

Myelosuppression:

Hold methotrexate dose for ANC $< 750/\mu\text{L}$ OR platelets $< 75,000/\mu\text{L}$.

Mucositis:

- For Grade 3-4 mucositis, withhold IV methotrexate until resolved. For next course of methotrexate, start leucovorin rescue (15 mg/m² IV/PO every 6 hours) at hour 36 and continue until MTX level $< 0.1 \mu\text{M}$.
 - If subsequent course is not associated with Grade 3-4 mucositis, attempt to resume standard leucovorin timing (start at hour 42).
 - If Grade 3-4 mucositis recurs despite early leucovorin, decrease the subsequent doses of methotrexate by 25%, increase post-hydration to 200 mL/m²/hr and continue early leucovorin as above.
 - If Grade 3-4 mucositis recurs despite these interventions, decrease the subsequent methotrexate dose by 50% and continue increased post-hydration and early leucovorin as above.
 - Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery.
- Consider culturing lesions for herpes simplex if mucositis persists or recurs.

Renal dysfunction:

Postpone course if pre-treatment (methotrexate) serum creatinine is $> 1.5x$ baseline or GFR creatinine clearance $< 65 \text{ mL/minute}/1.73\text{m}^2$. If renal function does not recover, omit methotrexate. Do not give HD methotrexate to a patient with this degree of renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

For patients who have markedly delayed methotrexate clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G2, Voraxaze). Patients requiring glucarpidase rescue may continue to receive subsequent scheduled doses of HD methotrexate and remain on study.

Liver dysfunction:

- a. **Hyperbilirubinemia:** Hold IV methotrexate for direct hyperbilirubinemia of $> 2.0 \text{ mg/dL}$.
- b. **Elevated ALT:** Samples for the determination of ALT value must be drawn within 72 hours PRIOR to a dose of intravenous methotrexate. Blood samples for ALT should not be drawn following the start of methotrexate infusions as methotrexate causes significant short term elevation in ALT levels. Adjust methotrexate dosing as below:

5.7.3 Capizzi methotrexate

Infection: All therapy should be interrupted for patients with presumed or proven serious infections and resumed when the signs of infection have abated.

Hematologic: Obtain blood counts prior to each dose of methotrexate

- a. If ANC is $\geq 750/\mu\text{L}$ AND platelets $\geq 75,000/\mu\text{L}$, escalate methotrexate dose by 50 mg/m^2
- b. If ANC is $\geq 500/\mu\text{L}$ but $< 750/\mu\text{L}$ OR platelets are $\geq 50,000/\mu\text{L}$ but $< 75,000/\mu\text{L}$, give the same dose of methotrexate as previously (no escalation)
- c. If ANC is $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, hold all chemotherapy and repeat blood counts in 4 days.
 - i. In 4 days, if ANC is $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, give the same dose of methotrexate as previously (no escalation) with scheduled vinCRISTine. Proceed to subsequent methotrexate and vinCRISTine doses in 10 days.
 - ii. In 4 days, if ANC is still $< 500/\mu\text{L}$ OR platelets $< 50,000/\mu\text{L}$, omit methotrexate dose. Give vinCRISTine (and IT methotrexate if day 31) and pegasparagase (if due). Pegasparagase may be given on the same day as the vinCRISTine dose if the IV methotrexate is omitted. Repeat blood counts in 7 days to proceed with subsequent methotrexate and vinCRISTine doses. Do not make up omitted dose of methotrexate.
 1. In 7 days, if ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$, resume methotrexate at 80% of the previously administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.
 2. In 7 days, if ANC is still $< 500/\mu\text{L}$ OR platelets are $< 50,000/\mu\text{L}$, hold all chemotherapy until counts recover to ANC $\geq 500/\mu\text{L}$ AND platelets $\geq 50,000/\mu\text{L}$. At that time resume methotrexate at 80% of the previously administered dose and administer scheduled vinCRISTine. For subsequent doses, resume standard methotrexate escalation.

Mucositis: Hold methotrexate for grade 3 or higher mucositis. When resolved, resume methotrexate at 80% of the final administered dose. For subsequent doses, resume standard escalation.

Renal dysfunction: Postpone methotrexate dose if serum creatinine is $> 1.5 \times$ baseline or GFR creatinine clearance is $< 65 \text{ mL/min}/1.73\text{m}^2$

Liver dysfunction:

- a. Hyperbilirubinemia: Hold IV methotrexate for direct hyperbilirubinemia of $> 2.0 \text{ mg/dL}$.
- b. Elevated ALT: Samples for the determination of ALT value must be drawn within 72 hours PRIOR to a dose of intravenous methotrexate. Blood samples for ALT should not be drawn following the start of methotrexate infusions as methotrexate causes significant short term elevation in ALT levels. Adjust methotrexate dosing as below:

| ALT | IV MTX |
|--|---|
| < 10 X ULN | Continue with therapy as scheduled |
| 10 – 20 X ULN | Continue with therapy as scheduled for 1 cycle |
| 10 – 20 X ULN for 2 consecutive cycles | Discontinue TMP/SMX* Hold therapy until ALT $< 10 \text{ X ULN}$, then resume at full doses at point of interruption. Do not skip doses. |
| > 20 X ULN | Discontinue TMP/SMX* Hold therapy until ALT $< 10 \text{ X ULN}$, then resume at full doses at point of interruption. Do not skip doses. |
| > 20 X ULN for > 2 weeks | Evaluate with AST, bili, alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given. |

5.8 PO Methotrexate, and 6-Mercaptopurine (6-MP)

Thiopurine Pharmacology Testing and Dosage Adjustments in All Blocks that Contain Thiopurines

Mercaptopurine and thioguanine are methylated by thiopurine methyltransferase (*TPMT*) to an inactive metabolite. Patients with polymorphisms in *TPMT* resulting in decreased activity are more susceptible to toxicities when given mercaptopurine/thioguanine (i.e., myelosuppression). More recently, germline variants in the gene encoding the nucleoside diphosphate-linked moiety X-type motif 15 (*NUDT15*) have been reported in approximately 4% of Hispanic/Native American and nearly 10% of East Asian children with ALL; these polymorphisms are strongly associated with mercaptopurine intolerance. There are CLIA certified tests for *TPMT* genotype and phenotype (genotyping can be performed even after recent RBC transfusions), thiopurine metabolites (MMP and TGN measurements), and for *NUDT15* polymorphisms.

General comments about TGN metabolite testing:

High TGN concentrations: high values should not preclude further increases in mercaptopurine doses if ANC is high and there are no contraindications to dose increases. Likewise, high concentrations of methylated derivatives should not influence dosing in asymptomatic patients without hyperbilirubinemia.

When ANC is high despite dose increases, consider non-adherence. Although there are no specific values to use to indicate non-adherence, low concentrations of TGN and methylated derivatives in a sample taken after at least three weeks after continuous dosing may indicate non-adherence.

Table 5.8.1 Mercaptopurine Starting Dose[#] Recommendations for known TPMT/NUDT15 variants

Suggested starting doses of mercaptopurine for patients with known mutations in *TPMT*/*NUDT15* are as follows:

| 6MP Dose | Phase(s) | <i>TPMT or NUDT15</i> Heterozygous Variant | <i>TPMT</i> Homozygous Variant | <i>NUDT15</i> Homozygous Variant |
|--|---|--|--|--|
| 75 mg/m ² /day | SR-Fav/SR-Avg Consolidation* Maintenance (all patients) | Start at full dose Reduce subsequent courses by at least 20% for ≥ 2 week delay for myelosuppression | 30 mg/m² TOTAL per week (i.e., 10 mg/m ² /dose 3x/week*) *may give on fewer days/week if needed to round for tablet size | 70 mg/m² TOTAL per week (i.e., 10 mg/m ² /dose daily*) *may give on fewer days/week if needed to round for tablet size |
| 60 mg/m ² /day | SR-High/ DS-High Consolidation* | Start at full dose Reduce subsequent courses by at least 20% for ≥ 2 week delay for myelosuppression | 24 mg/m² TOTAL per week (i.e., 8 mg/m ² /dose 3x per week*) *may give on fewer days/week if needed to round for tablet size | 56 mg/m² TOTAL per week (i.e., 8 mg/m ² /dose daily*) *may give on fewer days/week if needed to round for tablet size |
| 25 mg/m ² /day | SR-High/ DS-High Interim Maintenance #1* | Start at full dose Reduce subsequent courses by at least 20% for ≥ 2 week delay for myelosuppression | 10 mg/m² TOTAL per WEEK* *may give on 1 day every two or more weeks if needed to round for tablet size | 21 mg/m² TOTAL per week (i.e., 7 mg/m ² /dose 3x per week*) *may give on fewer days/week if needed to round for tablet size |
| <p><i>#Further dose adjustments should be based on the degree (or absence) of myelosuppression.</i></p> <p><i>* do not increase mercaptopurine doses during these phases</i></p> | | | | |

For patients with heterozygous *TPMT/NUDT* mutations, dose escalation for high ANC is not recommended for any phase except Maintenance. As 65% of *TPMT* heterozygous patients will tolerate full dose mercaptopurine in Maintenance, doses may be increased above the starting dose for persistent ANC >1500/ μ L using the same ANC and timing guidelines to decide on escalation. Dose escalation for homozygous *TMPT/NUDT15* deficient patients must be done slowly.

5.8.1 PO mercaptopurine (6-MP) (See table 5.8.1 for dosing considerations for patients with *TPMT/NUDT15* mutations)

Consolidation (SR-Fav/SR-Avg)

Myelosuppression: Do not increase dose for high or low ANC during Consolidation.

Liver Dysfunction:

For Grade 3 increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total and direct bilirubin. Monitor SGPT/ALT or SGOT/AST and total and direct bilirubin weekly during Consolidation as long as transaminases remain over 5x ULN.

Continue full dose therapy unless either of the following occurs:

- Direct bilirubin > 2 mg/dL
- Grade 4 SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) elevation on 2 determinations at least 1 week apart.

If either of these occurs, hold mercaptopurine and monitor labs as above, weekly. Restart at full dose therapy when the transaminase elevation is < Grade 3 (less than 5x ULN), as long as direct bilirubin is < 2 mg/dL.

- Exclude infectious hepatitis for persistent (> 1 month) Grade 3 elevations in SGPT/ALT or SGOT/AST above 5x ULN.
- Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis.

Interim Maintenance I (SR-High/DS-High)

Myelosuppression: For ANC < 750/ μ L and/or platelets < 75,000/ μ L, hold mercaptopurine until ANC recovers \geq 750/ μ L and platelets are \geq 75,000/ μ L. Restart at same dose when the next dose of HD methotrexate is administered during IM I.

Liver Dysfunction:

For Grade 3 increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total and direct bilirubin.

Continue full dose therapy unless either of the following occurs:

- Direct bilirubin > 2 mg/dL
- Grade 4 SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) elevation on 2 determinations at least 1 week apart.

If either of these occurs, hold mercaptopurine and monitor labs as above, weekly. Restart at full dose therapy when the transaminase elevation is < Grade 3 (less than 5x ULN), as long as direct bilirubin is < 2 mg/dL.

- Exclude infectious hepatitis for persistent (> 1 month) Grade 3 elevations in SGPT/ALT or SGOT/AST above 5x ULN.
- Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis.

5.8.2 PO Methotrexate (MTX) and Mercaptopurine (6-MP) – Maintenance

See Table 5.8.1 for dosing considerations for patients with TPMT/NUDT15 mutations.

Myelosuppression: If absolute neutrophil count (ANC) falls below 500/ μ L or if platelet count falls below 50,000/ μ L during Maintenance, mercaptopurine and methotrexate should be held until recovery above these levels.

1. For the first drop below 500/ μ L ANC or platelet count < 50,000/ μ L, resume mercaptopurine and methotrexate at the same dose the patient was taking prior to the episode of myelosuppression when ANC \geq 500 / μ L and platelet count \geq 50,000/ μ L.
2. If ANC falls below 500/ μ L or if platelet count falls below 50,000/ μ L for a second (or greater) time, hold mercaptopurine and methotrexate until ANC is \geq 750/ μ L and platelets are \geq 75,000/ μ L. Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis.
 - a. When ANC \geq 750/ μ L and platelet count \geq 75,000/ μ L, restart mercaptopurine and methotrexate at 50% of the dose prescribed at the time that the medications were stopped.
 - b. Increase doses of mercaptopurine and methotrexate to 75% and then 100% of dose prescribed prior to stopping the medications at 2-4 week intervals provided ANC remains $>$ 750 / μ L and platelets remain $>$ 75,000/ μ L. May increase both mercaptopurine and methotrexate simultaneously.
 - c. Once at 100% of the dose prescribed prior to stopping, see below for instructions regarding further dose escalation.

Continue to follow ANC q 2-4 weeks with target ranges ANC 500 – 1,500/ μ L and platelet count \geq 50,000/ μ L

If patient develops severe or unexpected myelosuppression, i.e., does not tolerate at least half dose mercaptopurine, in the absence of TMP/SMZ or other myelosuppressive agents, strongly consider evaluation of *TPMT* and/or *NUDT15* status if not already done.

Prolonged cytopenia is defined as ANC < 500/ μ L and/or platelets < 50,000/ μ L after withholding therapy for > 2 - 4 weeks. Consider a marrow evaluation in the face of persistent or prolonged neutropenia if no recovery is apparent. If monocyte count is increasing or viral myelosuppression is clinically suspected, the bone marrow examination may be postponed for 1-2 weeks and omitted if ANC and platelets fully recover by the 4th week after therapy is withheld.

Inadequate Myelosuppression: For persistent ANC \geq 1,500/ μ L, no dose escalations are recommended during the first cycle of Maintenance.

- For ANC \geq 1,500/ μ L on 3 CBC(s) done over 6 weeks or 2 successive monthly CBC(s), alternately increase doses of methotrexate or mercaptopurine by 25%. Always wait at least 4 weeks before making another dose adjustment.
- If both methotrexate and mercaptopurine are increased once without a fall in ANC, consider noncompliance as a possibility. Noncompliance can be assessed by obtaining a sample for thiopurine metabolites. Although there are no specific values to use to indicate non-adherence, low

concentrations of TGN and methylated derivatives in a sample taken after at least three weeks after continuous dosing may indicate non-adherence. Also consider observing the administration of an oral dose of methotrexate and checking plasma methotrexate concentration 2-4 hours later; this value should be $\geq 0.2 \mu\text{M}$.

- If ANC remains high after intervention for possible noncompliance:
 - For patients who are heterozygous or homozygous deficient for *TPMT/NUDT15* and have high ANCs as described above, increase methotrexate alone by 25% and repeat evaluation. Unless noncompliance is suspected, increase methotrexate preferentially over mercaptopurine Consider carefully increasing mercaptopurine doses as well, if high ANCs persist. Increase the mercaptopurine dose in 25% increments until ANC is in target. Always wait at least 4 weeks before making another dose adjustment or re-measuring TGN. If ANC remains high, alternate mercaptopurine dose increases with methotrexate dose increases.
 - If the methylated derivatives are significantly elevated, in concert with abdominal symptoms or Grade 4 SGPT/ALT, SGOT/AST and/or direct bilirubin $\geq 2 \text{ mg/dL}$, and ANC indicates that the 6-MP should be increased, consider adding allopurinol at a dose of 50 mg/m^2 with a dose of 6-MP that has been decreased by 50-75%.⁷¹ Since there is a significant risk of myelosuppression with this approach due to the interaction of 6-MP and allopurinol, vigilant ANC monitoring should be considered.

Liver Dysfunction:

- For Grade 3 toxicity, increase in hepatic transaminases (SGPT/ALT or SGOT/AST to greater than $>5.0 - 20.0 \times \text{ULN}$), obtain total and direct bilirubin. Monitor SGPT/ALT or SGOT/AST and total and direct bilirubin weekly during Consolidation as long as transaminases remain over 5x ULN.
- Continue full dose therapy unless either of the following occurs:
 - Direct bilirubin $> 2 \text{ mg/dL}$
 - Grade 4 SGPT/ALT or SGOT/AST $> 20 \times \text{ULN}$ (consistent with Grade 4 toxicity) elevation on 2 determinations at least 1 week apart.
- If either of these occurs, hold mercaptopurine and monitor labs as above, weekly. Restart at full dose therapy when the transaminase elevation is $<$ Grade 3 (less than 5x ULN), as long as direct bilirubin is $< 2 \text{ mg/dL}$
- Exclude infectious hepatitis for persistent (> 1 month) Grade 3 elevations in SGPT/ALT or SGOT/AST(above 5x ULN). Consider discontinuing trimethoprim/sulfamethoxazole (TMP/SMX) in favor of an alternative approach to Pneumocystis prophylaxis

5.9 Steroids (Dexamethasone and PredniSO(LO)ne)

Hypertension: Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension.

Hyperglycemia: Dose should not be reduced for hyperglycemia.

Pancreatitis: Every effort should be made not to hold any Induction steroids. Do not modify dose for asymptomatic elevations of amylase and/or lipase. In extreme circumstances, consider discontinuation of steroids, except for stress doses, in the presence of Grade 3 or 4 pancreatitis.

Osteonecrosis (ON): Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during Induction or Delayed Intensification. Omit Maintenance steroid for osteonecrosis Grade 2 or greater. Consider resuming Maintenance steroid after 6 months if joint symptoms have resolved and if MRI findings have significantly improved or normalized.

Varicella: Steroids should be held during active infection except during Induction. Do not hold during incubation period following exposure in patients with laboratory evidence of immunity or patients who received appropriate post-exposure prophylaxis.

Inability to use oral doses: For dexamethasone, substitute the IV preparation mg for mg. For predniSO(LO)ne, substitute IV methylprednisolone at 80% of the oral predniSO(LO)ne dose. Note that if substituting oral prednisolone for predniSO(LO)ne, the doses are the same; predniSO(LO)ne is converted in the liver to prednisolone.

Severe infection: Do not hold or discontinue steroids during Induction without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for “stress doses.”

5.10 PO 6-Thioguanine (6-TG)

In Delayed Intensification, consider the following thioguanine dosing based on *TPMT/NUDT15* status:

| 6TG Dose | Phase(s) | <i>TPMT or NUDT15</i> | <i>TPMT or NUDT15</i> |
|---------------------------|-------------------------|---|---|
| | | Heterozygous Variant | Homozygous Variant |
| 60 mg/m ² /day | Delayed Intensification | Start at full dose Reduce subsequent courses by at least 20% for \geq 2 week delay for myelosuppression | 30 mg/m² TOTAL per week (i.e., 10 mg/m ² /dose 3x/week*) *may give on fewer days/week if needed to round for tablet size |

Infection: Consider holding thioguanine; should be held for suspected or proven serious infection.

Liver dysfunction: For clinical jaundice, hepatomegaly or splenomegaly during or within 2 weeks of completing the 2 week course(s) of thioguanine, obtain an ALT/AST/total and direct bilirubin. Consider Doppler ultrasound with an assessment for ascites and portal blood flow to assess for possible sinusoidal obstruction syndrome (SOS; formerly veno-occlusive disease, VOD). Hold thioguanine for a direct bilirubin of > 2.0 mg/dL or for new onset hepatomegaly or splenomegaly until SOS is ruled out. SOS may also present with unexplained thrombocytopenia and splenomegaly. Consider Doppler ultrasound in the presence of these symptoms. No further thioguanine should be administered in a patient with prior SOS.

Severe and/or unexpected myelosuppression: Evaluate for *TPMT* activity as described in [Section 5.8](#)

5.11 VinCRISTine

PLEASE USE “BALIS” SCALE FOR GRADING MOTOR AND SENSORY NEUROPATHY (See next page)

Severe Neuropathic Pain (Grade 3 or greater): Hold dose(s). When symptoms subside, resume at 50% previous **calculated** dose (**maximum dose: 1 mg**), and then escalate to full dose as tolerated. NOTE: neuropathic pain can be severe and difficult to treat. However, because vinCRISTine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vinCRISTine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

Vocal Cord Paralysis: Hold dose(s). When symptoms subside, resume at 50% previous **calculated** dose (**maximum dose: 1 mg**), and then escalate to full dose as tolerated. See above for comment on CMT.

Foot Drop, Paresis (Grade 3 or greater): Consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vinCRISTine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion as well as to provide ankle-foot orthotics (AFOs) and other forms of support. Drugs such as gabapentin may be of value.

Jaw Pain: Treat with analgesics; do not modify vinCRISTine dose.

Hyperbilirubinemia^{72,73}

| Direct Bilirubin | VinCRISTine Dose Adjustment |
|------------------|--|
| ≤ 3.0 mg/dL | None (maximum dose: 2 mg) |
| 3.1- 5.0 mg/dL | 50% of calculated dose (maximum dose: 1 mg) |
| 5.1-6.0 mg/dL | 25% of calculated dose (maximum dose: 0.5 mg) |
| > 6.0 mg/dL | Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses |

Constipation or ileus (Grade 3 or greater) or typhlitis: Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of **calculated** dose (**maximum dose: 1 mg**) and escalate to full dose as tolerated.

Extravasation: In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://cogmembers.org/_files/disc/pharmacy/ExtravasationReference.pdf for COG reference.

“BALIS” SCALE FOR GRADING MOTOR AND SENSORY NEUROPATHY

Modified (“Balis”) Pediatric Scale of Peripheral Neuropathies

Motor neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Sensory neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

6 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled “Drug Information for Commercial Agents used by the Children’s Oncology Group.” This manual is provided under Standard Sections for Protocols at: https://members.childrensoncologygroup.org/prot/reference_materials.asp

6.1 BLINATUMOMAB

(11/18/2019)

(Blincyto®, AMG103, MT103, recombinant bispecific antibody derivative, NSC# 765986), IND# 117467

Source and Pharmacology

Blinatumomab is a fusion protein composed of two single-chain antibodies (scFv), murine anti-CD19 scFv and murine anti-CD3 scFv. Through CD3 binding, blinatumomab recruits and engages T cells for redirected lysis of CD19-positive B cells, including those expressed with B-cell malignancies. T cells are bound by its anti-CD3 moiety, whereas B cells are bound by the anti-CD19 moiety. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T cell reaction. Treatment with blinatumomab is associated with a rapid depletion of peripheral B cells, accompanied by T cell activation and a transient increase in cytokines.

Blinatumomab consists of a single chain of 504 amino acids with a molecular weight of approximately 54 kDa. The pharmacokinetics of blinatumomab was assessed over a dose range from 5 to 90 mcg/m²/day (approximately equivalent to 9-162 mcg/day). Following continuous intravenous infusion, the steady state serum concentration (Css) was achieved within a day and remained stable over time. The estimated mean (SD) volume of distribution based on terminal phase (Vz) was 4.52 (2.89) L. The estimated mean (SD) systemic clearance was 2.92 (2.83) L/hour and the estimated mean (SD) half-life was 2.11(1.42) hours. Negligible amounts of blinatumomab were excreted in the urine at the tested clinical doses. Like other protein therapeutics, blinatumomab is expected to be degraded into small peptides and amino acids via catabolic pathways. At the clinical doses of 9 mcg/day and 28 mcg/day for the treatment of adult relapsed/refractory ALL, the mean (SD) Css was 211 (258) pg/mL and 621 (502) pg/mL, respectively.

At this time there are no known drug interactions with blinatumomab.

Toxicity:

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Blinatumomab (AMG 103, NSC 765986)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.
Frequency is provided based on 1276 patients. Below is the CAEPR for Blinatumomab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, September 4, 2019¹

| Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|--|---|---|
| Likely (>20%) | Less Likely (<=20%) | Rare but Serious (<3%) | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | <i>Anemia (Gr 2)</i> |
| | Blood and lymphatic system disorders - Other (coagulopathy) ² | | <i>Blood and lymphatic system disorders - Other (coagulopathy)² (Gr 2)</i> |
| | | Blood and lymphatic system disorders - Other (hematophagic histiocytosis) | |
| | | Blood and lymphatic system disorders - Other (lymphadenitis) | |
| | | Blood and lymphatic system disorders - Other (lymphadenopathy) | |
| | | Blood and lymphatic system disorders - Other (pancytopenia) | |
| | Disseminated intravascular coagulation ^{2,3} | | <i>Disseminated intravascular coagulation^{2,3} (Gr 2)</i> |
| | Febrile neutropenia | | <i>Febrile neutropenia (Gr 3)</i> |
| CARDIAC DISORDERS | | | |
| | Sinus tachycardia | | <i>Sinus tachycardia (Gr 2)</i> |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | <i>Abdominal pain (Gr 2)</i> |
| | Constipation | | <i>Constipation (Gr 2)</i> |
| | Diarrhea | | <i>Diarrhea (Gr 2)</i> |
| | | Gastric hemorrhage | |
| | | Gastrointestinal disorders - Other (pneumoperitoneum) | |
| | Mucositis oral | | |
| Nausea | | | <i>Nausea (Gr 2)</i> |
| | | Oral hemorrhage | |
| | | Pancreatitis | |

| Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|--|--|--|---|
| Likely (>20%) | Less Likely (<=20%) | Rare but Serious (<3%) | |
| | Vomiting | | <i>Vomiting (Gr 2)</i> |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Chills ³ | | <i>Chills³ (Gr 2)</i> |
| | Edema limbs | | <i>Edema limbs (Gr 2)</i> |
| Fatigue ³ | | | <i>Fatigue³ (Gr 2)</i> |
| Fever ³ | | | <i>Fever³ (Gr 2)</i> |
| | Generalized edema | | |
| | Non-cardiac chest pain | | |
| | Pain | | |
| HEPATOBILIARY DISORDERS | | | |
| | Hepatobiliary disorders - Other (hepatic function abnormal) ⁴ | | <i>Hepatobiliary disorders - Other (hepatic function abnormal)⁴ (Gr 2)</i> |
| IMMUNE SYSTEM DISORDERS | | | |
| | | Allergic reaction ³ | |
| | Cytokine release syndrome ³ | | <i>Cytokine release syndrome³ (Gr 3)</i> |
| | Immune system disorders - Other (immunodeficiency [immunoglobulin decreased]) ⁵ | | <i>Immune system disorders - Other (immunodeficiency [immunoglobulin decreased])⁵ (Gr 2)</i> |
| INFECTIONS AND INFESTATIONS | | | |
| Infection ⁶ | | | <i>Infection⁶ (Gr 4)</i> |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | Infusion related reaction | | |
| | | Injury, poisoning and procedural complications - Other (overdose) ⁷ | |
| INVESTIGATIONS | | | |
| | | Activated partial thromboplastin time prolonged ² | |
| | Alanine aminotransferase increased ⁴ | | <i>Alanine aminotransferase increased⁴ (Gr 3)</i> |
| | Alkaline phosphatase increased ⁴ | | <i>Alkaline phosphatase increased⁴ (Gr 2)</i> |
| | Aspartate aminotransferase increased ⁴ | | <i>Aspartate aminotransferase increased⁴ (Gr 4)</i> |
| | Blood bilirubin increased ⁴ | | <i>Blood bilirubin increased⁴ (Gr 2)</i> |
| | Blood lactate dehydrogenase increased | | |
| | | Creatinine increased ⁸ | |
| | GGT increased ⁴ | | <i>GGT increased⁴ (Gr 2)</i> |
| | | Investigations - Other (blood fibrinogen increased) ² | |
| | Investigations - Other (C-reactive protein increased) | | <i>Investigations - Other (C-reactive protein increased) (Gr 2)</i> |
| | Investigations - Other (fibrin D dimer increased) ² | | |
| Lymphocyte count decreased | | | <i>Lymphocyte count decreased (Gr 4)</i> |
| Neutrophil count decreased | | | <i>Neutrophil count decreased (Gr 4)</i> |
| Platelet count decreased ² | | | <i>Platelet count decreased² (Gr 2)</i> |

| Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|--|--|---|---|
| Likely (>20%) | Less Likely (<=20%) | Rare but Serious (<3%) | |
| | Weight gain | | <i>Weight gain (Gr 2)</i> |
| | Weight loss | | |
| | White blood cell decreased | | <i>White blood cell decreased (Gr 4)</i> |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | |
| | Hyperglycemia | | <i>Hyperglycemia (Gr 2)</i> |
| | Hyperuricemia | | |
| | Hypoalbuminemia | | |
| | Hypocalcemia | | |
| Hypokalemia | | | <i>Hypokalemia (Gr 2)</i> |
| | Hypomagnesemia | | |
| | Hypophosphatemia | | |
| | | Tumor lysis syndrome ⁹ | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | Back pain | | <i>Back pain (Gr 2)</i> |
| | Bone pain | | |
| | Generalized muscle weakness | | |
| | Myalgia | | |
| | Pain in extremity | | <i>Pain in extremity (Gr 2)</i> |
| NERVOUS SYSTEM DISORDERS | | | |
| | Ataxia ¹⁰ | | |
| | Cognitive disturbance ¹⁰ | | |
| | Dizziness ¹⁰ | | <i>Dizziness¹⁰ (Gr 2)</i> |
| | | Dysarthria ¹⁰ | |
| | Dysphasia ¹⁰ | | |
| | Encephalopathy ¹⁰ | | |
| | | Facial nerve disorder ¹⁰ | |
| Headache ¹⁰ | | | <i>Headache¹⁰ (Gr 2)</i> |
| | | Intracranial hemorrhage | |
| | | Leukoencephalopathy | |
| | Memory impairment ¹⁰ | | |
| | Nervous system disorders - Other (apraxia) | | |
| | Nervous system disorders - Other (cerebellar syndrome) ¹⁰ | | |
| | | Nervous system disorders - Other ¹⁰ | |
| | Paresthesia ¹⁰ | | |
| | | Reversible posterior leukoencephalopathy syndrome | |
| | Seizure ¹⁰ | | |
| | Somnolence ¹⁰ | | |
| | | Transient ischemic attacks ¹⁰ | |
| | Tremor ¹⁰ | | <i>Tremor¹⁰ (Gr 2)</i> |
| PSYCHIATRIC DISORDERS | | | |
| | | Agitation ¹⁰ | |
| | Anxiety ¹⁰ | | |

| Adverse Events with Possible Relationship to Blinatumomab (AMG 103) (CTCAE 5.0 Term) [n= 1276] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|--|---|--------------------------------------|--|
| Likely (>20%) | Less Likely (<=20%) | Rare but Serious (<3%) | |
| | Confusion ¹⁰ | | |
| | | Hallucinations ¹⁰ | |
| | Insomnia | | <i>Insomnia (Gr 2)</i> |
| | | Personality change ¹⁰ | |
| | | Psychosis ¹⁰ | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | <i>Cough (Gr 2)</i> |
| | Dyspnea | | |
| | Epistaxis | | |
| | | Hypoxia | |
| | Oropharyngeal pain | | |
| | | Pneumonitis | |
| | Voice alteration ¹⁰ | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Hyperhidrosis | | |
| | Pruritus | | |
| | Skin and subcutaneous tissue disorders - Other (rash) ¹¹ | | <i>Skin and subcutaneous tissue disorders - Other (rash)¹¹ (Gr 2)</i> |
| VASCULAR DISORDERS | | | |
| | | Capillary leak syndrome ³ | |
| | Flushing ³ | | |
| | Hypertension ³ | | <i>Hypertension³ (Gr 2)</i> |
| | Hypotension ³ | | <i>Hypotension³ (Gr 2)</i> |
| | Thromboembolic event ² | | <i>Thromboembolic event² (Gr 2)</i> |

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Blinatumomab (AMG 103) is known to cause a variety of adverse events associated with coagulopathy which may include: Activated partial thromboplastin time prolonged, Disseminated intravascular coagulation, Fibrinogen decreased, INR increased, Investigations - Other (blood fibrinogen increased), Investigations - Other (fibrin D dimer increased), Investigations - Other (activated partial thromboplastin time shortened), Investigations - Other (antithrombin III decreased), Investigations - Other (coagulation factor XII level decreased), Investigations - Other (coagulation factor XIII level increased), Investigations - Other (haptoglobin decreased), Investigations - Other (protein S decreased), Platelet count decreased, and Thromboembolic events.

³Symptoms of cytokine release syndrome (CRS) and/or allergic reaction may include chills, fever, fatigue, flushing, bronchospasm, and hypotension. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

⁴Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

⁵Immunodeficiency (immunoglobulin decreased) includes immunoglobulins decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, and blood immunoglobulin A decreased.

⁶Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

⁷Overdoses have been observed. Overdoses resulted in adverse reactions, which were consistent with the reactions observed at the recommended therapeutic dose and included fever, tremors, and headache. In the event of overdose, interrupt the infusion, monitor the patient for signs of toxicity, and provide supportive care. Consider re-initiation of blinatumomab at the correct therapeutic dose when all toxicities have resolved and no earlier than 12 hours after interruption of the infusion.

⁸Acute kidney injury (acute renal failure) is associated with increased creatinine levels.

⁹Tumor lysis syndrome is defined as a massive overload of potassium, phosphate, uric acid, plus hypocalcemia, potentially causing lethal cardiac arrhythmias and/or renal failure.

¹⁰Blinatumomab (AMG103) is known to cause a variety of nervous system disorders which may include: Ataxia, Cognitive disturbance, Concentration impairment, Depressed level of consciousness, Dizziness, Dysphagia, Dysarthria, Dysesthesia, Dysphasia, Encephalopathy, Facial nerve disorder, Headache, Lethargy, Memory impairment, Paresthesia, Peripheral sensory neuropathy, Seizure, Somnolence, Syncope, Transient ischemic attacks, Tremor, Voice alteration, Nervous system disorders - Other (allodynia), Nervous Systems disorders - Other (cerebellar syndrome), Nervous system disorders - Other (dysgraphia), Nervous system disorders - Other (epilepsy), Nervous system disorders - Other (facial palsy), Nervous system disorders - Other (hemiparesis), Nervous system disorders - Other (hypertonia), Nervous system disorders - Other (hypotonia), Nervous system disorders - Other (pleocytosis), and Nervous system disorders - Other (polyneuropathy). Additionally, symptoms of some nervous system disorders are adverse events under the PSYCHIATRIC DISORDERS SOC and may include: Agitation, Anxiety, Confusion, Hallucinations, Personality change, and Psychosis.

¹¹Rash includes rash, rash maculo-papular, erythema, local erythema, erythematous rash, generalized rash, exanthema, allergic dermatitis, and palmar-plantar erythrodysesthesia syndrome.

Adverse events reported on blinatumomab (AMG 103) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that blinatumomab (AMG 103) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Sinus bradycardia; Supraventricular tachycardia

CONGENITAL, FAMILIAL AND GENETIC DISORDERS - Congenital, familial and genetic disorders - Other (aplasia)

EAR AND LABYRINTH DISORDERS - Vertigo

EYE DISORDERS - Blurred vision; Optic nerve disorder; Papilledema; Periorbital edema; Photophobia

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Dyspepsia; Dysphagia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (thrombosis in device); Hypothermia; Malaise; Multi-organ failure

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Vascular access complication

INVESTIGATIONS - Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hypoproteinemia); Investigations - Other (lipase decreased); Lipase increased; Lymphocyte count increased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperkalemia; Hyperphosphatemia; Hyponatremia; Metabolism and nutrition disorders - Other (fluid overload)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Muscle cramp; Neck pain

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Amnesia; Facial muscle weakness; Muscle weakness left-sided; Nervous system disorders - Other (difficulty following commands); Neuralgia

PSYCHIATRIC DISORDERS - Delirium; Depression; Psychiatric disorders - Other (altered mental status); Psychiatric disorders - Other (sleep disorder); Restlessness

RENAL AND URINARY DISORDERS - Acute kidney injury⁷; Hematuria; Proteinuria; Urinary incontinence

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchospasm³; Pleural effusion; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura; Skin and subcutaneous tissue disorders - Other (skin irritation)

VASCULAR DISORDERS - Hematoma

Note: Blinatumomab (AMG 103) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Pregnancy and lactation

Pregnancy Category Unknown: The effect of blinatumomab on fertility has not been evaluated. Blinatumomab is not recommended in pregnant women and in women of childbearing potential not using contraception. It is not known whether blinatumomab or its metabolites are excreted in human milk. Women are not allowed to breastfeed while receiving blinatumomab.

Formulation and Stability

Blinatumomab is available as a 38.5 mcg preservative-free, white to off-white lyophilized powder for injection in 4 mL single-use vial. The agent is formulated with 3.68 mg citric acid monohydrate, 105 mg trehalose dihydrate, and 25.55 mg lysine hydrochloride, and 0.7 mg polysorbate 80, pH 7. The stopper of the vial is latex free.

IV solution stabilizer for blinatumomab (NSC 773150) is not for reconstitution of blinatumomab; it is a component of the final intravenous product. The stabilizer is available as a 10 mL single-use vial of a preservative-free, clear, colorless-to-slightly yellow liquid solution. Each solution consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate 80, pH 7. The stopper of the vial is latex free.

Store intact vials of blinatumomab and the IV solution stabilizer of blinatumomab refrigerated at 2° – 8°C (36° – 46°F). Protect from light. Shelf life stability studies of the intact vials of blinatumomab and stabilizer solution are on-going.

The stability of the prepared IV solution in **preservative-free 0.9% NaCl** is 8 days when stored refrigerated at 2° – 8°C (36° – 46°F). For storage prior to administration, the prepared infusion solution must be kept at 2° C – 8° C (36°F – 46°F). The total storage and administration time must not exceed 8 days. Once at room temperature, discard the IV bag after 96 hours (4 days).

The stability of the prepared IV solution in **Bacteriostatic 0.9% NaCl** is 14 days when stored refrigerated at 2° – 8°C (36° – 46°F). For storage prior to administration, the prepared infusion solution must be kept at 2° C – 8° C (36°F – 46°F). The total storage and administration time must not exceed 14 days. Once at room temperature, discard the IV bag after 168 hours (7 days). **The 7-day infusion with Bacteriostatic 0.9% NaCl preserved with benzyl alcohol is not allowed in patients weighing less than 22 Kg.**

Preparation

Only trained staff may prepare the blinatumomab IV solution. Blinatumomab must be prepared in an ISO Class 5 containment device, ideally in an ISO Class 7 room as described in USP <797>, but ISO Class 7 is not required. Use aseptic technique and prepare blinatumomab IV solution under a qualified biological safety cabinet.

The label on the IV bag must include the following:

- Patient name and number
- Name of the drug
- Dose (mcg/day and volume/day)
- Infusion rate
- Expiration date and time
- CAUTION: NEW DRUG – Limited by United States law to investigational use.
- Additional information as required by state, local, and country pharmacy regulations.

Blinatumomab must be dispensed in an acceptable IV bag. Acceptable bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP.

The final IV solution **must** be prepared in the following sequential order (do not deviate from this order; refer to the table below for volume details):

1. Reconstitute blinatumomab lyophilized powder

| Blinatumomab 38.5 mcg/vial |
|---|
| Add 3 mL of Sterile Water for Injection (SWFI) to the vial to yield 3.08 mL of blinatumomab at a final concentration of 12.5 mcg/mL. |

- a. Rotate the vial to dissolve all powder. Do not shake.
- b. The stability of the reconstituted vial is 4 hours at room temperature (22°C – 27°C) or 24 hours refrigerated at 2° – 8°C.

2. Add the appropriate amount of 0.9% NaCl into the IV bag

3. Add the IV solution stabilizer for blinatumomab to the IV bag

- a. Gently mix the contents of the bag to avoid foaming.
- b. Discard remaining IV solution stabilizer vial.

4. Add the calculated dose (mL) of blinatumomab into the solution in the IV bag

- a. Rotate the IV bag to mix the solution thoroughly. Do not shake. Avoid foaming the IV bag.
- b. Visually inspect for floating particles or discoloration of the IV solution. If floaters or discoloration is present, do not use the prepared solution.
- c. The total volume of blinatumomab IV solution will account for the volume of the IV infusion set for the inpatient or outpatient setting.

Note: Overfill volume depends on the volume of **the IV set** used at each institution. See Volume Calculation Table on the following page for details.

VOLUME CALCULATION TABLE

| | Volume to be prepared | Volume to be infused (rate) |
|---|---|---|
| 24-hour IV bag (includes 30 mL overfill) | <ol style="list-style-type: none"> 1. Add ____ mL NaCl (calculated volume of 0.9% NaCl)¹ into approved IV bag* 2. Add 3 mL IV solution stabilizer for blinatumomab² 3. Add ____ mL blinatumomab (calculated dose volume per 150 mL bag)³ <hr/> 150 mL total volume ⁴ | 120 mL (5 mL/hr) |
| | ¹ 0.9% NaCl (mL) = total volume to be prepared (150 mL) – stabilizer solution volume (3 mL) – blinatumomab calculated dose volume (mL) per 150 mL bag | |
| | ² Stabilizer solution (3 mL) = 0.02 x total volume to be prepared (150 mL) | |
| | ³ Blinatumomab calculated dose volume per 150 mL bag (mL) = 24 hour dose (mcg) ÷ 24 hour infusion volume (120 mL) x total volume to be prepared (150 mL) ÷ blinatumomab concentration (12.5 mcg/mL) | |
| | ⁴ Total volume (150 mL) = Volume to be infused (120 mL) + IV infusion set volume (30 mL) | |
| | Volume to be prepared | Volume to be infused (rate) |
| ALTERNATE 24-hour IV bag (includes 30 mL overfill) | <ol style="list-style-type: none"> 1. Add ____ mL NaCl (calculated volume of 0.9% NaCl)¹ into approved IV bag* 2. Add 5.4 mL IV solution stabilizer for blinatumomab² 3. Add ____ mL blinatumomab (calculated dose volume per 270 mL bag)³ <hr/> 270 mL total volume ⁴ | 240 mL (10 mL/hr) Note rate difference |
| | ¹ 0.9% NaCl (mL) = total volume to be prepared (270 mL) – stabilizer solution volume (5.4 mL) – blinatumomab calculated dose volume (mL) per 270 mL bag | |
| | ² Stabilizer solution (5.4 mL) = 0.02 x total volume to be prepared (270 mL) | |
| | ³ Blinatumomab calculated dose volume per 270 mL bag (mL) = 24 hour dose (mcg) ÷ 24 hour infusion volume (240 mL) x total volume to be prepared (270 mL) ÷ blinatumomab concentration (12.5 mcg/mL) | |
| | ⁴ Total volume (270 mL) = Volume to be infused (240 mL) + IV infusion set volume (30 mL) | |

| | Volume to be prepared | Volume to be infused (rate) |
|--|---|--|
| 48-hour IV bag (includes 30 mL overfill) | <p>4. Add ____ mL NaCl (calculated volume of 0.9% NaCl)¹ into approved IV bag*</p> <p>5. Add 5.4 mL IV solution stabilizer for blinatumomab²</p> <p>6. Add ____ mL blinatumomab (calculated dose volume per 270 mL bag)³</p> <hr/> <p style="text-align: right;">270 mL total volume⁴</p> | 240 mL (5 mL/hr) |

¹0.9% NaCl (mL) = total volume to be prepared (270 mL) – stabilizer solution volume (5.4 mL) – blinatumomab calculated dose volume (mL) per 270 mL bag

²Stabilizer solution (5.4 mL) = 0.02 x total volume to be prepared (270 mL)

³Blinatumomab calculated dose volume per 270 mL bag (mL) = 48 hour dose (mcg) ÷ 48 hour infusion volume (240 mL) x total volume to be prepared (270 mL) ÷ blinatumomab concentration (12.5 mcg/mL)

⁴Total volume (270 mL) = Volume to be infused (240 mL) + IV infusion set volume (30 mL)

| | Volume to be prepared | Volume to be infused (rate) |
|--|---|--|
| 72-hour IV bag (includes 30 mL overfill) | <p>1. Add ____ mL NaCl (calculated volume of 0.9% NaCl)¹ into approved IV bag*</p> <p>2. Add 7.8 mL IV solution stabilizer for blinatumomab²</p> <p>3. Add ____ mL blinatumomab (calculated dose volume per 390 mL bag)³</p> <hr/> <p style="text-align: right;">390 mL total volume⁴</p> | 360 mL (5 mL/hr) |

¹0.9% NaCl (mL) = total volume to be prepared (390 mL) – stabilizer solution volume (7.8 mL) – blinatumomab calculated dose volume (mL) per 390 mL bag

²Stabilizer solution (7.8 mL) = 0.02 x total volume to be prepared (390 mL)

³Blinatumomab calculated dose volume per 390 mL bag (mL) = 72 hour dose (mcg) ÷ 72 hour infusion volume (360 mL) x total volume to be prepared (390 mL) ÷ blinatumomab concentration (12.5 mcg/mL)

⁴Total volume (390 mL) = Volume to be infused (360 mL) + IV infusion set volume (30 mL)

| | Volume to be prepared | Volume to be infused (rate) |
|--|--|--|
| 96-hour IV bag (includes 30 mL overfill) | <ol style="list-style-type: none"> 1. Add _____ mL NaCl (calculated volume of 0.9% NaCl)¹ into approved IV bag* 2. Add 10.2 mL IV solution stabilizer for blinatumomab² 3. Add _____ mL blinatumomab (calculated dose volume per 510 mL bag)³ <hr/> <p style="text-align: center;">510 mL total volume⁴</p> | 480 mL (5 mL/hr) |

¹0.9% NaCl (mL) = total volume to be prepared (510 mL) – stabilizer solution volume (10.2 mL) – blinatumomab calculated dose volume (mL) per 510 mL bag

²Stabilizer solution (10.2 mL) = 0.02 x total volume to be prepared (510 mL)

³Blinatumomab calculated dose volume per 510 mL bag (mL) = 96 hour dose (mcg) ÷ 96 hour infusion volume (480 mL) x total volume to be prepared (510 mL) ÷ blinatumomab concentration (12.5 mcg/mL)

⁴Total volume (510 mL) = Volume to be infused (480 mL) + IV infusion set volume (30 mL)

* Approved bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP.

VOLUME CALCULATION TABLE: 168 hour (7 day) bags (for patients \geq 22 Kg)

| | Volume to be prepared | Volume to be infused (rate) |
|---|--|--|
| 168-hour IV bag (includes 10 mL overfill) | <ol style="list-style-type: none"> 1. Add 90 mL Bacteriostatic Sodium Chloride preserved with 0.9% benzyl alcohol into compatible empty IV bag.¹ 2. Add 2.2 mL IV Solution Stabilizer into 90 mL Bacteriostatic Sodium Chloride IV bag² 3. Add the calculated dose volume of blinatumomab into solution.³ 4. Q.S. with preservative-free 0.9% NaCl to final volume of 110 mL.⁴ | 100.8 mL (0.6 mL/hr) |

¹Approved bags include those made of polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP.

²Stabilizer solution (2.2 mL) = 0.02 x total volume to be prepared (110 mL)

³Blinatumomab calculated dose volume per 110 mL bag (mL) = 168-hour dose (mcg) ÷ volume to be infused (100.8 mL) x total volume to be prepared (110 mL) ÷ 12.5 mcg/mL of blinatumomab

⁴Calculated volume of preservative-free 0.9% NaCl (mL):

[Total volume to be prepared (110 mL)] – [Bacteriostatic Sodium Chloride volume (90 mL)] - [IV stabilizer solution volume (2.2 mL)] – [blinatumomab calculated dose volume (mL)] = _____ mL preservative-free NS

Guidelines for Administration: See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Premedication with dexamethasone is required prior to the first dose of blinatumomab in the first cycle, prior to a step dose.

IV infusion and infusion set details:

Blinatumomab must be administered as an infusion through an acceptable central line at rates described in the tables above to deliver the intended daily dose. Only **non-DEHP PVC, polyolefin, or EVA tubing/lines with a 0.2 µm inline filter are acceptable for bags prepared for 24 to 96 hour infusions (i.e., prepared with preservative-free normal saline).**

For 168 hour (7-day) infusions prepared with bacteriostatic sodium chloride, use non-DEHP PVC, polyolefin, or EVA tubing/lines; an in-line filter is NOT required during the administration of blinatumomab 7-day IV bag. This is to alleviate the IV pressure or backflow into the IV line during the IV infusion of 7-day bag.

Avoid flushing the line during the Blinatumomab infusion to avoid bolus dosing. There are some times when there will be unavoidable flushing for central line care. It is also unavoidable to flush the line at completion of the Blinatumomab 28 day cycle. For outpatient administration, use FDA approved pumps. Only the exact volume should be administered; any remaining overfill should be discarded appropriately.

Infusion pump requirements:

Use a programmable pump that is approved by the appropriate regulatory authority for the country in which the subject is undergoing treatment. The pump alarm must be visual and auditory. **The pump must be lockable. Elastomeric pumps are NOT allowed.** CADD pumps are allowed; non-DEHP (TOTM) 250 mL CADD cassettes are allowed, however, all other cassettes used in CADD pumps are not compatible with blinatumomab and thus, **not** allowed.

Should blinatumomab need to be administered through a pharmacy satellite or home health care service center, refer to the outpatient administration guidelines in [Appendix X-A](#).

Record all infusion interruptions. Blinatumomab continuous infusion administration should not be interrupted, if possible. In case of infusion interruption due to any technical or logistical reasons (e.g. routine PORT needle changes, procedural sedation), the interruption should be as short as possible and the infusion restarted as soon as possible.

For interruptions lasting longer than four hours, the re-initiation of the infusion must take place in the hospital under supervision of the investigator for at least 12 hours after re-initiation of the infusion to evaluate for possible side effects. Monitor patients for potential adverse events as described in the protocol and the Investigator Brochure.

Monitor patients for cytokine release syndrome, tumor lysis syndrome, and infusion reaction. Refer to protocol for specific recommendation. Monitor patients for psychiatric events such as confusion, disorientation, and cognitive attention disturbances. Patients should not drive or operate dangerous machinery while receiving blinatumomab.

Supplier

Blinatumomab and the solution stabilizer for blinatumomab is supplied by Amgen, Inc. and distributed by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **Do not use commercial supply.**

Obtaining the Agent**Agent Ordering:**

NCI supplied agent may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NIH Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution. This study does not need a starter supply. Confirmation of patient enrollment to an arm with blinatumomab is required for initial drug shipment.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the Maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

Agent Accountability**Agent Inventory Records:**

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP IAM account and the Maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: <http://ctep.cancer.gov/forms/>
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:
<https://ctepcore.nci.nih.gov/OAOP/>
- CTEP Identity and Access Management (IAM) account:
<https://ctepcore.nci.nih.gov/iam/>
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

6.2 ASPARAGINASE ERWINIA CHRYSANTHEMI

(*Erwinia Chrysanthemi*, Erwinase®, Erwinaze™, Crisantaspase) NSC #106977

(05/07/19)

Source and Pharmacology:

L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of L-asparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

Asparaginase *Erwinia chrysanthemi* (Erwinase®) is asparaginase derived from cultures of *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase *Erwinia chrysanthemi* is immunologically distinct from *E.coli* L-asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to *Escherichia coli*-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase *Erwinia chrysanthemi*. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease state. The following data have been reported on each of the three preparations of asparaginase:

| Clinical Pharmacology of Asparaginase Formulation | Elimination half-life (IM) | % Anti-Asparaginase Antibody positive patients |
|---|------------------------------------|--|
| Native <i>Escherichia Coli</i> | 26-30 hours | 45-75 |
| Pegylated-asparaginase | 5.5-7 days | 5-18 |
| Erwinia Asparaginase | 16 hours (7-13 hrs package insert) | 30-50 |

From: Avramis, V; Panosyan, E; Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations: The Past, the Present and Recommendations for the Future. *Clin Pharmacokinet* 2005; 44 (4): 367-393.

Effective asparaginase levels have been defined as activity of ≥ 0.1 International Units per mL. Clinical trials with asparaginase *Erwinia chrysanthemi* demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule using the IM route of administration. In a multicenter study characterizing the pharmacokinetic profile of 25,000 International Units/m² Erwinaze® given intravenously over one hour on the same dosing schedule of Monday, Wednesday, Friday for 2 consecutive weeks, 83% (20/24) and 43% (9/21) of evaluable patients achieved an asparaginase activity level of ≥ 0.1 International Units/mL at 48 post-dose 5 and 72 hours post-dose 6, respectively. No formal drug interaction studies have been performed with asparaginase *Erwinia chrysanthemi*.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|---|---|--|
| Immediate: Within 1-2 days of receiving drug | | Allergic reactions, anaphylaxis, urticaria | Local injection site reactions, fever |
| Prompt: Within 2-3 weeks, prior to the next course | | | Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure |
| Unknown Frequency and Timing: | Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. Adequate, well-controlled studies of asparaginase <i>Erwinia chrysanthemi</i> have NOT been conducted. It is not known whether asparaginase <i>Erwinia chrysanthemi</i> will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase <i>Erwinia chrysanthemi</i> is excreted into breast milk. The use of asparaginase <i>Erwinia chrysanthemi</i> should be avoided in pregnant or lactating patients. | | |

(L) Toxicity may also occur later.

Formulation and Stability:

Asparaginase *Erwinia chrysanthemi* is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi* and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store intact vials between 2°C and 8°C (36° to 46°F). Protect from light.

Guidelines for Administration:

See Treatment and Dose Modification sections of the protocol.

Erwinia asparaginase can be administered by intramuscular injection or by intravenous infusion. Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution.

For intramuscular administration, the contents of each vial should be reconstituted by slowly adding 1 mL or 2 mL of sterile, preservative-free NS to the inner vial wall. The final concentration is 10,000 International Units per mL when using 1 mL for reconstitution or 5,000 International Units per mL when using 2 mL for reconstitution. Gently mix or swirl the contents to dissolve the contents of the vial. Do not shake or invert the vial. The resulting solution should be clear and colorless. Discard if any particulate matter or protein aggregates are visible. **Withdraw the appropriate dosing volume into a polypropylene syringe within 15 minutes of reconstitution.** Polycarbonate luer-lok syringes from B-D (1 mL) are also acceptable (personal communication, EUSA Pharma). Discard any unused drug; do not save or use any unused drug remaining in the vial. No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

For intravenous use, slowly inject the appropriate volume of reconstituted solution into a Normal Saline 100 mL infusion bag; do not shake or squeeze the bag. Infuse *Erwinia* asparaginase over 1-2 hours. Do not infuse other intravenous drugs through the same intravenous line while infusing *Erwinia* asparaginase. Please see <http://www.erwinazesupply.com> to check which batches may require the use a 0.2-micron, low protein binding, in-line filter for IV administration.

Administer the dose within a 4 hour time period from reconstitution. If the dose is not used within this time period, discard the dose. Do not freeze or refrigerate the reconstituted solution.

The product used in Australia has an 8 hour expiry (from Porton Biopharma, Salisbury, UK).

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

Drug Ordering:

In the United States, asparaginase *Erwinia chrysanthemi* (Erwinaze®) is distributed by McKesson Plasma and Biologics. Verify your institution has a contract with McKesson Plasma and Biologics before ordering. If not, contact McKesson at 877-625-2566 for assistance setting up an account.

Orders may be placed online or via phone, fax, or email.

- Orders may be placed online via <http://Connect.McKesson.com>
- Orders may be submitted via fax to 888-752-7626
- Orders may be submitted via email or MPBOrders@McKesson.com
- Email all other information requests to MPB@McKesson.com

Regular order hours: M-F 9:00 am – 7:30 pm EST;

Emergency order after hours services (24/7/365): 877-625-2566

Orders placed by 7:30 pm EST will ship the next day.

CANADIAN SITES:

Asparaginase *Erwinia chrysanthemi* is commercially available in Canada. Canadian sites may purchase the Canadian commercial supply from Jazz Pharmaceuticals via CGF Pharmatech, Montreal, Quebec (order desk phone: 1-514-343-0344 or 1-866-343-0344, fax: 1-514-343-0340). CGF requests that a site fax a Purchase Order number. There is no special fax order form. Shipments are sent Monday to Wednesday only and usually arrive at the site within 48-72 hours.

6.3 CYCLOPHOSPHAMIDE INJECTION

(03/13/13)

(Cytoxan) NSC #26271

Source and Pharmacology:

Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent *in vitro* than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|---|--|
| Immediate: Within 1-2 days of receiving drug | Anorexia, nausea & vomiting (acute and delayed) | Abdominal discomfort, diarrhea | Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH |
| Prompt: Within 2-3 weeks, prior to the next course | Leukopenia, alopecia, immune suppression | Thrombocytopenia, anemia, hemorrhagic cystitis (L) | Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression |
| Delayed: Any time later during therapy | Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent) ¹ (L) | Amenorrhea ¹ | Gonadal dysfunction: ovarian failure ¹ (L), interstitial pneumonitis, pulmonary fibrosis ² (L) |
| Late: Any time after completion of treatment | | | Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis |
| Unknown Frequency and Timing: | Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects. | | |

¹ Dependent on dose, age, sex, and degree of pubertal development at time of treatment.² Risk increased with pulmonary chest irradiation and higher doses.

(L) Toxicity may also occur later.

Formulation and Stability:

Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25°C (77°F) is recommended. The product will withstand brief exposures to temperatures up to 30°C (86°F).

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Cyclophosphamide for Injection:

If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution further dilute in dextrose or saline containing solutions for IV use.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.4 CYTARABINE - ALL ROUTES

(07/13/15)

(Cytosine arabinoside, Ara-C, Cytosar®) NSC #63878

Source and Pharmacology:

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{1/2}$ of about 10 minutes, with a secondary elimination phase $t_{1/2}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{1/2}$ of about 2 hours.

Toxicity: (Intravenous, SubQ, IM)

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|---|---|
| Immediate: Within 1-2 days of receiving drug | Nausea, vomiting, anorexia <i>With High Dose:</i> conjunctivitis | Flu-like symptoms with fever, rash | Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis, swelling, pain and redness at the site of the medication injection (SubQ or IM injection) <i>With High Dose:</i> cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia, nystagmus, a decreased level of |

| | | | |
|--|--|---|---|
| | | | consciousness, personality changes, somnolence, seizures |
| Prompt: Within 2-3 weeks, prior to the next course | Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia | Diarrhea, hypokalemia, hypocalcemia, hyperuricemia <i>With High Dose:</i> capillary pulmonary leak syndrome (RDS, pulmonary edema) | Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles |
| Delayed: Any time later during therapy, excluding the above conditions | | | Asymptomatic nonoliguric rhabdomyolysis |
| Unknown Frequency and Timing: | Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk. | | |

Toxicity: (Intrathecal)

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|---|--|--|---|
| Immediate: Within 1-2 days of receiving drug | Nausea, vomiting, fever, headache | Arachnoiditis | Rash, somnolence, meningismus, convulsions, paresis |
| Prompt: Within 2-3 weeks, prior to the next course | | | Myelosuppression, ataxia |
| Delayed: Any time later during therapy, excluding the above condition | | | Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy) |

Formulation:

Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

IV Infusion:

Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS injection. Solution containing bacteriostatic agent should not be used for the preparation of doses $> 200 \text{ mg/m}^2$. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

Low Dose ($\leq 200 \text{ mg/m}^2/\text{dose}$): For administration by IV push, reconstitute to a concentration of 20-100 mg/mL.

High Dose ($\geq 1,000 \text{ mg/m}^2/\text{dose}$): Administer steroid eye drops (dexamethasone or prednisolone), 2 drops each eye q6h beginning immediately before the first dose and continuing 24 hours after the final dose. If patient does not tolerate steroid eye drops, administer artificial tears on a q2-4 hour schedule.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5W or NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

Subcutaneous or IM:

Dilute with Bacteriostatic Water for Injection or NS to a concentration not to exceed 100 mg/mL. Rotate injection sites for subcutaneous/IM administration.

Intrathecal:

For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least $\frac{1}{2}$ the volume delivered.

| Patient Age (years) | Recommended volume | 10% CSF volume | CSF Volume * |
|---------------------|--------------------|----------------|---|
| 1 – 1.99 | 5 – 10 mL | 5 mL | $50 \pm 10 \text{ mL}$ (babies) |
| 2 – 2.99 | 5 – 10 mL | 8 mL | $80 \pm 20 \text{ mL}$ (younger children) |
| 3 – 8.99 | 5 – 10 mL | 10 mL | $100 \pm 20 \text{ mL}$ (older children) |
| 9 or greater | 5 – 10 mL | 13 mL | $130 \pm 30 \text{ mL}$ (adults) |

*Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; *N Engl J Med.* 1962 Dec 20; 267:1273-8

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25°C but contains no preservative and should be administered as soon as possible after preparation.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.5 DEXAMETHASONE

(05/07/19)

(Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC #34521

Source and Pharmacology:

Dexamethasone is a synthetic fluorinated glucocorticoid devoid of mineralocorticoid effects. Dexamethasone, 0.75 mg, has potent anti-inflammatory activity equivalent to approximately 5 mg of predniSO(LO)ne. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce

the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age: 2.3 to 9.5 hours, 8 to 16 years: 2.82 to 7.5 hours, and adults (age not specified): 3 to 6 hours. The biologic half-life is 36-72 hours. It is primarily metabolized in the liver and excreted by the kidneys.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|---|---|---|
| Immediate: Within 1-2 days of receiving drug | Insomnia, hyperphagia | Gastritis | Hyperuricemia |
| Prompt: Within 2-3 weeks, prior to the next course | Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L) | Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema | Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache |
| Delayed: Any time later during therapy | Cushing's syndrome (moon facies, truncal obesity) | Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia | Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis ¹ (L) |
| Late: Any time after completion of treatment | | Cataracts (which may be reversible on discontinuation of dexamethasone in children) | |
| Unknown Frequency and Timing: | Fetal and teratogenic toxicities: dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk. | | |

¹ Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.

(L) Toxicity may also occur later.

Formulation and Stability:

Oral:

Available in 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg tablets; liquid formulations are available in 0.5 mg/5 mL and 1 mg/1 mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magnesium stearate, corn starch, lactose, and various dyes. Liquid formulations may include: 5%-30% alcohol, benzoic acid, sorbitol, sodium saccharin, glycerin, purified water, and various dyes.

Australia – only 0.5 mg and 4 mg tablets available.

Injection:

Dexamethasone Sodium Phosphate Solution for Injection is available as 4 mg/mL (1 mL, 5 mL, and 30 mL vials) and 10 mg/mL (1 mL and 10 mL vial sizes). Vials are available in multi-dose vials as well as unit of use vials and syringes. Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA.

Australia – 1 mg/mL solution for injection available.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) section of the protocol.

Dexamethasone Sodium Phosphate for Injection may be given IV, or IM undiluted. For IV use, it may be further diluted in dextrose or saline containing solutions. Avoid using benzyl alcohol-containing dexamethasone solutions in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.6 DOXORUBICIN
(Adriamycin®) NSC #123127

(05/09/11)

Source and Pharmacology:

An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of DOXOrubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of DOXOrubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of DOXOrubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of DOXOrubicin cytoidal activity. DOXOrubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of DOXOrubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH^\bullet). Free radical formation has been implicated in DOXOrubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with DOXOrubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. DOXOrubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

DOXOrubicin serum decay pattern is multiphasic. The initial distributive $t_{1/2}$ is approximately 5 minutes suggesting rapid tissue uptake of DOXOrubicin. The terminal $t_{1/2}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with DOXOrubicin metabolism are CYP2D6 and CYP3A4.

Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of DOXOrubicin and its major metabolite, DOXOrubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of DOXOrubicin.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|--|--|
| Immediate: Within 1-2 days of receiving drug | Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva | Hyperuricemia, facial flushing, sclerosis of the vein | Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias |
| Prompt: Within 2-3 weeks, prior to the next course | Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia | Mucositis (stomatitis and esophagitis), hepatotoxicity | Radiation recall reactions, conjunctivitis and lacrimation |
| Delayed: Any time later during therapy | | Cardiomyopathy ¹ (CHF occurs in 5-20% at cumulative doses $\geq 450 \text{ mg/m}^2$) (L) | Cardiomyopathy ¹ (CHF occurs in < 5% at cumulative doses $\leq 400 \text{ mg/m}^2$) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis |
| Late: Any time after completion of treatment | Subclinical cardiac dysfunction | CHF (on long term follow up in pediatric patients) | Secondary malignancy (in combination regimens) |
| Unknown Frequency and Timing: | Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of DOXOrubicin have been noted in animal models. DOXOrubicin is excreted into breast milk in humans | | |

¹ Risk increases with cardiac irradiation, exposure at a young or advanced age.

(L) Toxicity may also occur later.

Formulation and Stability:

DOXOrubicin is available as red-orange lyophilized powder for injection in 10 mg¹, 20 mg¹, 50 mg¹ vials and a preservative-free 2 mg/mL solution in 10 mg¹, 20 mg¹, 50 mg¹, 200 mg² vials.

¹: Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of DOXOrubicin, to enhance dissolution.

² Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration, 2°-8°C (36°-46°F) when protected from light. DOXOrubicin further diluted in 50 – 1,000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D₅W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.7 LEUCOVORIN CALCIUM

(05/07/19)

(LCV, Wellcovorin®, citrovorum factor, folic acid, Calcium folinate) NSC #003590

Source and Pharmacology:

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active compound of the mixture is the (-)-l-isomer, known as Citrovorum factor or (-)-folic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase. In contrast, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridyllic acid (an active metabolite of 5-FU) to thymidylate synthase and thereby enhances the inhibition of this enzyme. Peak serum levels of 5-methyl THF (an active metabolite) were reached at approximately 1.3-1.5 hours (IV/IM) and 2.3 hours for the oral form. The terminal half-life of total reduced folates was approximately 6.2 hours. Following oral administration, leucovorin is rapidly absorbed and expands the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the l-isomer (the biologically active form) but only 20% of the d-isomer is absorbed. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg doses. Both oral and parenteral leucovorin raise the CSF folate levels.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|--|---|
| Immediate: Within 1-2 days of receiving drug | | | Anaphylaxis, urticaria, seizure |
| Unknown Frequency and timing: | Fetal toxicities and teratogenic effects of leucovorin in humans are unknown. It is unknown whether the drug is excreted in breast milk. | | |

Formulation and Stability:

Leucovorin calcium for injection is supplied as a sterile ready to use liquid and a sterile powder for injection. The 10 mg/mL preservative free liquid is available in 50 mL vials containing sodium chloride 400 mg/vial. Store preservative free liquid in the refrigerator at 2°-8°C (36°-46°F)

protected from light. The powder for injection is available in 50 mg, 100 mg, 200 mg, and 350 mg vials. Store at room temperature 15°-25°C (59°-77°F) protected from light. Reconstitute the sterile powder with sterile water for injection or bacteriostatic water for injection to a concentration of 10 mg/mL leucovorin calcium. **Do not use diluents containing benzyl alcohol for doses > 10 mg/m² or in infants < 2 years of age or patients with allergy to benzyl alcohol.** When Bacteriostatic Water is used, the reconstituted solution is good for 7 days. If reconstituted with SWFI, use solution immediately as it contains no preservative. One milligram of leucovorin calcium contains 0.004 mEq of leucovorin and 0.004 mEq of calcium.

The oral form of leucovorin is available as 5 mg, 10 mg, 15 mg, and 25 mg tablets. Inactive ingredients vary depending on manufacturer but tablet formulations may include: corn starch, dibasic calcium phosphate, magnesium stearate, pregelatinized starch, lactose, microcrystalline cellulose, and sodium starch glycolate.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Injection:

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Oral:

Oral leucovorin should be spaced evenly (e.g., every six hours) throughout the day and may be taken without regard to meals. Doses > 25 mg should be given IV due to the saturation of absorption.

Leucovorin should not be administered < 24 hours after intrathecal injections which contain methotrexate unless there are special circumstances.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.8 MERCAPTOPURINE

(11/27/17)

(6-MP, Purinethol®, Purixan™, 6-mercaptopurine) NSC #000755

Source and Pharmacology:

Mercaptopurine is an analogue of the purine bases adenine and hypoxanthine. The main intracellular pathway for MP activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT) which catalyzes the conversion of MP to several active nucleotide metabolites including thioinosinic acid, a ribonucleotide which can interfere with various metabolic reactions necessary for nucleic acid (RNA and DNA) biosynthesis. It can also cause pseudofeedback inhibition of the first step in de novo purine biosynthesis or convert to another ribonucleotide which can cause feedback inhibition. Mercaptopurine can be incorporated into DNA in the form of TG nucleotides as well and thus produce toxicity. The absorption of an oral dose of MP is incomplete and variable, with only about 16%-50% of an administered dose reaching the systemic circulation secondary to a first pass metabolism in the liver. Food intake and co-administration with cotrimoxazole (TMP/SMX) significantly reduces absorption of MP. After IV

administration, MP has a plasma half-life of 21 minutes in children and 47 minutes in adults. Approximately 19% is bound to protein. Mercaptopurine is well distributed into most body compartments except the CSF. (With high dose IV MP the CSF to plasma ratio is 0.15.) MP is metabolized by xanthine oxidase in the liver to 6-Thiouric acid an inactive metabolite. In patients receiving both MP and allopurinol (a xanthine oxidase inhibitor) the dose of MP must be reduced by 50-75%. Since *TPMT*, 6-thiopurine methyltransferase, is also one of the enzymes involved in the metabolism of MP, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of MP and prone to develop rapid bone marrow suppression following the initiation of treatment. Mercaptopurine is excreted in urine as metabolites and some unchanged drug; about half an oral dose has been recovered in 24 hours. A small proportion is excreted over several weeks.

Toxicity:

| Incidence | Toxicities |
|---|---|
| Common (>20% of patients) | Neutrophil count decreased, white blood cell decreased, anorexia, fatigue. |
| Occasional (4 - 20% of patients) | Diarrhea, nausea, vomiting, malaise, oligospermia, infection, fever, platelet count decreased, anemia, mucositis, stomach pain, ulcerative bowel lesion, skin rash, alanine aminotransferase increased, aspartate aminotransferase increased |
| Rare (≤3% of patients) | Urticaria, skin hyperpigmentation, alopecia, hyperuricemia, hepatic failure, hepatic necrosis, blood bilirubin increased, pulmonary fibrosis, secondary malignant neoplasm, renal toxicity, uricosuria, pancreatitis |
| Pregnancy and Lactation | Pregnancy Category D Mercaptopurine can cause fetal harm, including an increased incidence of abortion and stillbirth. Advise women to avoid becoming pregnant while receiving mercaptopurine. Mercaptopurine was embryo-lethal and teratogenic in several animal species (rat, mouse, rabbit, and hamster). It is not known whether mercaptopurine is excreted in human milk; breastfeeding should be avoided. |

Formulation and Stability:

Mercaptopurine is available as a 50 mg tablet containing mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid. Store at 15°-25°C (59°-77°F) in a dry place. In the United States, mercaptopurine is also available as an oral suspension in a concentration of 20 mg/mL (2,000 mg/100 mL per bottle). The oral suspension is a pink to brown viscous liquid supplied in amber glass multiple-dose bottles with a child resistant closure. It should be stored at 15°-25°C (59°-77°F) in a dry place.

NOTE: the concentration of the commercially available suspension (20 mg/mL) and the compounded suspension (50 mg/mL) are NOT the same; doses should be prescribed in the milligrams required, not mL.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Mercaptopurine should be taken consistently at the same time every day.

If allopurinol is also given, the oral dose of mercaptopurine should be reduced by 67-75%. Patients with severe myelosuppression should have their thiopurine S-methyltransferase (*TPMT*) status and/or their thiopurine metabolite concentrations evaluated, so that the dose of mercaptopurine can

be reduced in patients with a *TPMT* defect. Patients with the rare homozygous deficient *TPMT* phenotype may tolerate only 1/10th to 1/20th the average mercaptopurine dose. *TPMT* testing and thiopurine metabolite measurements are commercially available.

Suspension:

For children unable to swallow the tablets whole, a 50 mg/mL oral suspension can be compounded. The suspension is prepared by crushing 50 mercaptopurine 50 mg tablets in a mortar and adding 8.5 mL sterile water for irrigation. The mixture is triturated to form a smooth paste. Next, 16.5 mL simple syrup (pH=7) are added with continuous mixing and finally cherry syrup (pH=7.1) is added to a total volume of 50 mL. The suspension is stable in amber glass bottles at room temperature (19°C -23°C) for up to 5 weeks. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Aliabadi HM, Romanick M, Desai S et al. Effect of buffer and antioxidant on stability of mercaptopurine suspension. *Am J Health-Syst Pharm.* 65:441-7, 2008.)

Supplier:

Commercially available from various manufacturers. See package insert for further information.
PLEASE NOTE there is a difference in the concentration of the commercially available (20 mg/mL) and extemporaneously compounded (50 mg/mL) oral suspensions.

6.9 METHOTREXATE – ALL ROUTES
(MTX, amethopterin, Trexall®, Xatmep®) NSC #000740

(05/07/19)

Source and Pharmacology:

A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 μmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m² dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m² absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to <5 children out of every 100 |
|--|--|---|--|
| Immediate: Within 1-2 days of receiving drug | Transaminase elevations | Nausea, vomiting, anorexia | Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures ¹ , photosensitivity |
| Prompt: Within 2-3 weeks, prior to the next course | | Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue | Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity ¹ (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) diarrhea, conjunctivitis |
| Delayed: Any time later during therapy, excluding the above conditions | | Learning disability ¹ (L) | Pneumonitis, pulmonary fibrosis (L), hepatic fibrosis (L), osteonecrosis (L), leukoencephalopathy ¹ (L), pericarditis, pericardial effusions, hyperpigmentation of the nails |
| Late: Any time after the completion of therapy | | | Progressive CNS deterioration ¹ |
| Unknown Frequency and Timing: | Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations. | | |

¹ May be enhanced by HDMTX and/or cranial irradiation.

(L) Toxicity may also occur later.

Intrathecal Therapy (Methotrexate Single Agent)**Toxicity:**

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|---|--|--|--|
| Immediate: Within 1-2 days of receiving drug | Nausea, headache | Arachnoiditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis) | Anaphylaxis, vomiting, seizures(L), malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000), |
| Prompt: Within 2-3 weeks, prior to the next course | | | Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction |
| Delayed: Any time later during therapy, excluding the above condition | | Cognitive disturbances (L) ¹ , learning disability (L) ¹ | Leukoencephalopathy ¹ (L) |
| Late: Any time after the completion of treatment | | | Progressive CNS deterioration ¹ |

¹ May be enhanced by HDMTX and/or cranial irradiation.

(L) Toxicity may also occur later.

Formulation & Stability:

Methotrexate tablets are available as 2.5 mg, 5 mg, 7.5 mg, 10 mg and 15 mg. Inactive ingredients vary depending on manufacturer but tablet formulations may include: anhydrous lactose, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium carbonate monohydrate, talc and titanium dioxide and various dyes. Store at controlled room temperature 15°-30°C (59°-86°F) and protect from light.

Australia/NZ – only 2.5 mg and 10 mg tablets available.

Methotrexate is also available as a clear yellow to orange oral solution (Xatmep®) that contains 2.5 mg of methotrexate per milliliter (equivalent to 2.74 mg of methotrexate sodium/mL) in a 120 mL bottle. Inactive ingredients include purified water, sodium citrate, citric acid, methylparaben sodium, propylparaben sodium, and sucralose. It may also contain sodium hydroxide or hydrochloric acid for pH adjustment. It is packaged in a high-density polyethylene (HDPE) bottle with a child-resistant cap and tamper-evident seal. Store oral solution under refrigeration (2°C to 8°C/36°F to 46°F) prior to dispensing. Avoid freezing and excessive heat. After dispensing, patients may store methotrexate oral solution at room temperature (20°C to 25°C/68°F to 77°F) for up to 60 days; excursions permitted to 15°C to 30°C (59°F to 86°F).

Methotrexate for Injection is available as a lyophilized powder for injection in 1,000 mg vials. The powder for injection contains approximately 7 mEq sodium in the 1,000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative.

Sterile methotrexate powder or solution is stable at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Protect from light

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of protocol. Leucovorin rescue may be necessary with certain doses of methotrexate.

Oral administration: Methotrexate injection diluted in water can be used for oral administration, if an oral solution formulation is not readily available (Marshall PS, Gertner E. Oral administration of an easily prepared solution of injectable methotrexate diluted in water: a comparison of serum concentrations vs methotrexate tablets and clinical utility. *J Rheumatol* 23:455-8, 1996).

For IM/IV use: Powder for injection: Dilute 1,000 mg vial with 19.4 mL of preservative free SWFI, D5W or NS to a 50 mg/mL concentration. The powder for injection may be further diluted in NS or dextrose containing solutions to a concentration of \leq 25mg/mL for IV use.

The 25 mg/mL solution may be given directly for IM administration or further diluted in Saline or Dextrose containing solutions for IV use. **Do not use the preserved solution for high dose methotrexate administration due to risk of benzyl alcohol toxicity.** Methotrexate dilutions are chemically stable for at least 7 days at room temperature but contain no preservative and should be used within 24 hours. Diluted solutions especially those containing bicarbonate exposed to direct sunlight for periods exceeding 4 hours should be protected from light.

High dose methotrexate requires alkalinization of the urine, adequate hydration and leucovorin rescue. Avoid sulfamethoxazole/trimethoprim, probenecid, penicillins, cephalosporins, aspirin, proton pump inhibitors, and NSAIDS as renal excretion of MTX is inhibited by these agents.

For Intrathecal use: Use **preservative free** 25 mg/mL solution.

For intrathecal administration, dilute with 5-10 mL preservative free NS, lactated Ringer's, or Elliot's B solution as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

| Patient Age (years) | Methotrexate dose | Recommended volume | 10% CSF volume | CSF Volume * |
|---------------------|-------------------|--------------------|----------------|-----------------------------------|
| 1-1.99 | 8 mg | 5-10 mL | 5 mL | 50 \pm 10 mL (babies) |
| 2-2.99 | 10 mg | 5-10 mL | 8 mL | 80 \pm 20 mL (younger children) |
| 3-8.99 | 12 mg | 5-10 mL | 10 mL | 100 \pm 20 mL (older children) |
| 9 or greater | 15 mg | 5-10 mL | 13 mL | 130 \pm 30 mL (adults) |

*Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; *N Engl J Med.* 1962 Dec 20; 267:1273-8

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Diluted methotrexate for intrathecal administration is stable for 24 hours at 25°C but contains no preservative and should be administered as soon as possible after preparation.

Supplier:

Commercially available from various manufacturers. See package insert for further information.

6.10 PEGASPARGASE

(06/05/17)

(PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase,

Oncaspar®)

NSC #624239

Source and Pharmacology:

Pegaspargase is a modified version of the enzyme L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Pegaspargase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L-asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of pegaspargase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with Pegaspargase. The approximate $t_{1/2}$ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or sex. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of pegaspargase (2,500 IU/m²), *E. coli* L-asparaginase (2,5000 IU/m²), or *Erwinia* (2,5000 IU/m²), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days, 1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of pegaspargase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to non-hypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|---|--|
| Immediate: Within 1-2 days of receiving drug | Allergic reactions (total likelihood of local, and/or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea | Allergic reactions (total likelihood of local, and/or systemic reaction if no previous hypersensitivity reaction to native asparaginase), rash | Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia |
| Prompt: Within 2-3 weeks, prior to the next course | Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L) | Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase | Hemorrhage (L), DIC, thrombosis, anorexia, weight loss, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis [SBE], URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain |
| Delayed: Any time later during therapy | | | Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure |
| Unknown Frequency and Timing: | Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk. | | |

(L)Toxicity may also occur later.

Formulation and Stability:

Each milliliter of pegaspargase contains: PEG-L-asparaginase 750 IU \pm 20%, monobasic sodium phosphate, USP 1.20 mg \pm 5% dibasic sodium phosphate, USP 5.58 mg \pm 5%, sodium chloride, USP 8.50 mg \pm 5%, Water for Injection, USP qs to 1 mL. The specific activity of pegaspargase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°-46°F). Do not use if stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

For IM administration: the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

For IV administration: dilute pegaspargase in 100 mL of NS or D5W and infuse over 1 to 2 hours through a NS or D5W running infusion line. Pegaspargase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. Pegaspargase diluted in 100 mL of NS is stable for up to 72 hours refrigerated (4°C [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy or if precipitate is present.

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

Supplier:

Commercially available. See package insert for further information.

6.11 PREDNISO(LO)NE

(11/16/17)

(Deltasone®, PredniSO(LO)ne Intensol®, Rayos®, Meticorten®, Liquid Pred®, Pediapred®, Millipred®, OraPred ODT®) NSC #10023 (predniSO(LO)ne), NSC# 9151 (prednisolone)

Source and Pharmacology:

PredniSO(LO)ne and prednisolone are synthetic compounds closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. PredniSO(LO)ne is approximately 75% protein bound with a plasma $t_{1/2}$ of 3.2 to 4 hours. (Biologic half-life is 12- 36 hours.)

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|---|---|---|
| Immediate: Within 1-2 days of receiving drug | Insomnia, hyperphagia | Gastritis | Hyperuricemia |
| Prompt: Within 2-3 weeks, prior to the next course | Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L) | Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema | Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache |
| Delayed: Any time later during therapy | Cushing's syndrome (moon facies, truncal obesity) | Striae and thinning of the skin, easy bruising, muscle weakness, osteopenia | Spontaneous fractures (L), growth suppression, peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis ¹ (L) |
| Late: Any time after completion of treatment | | Cataracts (which may be reversible on discontinuation of predniSO(LO)ne in children) | |
| Unknown Frequency and Timing: | Fetal and teratogenic toxicities: Corticosteroids cross the placenta (predniSO(LO)ne has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. PredniSO(LO)ne is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with predniSO(LO)ne doses \leq 20 mg/day. | | |

¹ Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.

(L) Toxicity may also occur later.

Formulation and Stability:

PredniSO(LO)ne is available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets. Also available as a solution in 1 mg/1 mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

Prednisolone is available as 5 mg scored tablets (base) and 10 mg, 15 mg, and 30 mg orally disintegrating tablets (ODT; sodium phosphate [strength expressed as base]). Liquid formulations of prednisolone are available as 15 mg/5 mL oral solution (base); 5 mg/5 mL, 10 mg/5 mL, 15 mg/5 mL, 20 mg/5 mL oral solution (sodium phosphate [strength expressed as base]); and 15 mg/5 mL oral syrup (base). Inactive ingredients vary depending on manufacturer. Tablet formulations may contain dyes and liquid formulations may contain edetate disodium, methylparaben, saccharin sodium.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

PredniSO(LO)ne and prednisoLONE are equipotent corticosteroids.

Supplier:

Commercially available from various sources. See package insert for further information.

6.12 THIOGUANINE

(12/05/16)

(6-thioguanine, tioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, WR-1141, Tabloid®, Lanvis®) NSC #752

Source and Pharmacology:

Thioguanine is a purine analogue of the nucleic acid guanine with the substitution of a thiol group in place of the hydroxyl group on guanine. The main intracellular pathway for 6-TG activation is catalyzed by the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT) which catalyzes the conversion of 6-TG to the active nucleotide, 6-thioguanlyc acid. The monophosphate nucleotide form of 6-TG inhibits *de novo* purine synthesis and purine interconversion reactions, whereas the nucleotide triphosphate metabolite is incorporated directly into nucleic acids. Incorporation of fraudulent nucleotides into DNA interferes with DNA replication and results in the formation of DNA strand breaks. The net consequence of its action is a sequential blockade of the synthesis and utilization of the purine nucleotides. The relative contribution of each of these actions to the mechanism of cytotoxicity of 6-TG is unclear. The absorption of an oral dose of 6-TG is incomplete and variable, averaging approximately 30% of the administered dose (range: 14% to 46%).

6-TG undergoes deamination by the enzyme guanine deaminase resulting in 6-thioxanthene, which is then oxidized by xanthine oxidase to 6-thiouric acid. In contrast to mercaptopurine, 6-TG is not a direct substrate for xanthine oxidase. Because the inhibition of xanthine oxidase results in the accumulation of 6-thioxanthene, an inactive metabolite, adjustments in 6-TG dosage are not required for patients receiving allopurinol. Since *TPMT*, 6-thiopurine methyltransferase, is one of the enzymes involved in the deactivation of 6-TG, those individuals who have an inherited deficiency of the enzyme may be unusually sensitive to the myelosuppressive effects of 6-TG and prone to developing rapid bone marrow suppression following the initiation of treatment.

Peak levels occur 2 to 4 hours after oral administration with a median half-life is about 90 minutes (range: 25-240 minutes). Very little unchanged drug is excreted renally.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|--|---|---|
| Immediate: Within 1-2 days of receiving drug | | Anorexia, nausea, vomiting, diarrhea, malaise | Urticaria, rash, hyperuricemia |
| Prompt: Within 2-3 weeks, prior to next course | Myelosuppression | | Toxic hepatitis (L), increased SGOT (AST)/SGPT (ALT), ataxia, mucositis |
| Delayed: Anytime later during therapy | | | Hepatic fibrosis (L), sinusoidal obstruction syndrome (SOS, formerly VOD) (L), hyperbilirubinemia |
| Unknown Frequency and Timing: | Fetal toxicities and teratogenic effects of thioguanine have been noted in animals. It is unknown whether the drug is excreted in breast milk. | | |

(L) Toxicity may also occur later.

Formulation and Stability:

Each greenish-yellow, scored tablet contains 40 mg thioguanine. Store at 15°- 25°C (59°-77°F) in a dry place.

For patients unable to swallow tablets, a 20 mg/mL oral suspension may be compounded. Crush fifteen (n=15) 40 mg tablets in a mortar and reduce to a fine powder. Add 10 mL methylcellulose 1% in incremental proportions and mix to a uniform paste. Transfer to a graduated cylinder, rinse mortar with simple syrup, and add quantity of simple syrup sufficient to make 30 mL. Dispense in an amber glass bottle and label "shake well" and "refrigerate". If methylcellulose is not available, substitute 15 mL of Ora-Plus in place of the methylcellulose and qs with Ora-Sweet (in place of simple syrup) to a final volume of 30 mL. Both preparations are stable for 63 days at 19°C-23°C. (Aliabadi HM, Romanick M, Somayah V, et al. Stability of compounded thioguanine oral suspensions. *Am J Health Syst Pharm* 2011;68:1278.)

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of the protocol.

Thioguanine should be taken consistently at the same time every day.

Substantial dosage reductions may be required in patients with an inherited deficiency of the enzyme thiopurine methyltransferase (*TPMT*) due to accumulation of active thioguanine metabolites resulting in a higher incidence of myelosuppression.

Supplier:

Commercially available. See package insert for more detailed information.

6.13 VINCRISTINE SULFATE
(Oncovin®, VCR, LCR) NSC #67574

(08/16/12)

Source and Pharmacology:

VinCRISTine is an alkaloid isolated from *Vinca rosea* Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vinCRISTine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vinCRISTine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

| | Common Happens to 21-100 children out of every 100 | Occasional Happens to 5-20 children out of every 100 | Rare Happens to < 5 children out of every 100 |
|--|---|---|--|
| Immediate: Within 1-2 days of receiving drug | | Jaw pain, headache | Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm |
| Prompt: Within 2-3 weeks, prior to the next course | Alopecia, constipation | Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia) | Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating |
| Delayed: Any time later during therapy | Loss of deep tendon reflexes | Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait | Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8 th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss |
| Unknown Frequency and Timing: | Fetal toxicities and teratogenic effects of vinCRISTine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk. | | |

Formulation and Stability:

VinCRISTine is supplied in 1 mL and 2 mL vials in which each mL contains vinCRISTine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vinCRISTine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2°-8°C or 36°-46°F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration:

See [Treatment](#) and [Dose Modifications](#) sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vinCRISTine. The delivery of vinCRISTine via either IV slow push or minibag is acceptable for COG protocols. VinCRISTine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. VinCRISTine is fatal if given intrathecally.

Injection of vinCRISTine sulfate should be accomplished as per institutional policy. VinCRISTine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

Special precautions:

FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Supplier:

Commercially available from various manufacturers. See package insert for more detailed information.

7 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

7.1 Follow-up & End of Therapy

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

| STUDIES TO BE OBTAINED | End of Therapy | Relapse |
|---|----------------|---------|
| History | X | |
| Physical Exam with VS | X | |
| CBC, differential, platelets | X | |
| Creatinine, ALT, bilirubin | X | |
| <u>SR-Avg, SR-High, and DS-HIGH B-ALL ONLY:</u> IgG, IgM, Absolute CD19 count, Absolute lymphocyte count | X | |
| Bone marrow for FISH/Cytogenetics to a COG-approved lab and Cytogenetic images & reports for central review (done through APEC14B1) | | X |
| <u>For B-LLY ONLY:</u> CT of involved areas, bone scan (only if positive at diagnosis) | | X |

Note: If enrolled in APEC14B1 and consented to optional cell banking, submit PB and BM specimens if relapse occurs.

Suggested studies after the completion of therapy for all patients*

- 1st-2nd year PE, CBC/diff/platelets Q4 weeks until count recovery, then at least Q3 months.
- 3rd year PE, CBC/diff/platelets Q4-6 months
- 4th-5th year PE, CBC/diff/platelets Q6-12 months

*This schedule is ultimately left to the treating physician's discretion. Obtain any of these studies and/or others at any time as clinically indicated.

**See COG Late Effects Guidelines for recommended long-term post-treatment follow-up:
<http://www.survivorshipguidelines.org/>**

7.2 Research Studies for which Patient Participation is REQUIRED

B-ALL

| Study | Day 8 | End of Induction | End of Consolidation |
|--|-----------------|------------------|----------------------|
| MRD by Flow Cytometry (COG-approved Flow Lab – Section 14.1) | PB [#] | BM [%] | |
| MRD by HTS (COG ALL Molecular Reference Lab – Section 14.2) | | BM* | |
| MRD by flow cytometry (University of Washington - Section 14.4) | | | BM [^] |

[#] Due to the importance of MRD in determining risk group assignment, the Day 8 PB MRD sample should be drawn no more than one day early or late. Must be obtained prior to intrathecal and intravenous Day 8 chemotherapy.

[%] Day 29 BM MRD sample no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level.

^{*} Excluding NCI HR DS B-ALL. Note: NCI SR with Double Trisomies 4 and 10 are required to send sample at EOI, however if EOI BM flow MRD result is 0.01-<0.1%, they are not required to have HTS MRD testing ordered through the Adaptive Portal.

[^] For NCI SR patients (with or without DS) with BM MRD $\geq 0.1\%$ by flow cytometry at the end of Induction, and NCI HR DS patients with MRD $\geq 0.01\%$ by flow cytometry at the end of Induction.

7.3 Research Studies for which Patient Participation is OPTIONAL

SR-FAV B-ALL

Non-DS SR-Fav B- ALL

| Correlative Study | Induction | Consolidation | Maintenance | End of Therapy | 1-year Off-Therapy |
|--|------------------------------|---------------|--|-------------------------------------|-----------------------------|
| Biobanking - Peripheral blood (Section 14.3) | Day 29 | | | | |
| Biobanking - CSF (Section 14.7) | Day 29 | At final LP | <ul style="list-style-type: none"> • Day 1 LP of Cycle 1 • Final LP of final cycle | | |
| Household Material Hardship Questionnaires (Section 17.1) | Prior to End of Induction LP | | Cycle 1* | 1 st off therapy visit** | 1 year off therapy visit*** |

* Flexible time point, must be administered between Day 1 of Cycle 1 and end of Cycle 2

**Must be administered ± 8 weeks from end of therapy

*** Must be administered ± 4 months of 1 year off-therapy

DS SR-Fav B-ALL

| Correlative Study | Pretreatment/ Diagnosis | Maintenance | 1 year Off-Therapy |
|---|-------------------------|--|---------------------|
| Immune function in DS B-ALL (Section 14.6) | X | Day 1 of Cycle 2* | |
| Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL (Section 17.2) | | Day 29 of: <ul style="list-style-type: none"> • Cycle 1* • Cycle 5* | 1 year off therapy* |

* Flexible timepoint, must be obtained/administered within ±4 weeks of time point

SR-AVG B-ALL**Non-DS SR-Avg B-ALL**

| Correlative Study | Induction | Consolidation | Interim Maintenance I | Blinatumomab Block 1 | Delayed Intensification | Blinatumomab Block 2 | Maintenance | End of Therapy | 1 year Off-Therapy |
|---|------------------------------|------------------|-----------------------|----------------------|-------------------------|----------------------|--|-------------------------------------|-----------------------------|
| Biobanking - Peripheral blood (Section 14.3) | Day 29 | | | | | | | | |
| Biobanking - CSF (Section 14.7) | Day 29 | At final LP | | | | | <ul style="list-style-type: none"> • Day 1 LP of Cycle 1 • Final LP of final cycle | | |
| Household Material Hardship Questionnaires (Section 17.1) | Prior to End of Induction LP | | | | | | Cycle 1* | 1 st off therapy visit** | 1 year off therapy visit*** |
| Caregiver Burden Arm A (Section 17.1) | | Day 1 (+14 days) | Day 21 (±14 days) | | Day 29 (±14 days) | | Day 29 Cycle 1 (±28 days) | | |
| Caregiver Burden Arm B (Section 17.1) | | Day 1 (+14 days) | | Day 15 (±14 days) | | Day 15 (±14 days) | Day 29 Cycle 1 (±28 days) | | |

* Flexible time point, must be administered between Day 1 of Cycle 1 and end of Cycle 2

**Must be administered ± 8 weeks from end of therapy

*** Must be administered ± 4 months of 1 year off-therapy

DS SR-Avg B-ALL

| Correlative Study | Pretreatment/ Diagnosis | Maintenance | Follow-up 1 year |
|--|-------------------------|---|---------------------|
| Immune Function in DS B-ALL (Section 14.6) | X | Day 1 of Cycle 2* | |
| Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL (Section 17.2) | | Day 29 of: <ul style="list-style-type: none"> • Cycle 1* • Cycle 5* | 1 year off therapy* |

* Flexible time point, must be obtained/administered within ± 4 weeks of time point

SR-HIGH B-ALL

| Correlative Study | Induction | Consolidation | Interim Maintenance I | Blinatumomab Block 1 | Delayed Intensification | Blinatumomab Block 2 | Maintenance | End of Therapy | 1 Year Off-Therapy |
|---|------------------|----------------------|-----------------------|----------------------|-------------------------|----------------------|--|-------------------------------------|-----------------------------|
| Biobanking - Peripheral blood (Section 14.3) | Day 29 | | | | | | | | |
| Biobanking - CSF (Section 14.7) | Day 29 | At final LP | | | | | <ul style="list-style-type: none"> • Day 1 LP of Cycle 1 • Final LP of final cycle | | |
| Biobanking - EOC BM (Section 14.5) [@] | | End of Consolidation | | | | | | | |
| Household Material Hardship Questionnaires (Section 17.1) | End of Induction | | | | | | Cycle 1* | 1 st off therapy visit** | 1 year off therapy visit*** |
| Caregiver Burden Arm C (Section 17.1) | | Day 1 (+14 days) | Day 29 (±14 days) | | Day 29 (±14 days) | | Day 29 Cycle 1 (±28 days) | | |
| Caregiver Burden Arm D (Section 17.1) | | Day 1 (+14 days) | | Day 15 (±14 days) | | Day 15 (±14 days) | Day 29 Cycle 1 (±28 days) | | |

* Flexible time point, must be administered between Day 1 of Cycle 1 and end of Cycle 2

**Must be administered ± 8 weeks from end of therapy

*** Must be administered ± 4 months of 1 year off-therapy

[@] For SR-High patients with EOI flow MRD ≥ 0.1%, and SR-High patients with EOI flow MRD 0.01-0.099% whose treating clinician chooses to assess BM for MRD at EOC.

DS-High B-ALL

| Correlative Study | Pretreatment/ Diagnosis | Maintenance | Follow-up 1 year |
|--|-------------------------|---|---------------------|
| Immune Function in DS B-ALL (Section 14.6) | X | Day 1 of Cycle 2* | |
| Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with DS-ALL (Section 17.2) | | Day 29 of: <ul style="list-style-type: none"> • Cycle 1* • Cycle 5* | 1 year off therapy* |

* Flexible time point, must be obtained/administered within ±4 weeks of time point

B-LLy

DS and non-DS B-LLy

| Special Study | Biopsy | Bone Marrow |
|--|---|---|
| Biobanking (Section 14.8) | <ul style="list-style-type: none">• Diagnosis• Residual mass leftover from any scheduled biopsy• Relapse (if it occurs) | |
| Minimal Marrow Disease Study (Section 14.9) | | <ul style="list-style-type: none">• Diagnosis |

8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy (See [Section 3.3](#) for B-ALL definitions and [Section 18.0](#) for B-LLy definitions)

- a) Progressive disease at the end of Induction (B-LLy only)
- b) Consolidation failure (B-ALL only)
- c) Failure to achieve CR at the end of Consolidation (B-LLy only)
- d) Definitive Relapse
- e) Identified as Philadelphia Chromosome-positive (*BCR-ABL1*)
- f) Incomplete Induction data for risk stratification (B-ALL only)
- g) Patient found at any point after enrollment to be inevaluable (e.g., major deviations from protocol therapy)
- h) Adverse Event requiring removal from protocol therapy
- i) Refusal of further protocol therapy by patient/parent/guardian
- j) Completion of planned therapy
- k) Physician determines it is in patient's best interest
- l) Development of a second malignancy

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless patient is taken off study.

8.2 Off Study Criteria

- a) Death
- b) Lost to follow-up
- c) Patient enrollment onto another COG anti-cancer therapeutic study (eg, at recurrence), except for AALL1721 and AALL1931.
- d) Withdrawal of consent for any further data submission
- e) Tenth anniversary of the date the patient was enrolled on this study

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Design

9.1.1 Primary Endpoints

- 9.1.1.1 The primary endpoint is improvement in post-Consolidation DFS due to the addition of 2 cycles of blinatumomab to standard therapy in patients with SR B-ALL and higher risk features, and patients with SR-Avg B-ALL who are negative for MRD by flow cytometry but have detectable or indeterminate MRD as measured by HTS at EOI.
- 9.1.1.2 To confirm that boys in the SR-Fav subset of SR B-ALL, with or without DS, will maintain a 5-year DFS of greater than 93% when treated with a standard chemotherapy regimen with a treatment duration of 2 years from the start of IM1.

9.1.2 Secondary Endpoints

- 9.1.2.1 To describe the DFS for patients with SR-Avg B-ALL who are negative for MRD measured by flow cytometry and HTS at EOI when treated with standard chemotherapy with a treatment duration of 2 years from the start of IM1, regardless of sex.
 - 9.1.2.2 To describe the DFS for patients with standard-risk favorable (SR-Fav) B-ALL when treated with a standard chemotherapy regimen.
 - 9.1.2.3 To determine if patients with DS-High achieve a reduction of treatment-related mortality (TRM) after replacement of intensive elements of standard chemotherapy (omission of anthracyclines in Induction, omission of the second month of DI) with 3 cycles of blinatumomab.
 - 9.1.2.4 To describe the DFS characterized by the replacement of intensive elements of standard chemotherapy with 3 cycles of blinatumomab in patients with DS-High B-ALL.
 - 9.1.2.5 To describe the DFS for patients with localized (Murphy stage I and II) B-Ly receiving standard-risk ALL therapy.
 - 9.1.2.6 To compare the change in neurocognitive functioning, as measured by the CogState Cognitive Composite, from baseline to end-of-therapy among patients with ALL ages 4-< 10 years at the time of diagnosis between children from poor families (defined as presence of household material hardship (HMH), including either food, housing or energy insecurity) and non-poor families (absence of HMH).
 - 9.1.2.7 To describe the impact of blinatumomab on caregiver burden and patient/proxy-reported symptoms among a subset of children enrolled in the HMH and neurocognitive outcome study.
- #### 9.1.3 Exploratory Objectives
- 9.1.3.1 To explore adaptive and innate immune functions and host genetic factors associated with severe infectious complications in children with DS B-ALL.

9.1.3.2 To explore the impact of ALL and its therapy on neurocognitive, functional, and quality of life outcomes in patients with DS and ALL, as measured by caregiver (parent/legal guardian) questionnaires.

9.1.3.3 To define the prevalence of minimal marrow disease (MMD) in B-Lly and to correlate MMD at diagnosis with outcome in patients with B-Lly.

9.2 Patient Accrual and Expected Duration of Trial

Total expected accrual for this study is expected to be up to 6,420-6,720 patients. An expected 1,284 eligible patients/year are expected to accrue. Of these, 1,062 SR patients/year without DS are expected to reach EOI and 1,024/year are expected to reach EOC. An expected 49.5% of these are eligible to be randomized (pending HTS status), which results in 507/year. An additional expected 15 DS SR-Avg will be eligible to be randomized per year (EOC), for a total of 522 patients/year. Of the 522 patients/year eligible for randomization, pending HTS MRD status, approximately 18 will be DT with MRD 0.01% - <0.1% and 365 will be DS SR-Avg or other SR-Avg. Assuming 20% of the latter group are HTS-undetectable gives 73 patients/year for the SR-Avg HTS-negative group (non-randomized) with the remaining 449 patients/year (SR-Avg with detectable/indeterminate/unknown HTS, and SR-High) eligible for the SR-randomization arm. 445 patients accrued over 5 years gives an estimated 2,245 randomized patients.

Randomization: The blinatumomab randomization will be 1:1 (standard therapy vs. standard therapy plus blinatumomab) and will be stratified for DS vs. non-DS (for SR-Avg), and Risk Group.

9.3 Statistical Analysis Methods

9.3.1 Analysis for Primary Endpoints

Power Calculations and Analysis Plan

For the primary endpoint 1, we will use an efficacy design and standard survival analysis methods to detect improvement in post-Consolidation DFS due to the addition of 2 cycles of blinatumomab to standard therapy in patients with SR B-ALL and higher risk features, and patients with SR-Avg B-ALL who are negative for MRD by flow cytometry but have detectable or indeterminate MRD as measured by HTS at EOI, and patients with DT with MRD (flow) 0.01% - <0.1%. We assume baseline (control) rate of 90.1% 5-year DFS excluding the patients with undetectable HTS (with assumed 5 year DFS=96%). It is expected that about 449 patients/year will have detectable EOI MRD (HTS), lack a clonal IgH sequence (HTS EOI MRD indeterminate), have EOI HTS unavailable, or are SR-High and eligible for the blinatumomab randomization. A total of 2245 patients will give approximately 81% power (two-sided alpha 5%, minimum follow-up of 3 years) to detect via group sequential log rank tests an improvement in 5-year post-Consolidation DFS from 90.1% to 93.4% (HR=0.655; total expected events=194). Final analysis will be performed at 194 observed events. All survival time analyses assume a Weibull distribution with shape parameter of 0.6 (based on historical data) unless otherwise noted.

For primary objective 2, we expect that about 536 SR-Fav patients and 3 DS SR-Fav patients per year will continue on therapy post-Induction, with 56% of the cohort being boys (derived from AALL0331 SR-Low percentage). The DFS for SR-Fav boys will be compared to that found for AALL0331 SR-Low boys. An estimated 1,509 SR-Fav boys with 3 years of minimum follow-up (116 events) would give 80% power (one sample log-rank test with 1 sided alpha=0.10) to detect a 5-year DFS of 93.0% as being lower than the control DFS rate

of 94.25. An exponential distribution is assumed based on observed data from AALL0331. The analysis will include interim monitoring at 25/50/75% information times using an alpha*t² spending function with final analysis at 116 observed events.

Methods of analysis

The study endpoints are Disease-free Survival (DFS) and overall survival (OS). For Primary Endpoint 1, DFS is defined as time from EOC to first event (relapse, second malignant neoplasm, remission death) or censored at date of last contact for those who are disease-free. For Primary Endpoint 2, DFS is defined as time from EOI to first event (relapse, second malignant neoplasm, death) or censored at date of last contact for those who are disease-free. OS is defined as time from EOI (Primary Endpoint 2) or EOC (Primary Endpoint 1) to death or censored at date of last contact for those alive at last contact. DFS and OS rates will be estimated using the Kaplan-Meier method and standard errors and confidence intervals estimated by the method of Peto.⁷⁶ Estimation of treatment effect will be done using intent-to-treat (ITT) analysis based on randomized group and testing for Primary Endpoint 1 will employ a stratified log rank test.

Definition of event for DFS

For Primary Endpoint 1, DFS is defined as time from EOC to first event (relapse, second malignant neoplasm, remission death) or censored at date of last contact for those who are disease-free. For Primary Endpoint 2, DFS is defined as time from EOI to first event (relapse, second malignant neoplasm, death) or censored at date of last contact for those who are disease-free.

Interim Monitoring

Interim monitoring of outcomes for the blinatumomab randomization (Arms A/C vs. Arms B/D) will be conducted. Efficacy and futility monitoring will be conducted when approximately 20 (futility only), 40, 60, 80, and 100% of expected information is observed, using the Alpha-t square spending function for efficacy monitoring and the futility monitoring method described by Anderson and High.⁷⁷ For the futility monitoring, the boundaries will be based on repeated testing of the alternative hypothesis at the 0.0186 level. This corresponds to the level that would hypothetically cause futility stopping if an observed hazard ratio was 1.0 or higher, when 50% of expected information is accrued.

Patients enrolled on the blinatumomab randomization will be closely monitored for toxicities. Observed rates for targeted toxicities will be summarized by arm every six months in the study reports with observed differences described and reviewed. Significant differences will be reviewed by study committee and submitted to the COG DSMC for review. Toxicities on the blinatumomab arm on the currently active trial for relapsed ALL (AALL1331) have been minimal but will be closely monitored on the blinatumomab arm in this study. Targeted toxicities of specific interest are cytokine release syndrome (CRS) and neurotoxicities. Rates of > 10% Grade 3/4 for these toxicities on Interim reports will lead to close review by study committee and the DSMC, for possible therapy modification.

The distribution of HTS MRD status at the end of Induction will be summarized at the time of each biannual study reporting, to monitor the proportion of subjects eligible for the blinatumomab randomization (detectable/indeterminate HTS MRD) as the study progresses; a serious deviation in the projected proportions will result in amending the study design appropriately to reflect the correct rate observed on study.

Toxic deaths will be closely monitored for all patients on study. Summaries of TRMs will be included in the bi-annual study reports to the DSMC; and will be reviewed in detail and any increased rates will result in review and possible modification of therapy.

All Grade 3/4 toxicities (including stomatitis, hyperglycemia, and infections) will be closely monitored in this cohort. Delays of > 2 weeks in beginning the next phase of therapy will also be monitored. Data on these toxicities will be summarized, compared to historical controls on AALL1131, and presented in each bi-annual report to the COG DSMC.

Outcomes for males and potential erosion due to the reduction in therapy duration from 3 to 2 years (from start of IM1), will be monitored for those randomized to control treatment. A total of 1123 SR-Avg patients (non-DS and DS) who are HTS positive will be randomized to the no blinatumomab arm. Approximately 54% (n=606) will be males. Of these, 552 are projected (based on data from AALL0331) to be event-free at the end of therapy (2 years post start of IM1). Outcomes will be compared to similar patients on AALL0331. Assuming 3% loss to follow up over the course of the study gives 1920 patients from AALL0331 vs. 535 patients from AALL1731. This study is to enroll for 5 years with 3-years of minimum follow-up, giving a planned 8 years study duration. Group sequential monitoring using the standard log rank test will compare DFS for accruing AALL1731 patients to historic control data using time to event starting with 2 years post IM1. Using a one sided 10% alpha and the Alpha-T square spending function, we plan on testing at 3 time points with the first being when approximately half of the subjects finish therapy (at ~4.7 years study time gives ~2.5 years of maximum follow-up time for the earliest enrollees at the first test). Subsequent monitoring will be approximately every 1.65 years with the third and final test at end of study (at 3 years minimum follow-up). From historic data from AALL0331, a survival function with Weibull distribution with shape parameter 0.6 is assumed. The historic control group gives a 3 year CCR estimate (SE) of 94.8% (0.5%). Group sequential testing with group sample sizes of 1920 and 535 at the final look achieve ~80% power to detect 3 yr CCR of 92.4 vs. 94.8 (HR=1.50) at the 0.10 significance level (alpha) using a one-sided log rank test.

Similar monitoring will also be done for the male SR-Fav patients with comparisons with appropriate historical controls from AALL0331. Approximately n=1,358 males in this group are projected to be event to be event-free at the end of therapy (2 years post start of IM1). Outcomes will be compared to similar patients on AALL0331 (SR-Low or Avg, Day 8 MRD<1%, Day 29 MRD <0.01%, favorable cytogenetics, CNS 1 or 2). Assuming 3% loss to follow up over the course of the study gives 1,317 patients from AALL1731 compared to n=436 similar patients from AALL0331. From historic data from AALL0331, a survival function with Weibull distribution with shape parameter 0.7 is assumed. The historic control group gives a 3 year CCR estimate (SE) of 96.7% (0.9%). Using the same analysis plan as for the SR-Avg group, group sequential testing at 3 time points achieves ~80% power to detect 3 yr CCR of 96.7 vs. 94.6 (HR=1.67) at the 0.10 significance level (alpha) using a one-sided log rank test.

9.3.2 Analysis for Secondary Endpoints

DFS for SR-Avg with undetectable HTS-MRD (Secondary Objective 1):

Expecting that about 73 SR-Avg patients with undetectable HTS-MRD patients/year will continue on therapy, a total of 365 patients are expected to shuttle to the SR-Fav arm. Five-year post Consolidation DFS will be estimated with an expected standard error of 1.1%. Three years of minimum follow-up at 96% 5 year DFS would give 15 expected events.

DFS for SR-fav (Secondary Objective 2):

We expect that about 2,695 patients will be evaluable for DFS within the SR-Fav cohort. Five-year post Induction DFS will be estimated with an expected standard error of 0.5%. Three years of minimum follow-up at 95% 5 year DFS would give 141 expected events.

Treatment Related Mortality in DS-High B-ALL (Secondary Objective 3):

The TRM rate will be estimated for DS-High patients after replacement of intensive elements of standard chemotherapy with 3 cycles of blinatumomab. The TRM rate for these patients on AALL1131 is approximately 8%. We expect approximately 30 patients per year to qualify for this cohort, for an expected total accrual of 150 DS-High patients. Using a one-sample test with n=150, a critical cut-point of ≤ 7 TRM events would give 75% power to detect a 50% relative reduction in TRM rate from the historical rate of 8%, with a type 1 error rate of 8.1%. Additionally, safety and futility monitoring rules will be included at n=50, 75, and 100 evaluable subjects in this cohort. If 5 or more TRMs occur among the first 50 subjects, the study will be temporarily closed to DS-High patients and the data on the TRMs reviewed closely by the study committee, with a decision made on possible modifications to therapy for these patients. With this rule, the probability of stopping is 37%, 57%, and 73% at true TRM rates of 8%, 10%, and 12%, respectively. If 6 or more TRMs occur among the first 75 subjects, this study will close for futility, with only 19% conditional power of eventual success under the alternative of interest. Similarly, if 7/100 subjects have TRM, then this study will close with a conditional power of only 13%.

DFS in DS with HR B-ALL (Secondary Objective 4):

Assuming a total of 150 DS-High patients available at the end of Consolidation, five-year post-Consolidation DFS will be estimated with an expected standard error of approximately 3.3%. In order to monitor for possible outcome erosion, the DFS for DS-High patients will be compared to that observed for AALL1131 DS-High patients with similar EOI/EOC MRD requirements. An estimated 150 patients with 3 years of minimum follow-up would give 80% power (one sample log-rank test with 1 sided alpha=0.10) to detect a 5-year DFS of 66% as being lower than the control DFS rate of 73.4%. An exponential distribution is assumed based on observed data from AALL1131. The analysis will include interim monitoring at 25/50/75% information times using an alpha*t-square spending function, with final analysis planned at 54 observed DFS events.

DFS in B-LLy (Secondary Objective 5):

The DFS and OS for localized B-LLy patients will be described. A sample size of 50 (10/year) will allow for estimation of 5 year DFS and OS with a maximum standard error of 7%.

Household Material Hardship and Neurocognition (Secondary Objective 6):

See [Section 17.1.10](#) for analysis plan.

Effects of blinatumomab on caregiver burden and patient/proxy-reported symptoms (Secondary Objective 7):

See [Section 17.1.11](#) for analysis plan.

9.3.3 Analysis for Exploratory Endpoints

Immune function and host genetic factors related to severe infectious complications in DS B-ALL (Exploratory Objective 1):

See [Section 15.1.5](#) and [Section 15.2.4](#) for analysis plan.

Neurocognitive Outcomes in DS (Exploratory Objective 2):

See [Section 17.2.6](#) for analysis plan.

To define the prevalence of minimal marrow disease (MMD) in B-LLy and to correlate MMD at diagnosis with outcome in patients with B-LLy (Exploratory Objective 3):

For this optional objective, available samples from B-LLy patients will evaluate MMD status at diagnosis and MRD positivity at end of induction. Percentages with MMD at induction and MRD positivity at end of induction will be described. Associations between these findings and long-term outcomes (e.g., OS, DFS) will be explored.

9.4 Sex and Minority Accrual Estimates

The sex and minority distribution of the study population is expected to be:

| DOMESTIC PLANNED ENROLLMENT REPORT | | | | | | |
|---|-------------------------------|-------------|---------------------------|-------------|--------------|--|
| Racial Categories | Ethnic Categories | | | | Total | |
| | Not Hispanic or Latino | | Hispanic or Latino | | | |
| | Female | Male | Female | Male | | |
| American Indian/ Alaska Native | 19 | 20 | 7 | 14 | 60 | |
| Asian | 127 | 130 | 4 | 4 | 265 | |
| Native Hawaiian or Other Pacific Islander | 11 | 8 | 2 | 1 | 22 | |
| Black or African American | 193 | 195 | 12 | 7 | 407 | |
| White | 1767 | 2003 | 602 | 711 | 5083 | |
| More Than One Race | 6 | 15 | 3 | 9 | 33 | |
| Total | 2123 | 2371 | 630 | 746 | 5870 | |

| INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT | | | | | | |
|--|-------------------------------|-------------|---------------------------|-------------|--------------|--|
| Racial Categories | Ethnic Categories | | | | Total | |
| | Not Hispanic or Latino | | Hispanic or Latino | | | |
| | Female | Male | Female | Male | | |
| American Indian/ Alaska Native | 9 | 10 | 0 | 0 | 19 | |
| Asian | 36 | 57 | 0 | 0 | 93 | |
| Native Hawaiian or Other Pacific Islander | 6 | 12 | 0 | 0 | 18 | |
| Black or African American | 6 | 6 | 0 | 0 | 12 | |
| White | 320 | 359 | 3 | 9 | 691 | |
| More Than One Race | 7 | 10 | 0 | 0 | 17 | |
| Total | 384 | 454 | 3 | 9 | 850 | |

This distribution was derived from observed distributions of known race/sex/ethnicity enrollments from 03-31-2018 cutoff of AALL0932.

10 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: ‘CTCAE v5.0’ is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (ie, v5.02 and all subsequent iterations prior to version 6.0).

10.2 Response Criteria for Patients with Leukemia and Lymphoma

See definitions in [Section 3.3](#) and [Section 18.0](#)

11 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration:* When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational

agents.

- *Sequential administration:* When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events that occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

Any AE that is serious qualifies for expedited reporting. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

- 1) Death.
- 2) A life-threatening adverse drug experience.
- 3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.4 Special Situations for Expedited Reporting

11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

11.4.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: Newborn death occurring during the first 28 days after birth.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 “*Disease progression*” in the system organ class (SOC) “*General disorders and administration site conditions*”. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) must also be reported via the routine reporting mechanisms outlined in this protocol.

11.4.5 Second Malignancy

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

11.4.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form, available at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to (301) 897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

11.4.6.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 “Pregnancy, puerperium and perinatal conditions - Other (pregnancy)”** under the **“Pregnancy, puerperium and perinatal conditions”** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.6.2 **Pregnancy Loss (Fetal Death)**

Pregnancy loss is defined in CTCAE as “*Death in utero*.” Any Pregnancy loss should be reported expeditiously, as **Grade 4 “Pregnancy loss” under the “Pregnancy, puerperium and perinatal conditions” SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.6.3 **Death Neonatal**

Neonatal death, defined in CTCAE as “*Newborn death occurring during the first 28 days after birth*”, should be reported expeditiously as **Grade 4, “Death neonatal” under the “General disorders and administration” SOC, when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as “Course Zero” using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

- a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
- b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
- c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

- 1) The grade increases OR
- 2) Hospitalization is associated with the recurring AE.

11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

11.8 General Instructions for Expedited Reporting via CTEP-AERS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at:

<https://eapps-ctep.nci.nih.gov/ctepaers>.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to (301) 897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
 - **24-Hour; 5 Calendar Days** - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
 - **7 Calendar Days** - A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**
- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours.**
- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours.**

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.

Fax supporting documentation for AEs related to investigational agents supplied under a CTEP IND to: **(301) 897-7404.**

Also: Fax or email supporting documentation to COG for all IND studies (Fax # (310) 640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 Reporting Table for Late Phase 2 and Phase 3 Studies – Table A

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention¹

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death.
- 2) A life-threatening adverse event.
- 3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|--|------------------------|-----------------------|------------------------|---|
| Resulting in Hospitalization ≥ 24 hrs | 7 Calendar Days | | | 24-Hour Notification 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not Required | | 7 Calendar Days | |

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
- “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- Grades ≤4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.
- Any blinatumomab-related AE that results in interruption of dosing as described in [Section 5.1](#) requires expedited reporting via CTEP-AERS.
- Any Grade 3 or higher infection that occurs more than 30 days after the last administration of blinatumomab and has an attribution of possible, probable, or definite must also be reported via CTEP-AERS expedited reporting.
- Any Grade 2 or higher cytokine release syndrome (CRS), psychiatric (confusion, hallucination, delirium, psychosis), encephalopathy, dysarthria, tremor, or seizure AE during blinatumomab infusion blocks requires expedited reporting via CTEP-AERS.

11.11 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study. Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days¹

| Attribution | Grade 4 | | Grade 5 |
|------------------------------|------------|----------|-----------|
| | Unexpected | Expected | |
| Unrelated or Unlikely | | | CTEP-AERS |
| Possible, Probable, Definite | CTEP-AERS | | CTEP-AERS |

¹This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.12 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 4 and higher non-hematologic Adverse Events, as well as the following specific toxicities identified by the ALL Toxicity Reporting Task Force are to be collected on all COG ALL trials:

1. CNS hemorrhage requiring medical intervention (Grade 2 or 3)
2. GI bleed requiring operative or interventional radiology intervention (Grade 3)
3. Pancreatitis requiring medical intervention (Grade 2 or 3)
4. Osteonecrosis/avascular necrosis interfering with function (Grade 2 or 3)
5. Transient ischemic attacks (All grades)
6. Stroke (All grades)
7. Encephalopathy (Grade 3)
8. Neuropathy; motor or sensory, interfering with ADL (Grade 3)
9. Seizure (Grade 2 or 3)
10. Allergic reaction (Grade 3)
11. Ileus (Grade 3)
12. Mucositis/stomatitis; functional (Grade 3)
13. Bilirubin (Grade 3)
14. Thrombosis (Grade 2 or 3)
15. Sinusoidal Obstruction Syndrome (SOS) (Grade 2 or 3)
16. Cytokine Release Syndrome (Grade 2 or 3)
17. Infectious toxicities (All Grade 3 or higher)

11.12.1 Additional adverse event reporting for DS-High B-ALL

In addition to the routine AE reporting required for all patients on this trial, the following additional AE is required to be reported for patients with Down syndrome and HR B-ALL:

1. Febrile neutropenia (Grade 3-4)

11.13 Syndrome Reporting

Unless otherwise specified in this protocol, syndromes should be reported as a single event using the CTCAE term for the composite syndrome, and not as the individual events that make up the syndrome. For example, Tumor Lysis Syndrome should be reported under the composite definition rather than reporting the component events (hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) separately.

12 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under “*Data Collection/Specimens*”. A submission schedule is included.

12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

12.2 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
 - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to

presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

13 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

13.1 Pathology Goals

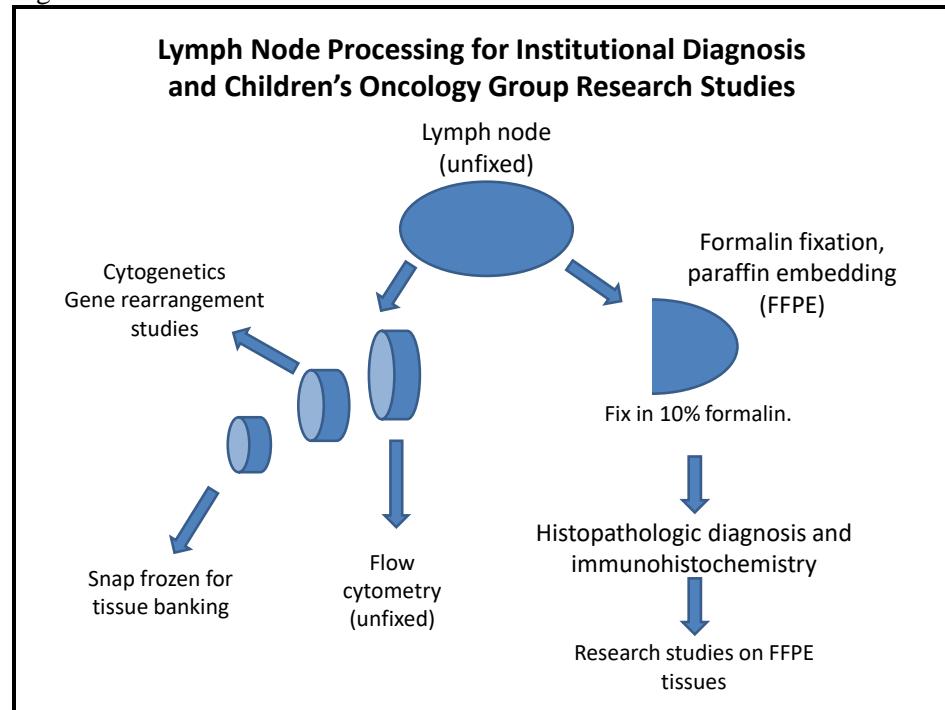
1. Provide quality control by central pathologic review with accurate diagnosis and classification of pediatric non-Hodgkin lymphoma. This is to be based on both morphologic and immunophenotypic criteria. **This study is limited to B-cell lymphoblastic lymphoma.** Patients with T-lineage lymphoblastic lymphoma are not eligible for this study.
2. Employ the 2016 World Health Organization (WHO) Lymphoma Classification ⁷⁸ to facilitate concordance in diagnosis.
3. Correlate morphologic, immunophenotypic, and cytogenetic data for the lymphomas included in this treatment protocol.

13.2 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

13.2.1 Tissue Specimens

Tissue should be preferentially, whenever possible, be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution (fixation, snap freezing, cytogenetics, etc.). Refer to the diagram entitled “Lymph Node Processing for Institutional Diagnosis and Children’s Oncology Group Research Studies” (Figure 13.1). Submit representative tissue sections for fixation including at least 1 block with 10% buffered formalin.

Figure 13.1



13.2.2 Cytology Specimens

Cytology or body fluid specimens (i.e., pleural fluid) should be delivered promptly to the pathology laboratory, and handled per primary institutional procedures. Sufficient material should be utilized for morphologic evaluation by cytocentrifuge preparations stained with a Romanowsky stain (i.e., Giemsa or Wright's stains). Provided enough specimen is available, at least 1 cell block should be prepared with specification of the fixative utilized (formalin preferred) and the time in fixative.

13.3 Immunophenotyping Recommendations for Primary Institutions

For eligibility in this study, the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include: flow cytometry, paraffin section immunohistochemistry, and cytocentrifuge (cytospin) immunocytochemistry. For eligibility in this study, a panel of antibodies should be employed for immunophenotypic evaluation. This can be done on fresh tissue by flow cytometry, on paraffin embedded tissue by immunohistochemistry, and on body fluid/cytology specimens by flow cytometry or cytocentrifuge (cytospin) immunocytochemistry. The panel of antibodies is listed as follows (useful but optional antibodies listed in parentheses):

T-Cell: CD3.

B-Cell: CD19, CD20, CD22, Kappa, Lambda (CD79a, PAX5).

Myeloid: CD13, CD33 MPO (CD15).

Other: CD10, CD34, CD45, TdT.

For cases in which no paraffin embedded tissue has been prepared, and only stained cytospin slides remain available, these cases will be acceptable for protocol submission and pathology review when adequate immunophenotypic data is available from the primary institution. This situation may occur with cases evaluated by cytospin immunocytochemistry or flow cytometry immunophenotyping. If specimen is limited preventing a complete immunophenotypic evaluation, a recommended minimum panel of antibodies should include: CD3, CD19, CD20, Ig kappa, Ig lambda, and TdT. If specimen is limited to paraffin embedded tissue only, a preferred panel of antibodies should include at least: CD3, CD79a, and TdT, and either CD19 or PAX5 as an additional B-cell marker. The method of TdT evaluation should be specified (i.e., flow cytometry or immunohistochemistry). Flow cytometry reports must be provided for review. If immunophenotyping studies are not available locally, the case may be sent as a consultation case for evaluation, including immunophenotyping studies to Dr. Rodney Miles (see address in [Section 13.5.1.10](#))

13.4 Pathology Staging Criteria

Cerebrospinal Fluid: CSF positivity is based on morphological evidence of lymphoma cells. CSF should be considered positive if any number of blasts are detected.

Bone Marrow: The presence of greater than 5% and less than 25% blasts in a bone marrow aspirate, or focal infiltration in a bone marrow biopsy, represents involvement of the marrow by lymphoblastic lymphoma.

13.5 Retrospective Central Pathology Review

13.5.1 Required Materials

Materials to be submitted for retrospective pathology review to the Biopathology Center include the following:

1. Initial diagnostic material prior to therapy
2. Specimens demonstrating relapse of lymphoma at any time
4. A copy of all final pathology reports including initial staging bone marrow report (see details in [Section 13.5.1.5](#))
5. Pathology Data Collection Form (Institutional Pathology Form)
6. Transmittal form

Labeling

Please label all materials with the patient's COG patient identification number and the institutional pathology number and block number found on the corresponding pathology report. The materials to be submitted are described below and listed in Table 13.1.

13.5.1.1 **H&E Stained Slides**

Submit two (2) H&E stained slides from each block placed on sialinized slides (i.e., Fisher Superfrost Plus).

13.5.1.2 **Paraffin Blocks**

If possible, it is preferred that paraffin blocks be submitted to the COG Biopathology Center. For surgical biopsy specimens, this should include a paraffin block of tissue prepared in 10% Buffered Formalin (as described in [Section 13.2.1](#)). For cytology specimens, a paraffin block may be available as a cell block preparation (see [Section 13.2.2](#)). If paraffin blocks cannot be submitted, then submit twenty (20) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature from one representative block. These sections should be place on sialinized slides (i.e., Fisher Superfrost Plus).

13.5.1.3 **Cytology Slides**

When paraffin blocks have not been prepared, a cytologic preparation of one stained, air-dried cytopsin slide (i.e., Romanowsky stain such as Giemsa or Wright's stain) and 10 unstained slides should be submitted.

13.5.1.4 **Specimens Demonstrating Relapse**

For relapse specimens, send a recut slide (hematoxylin and eosin stain) from all of the paraffin blocks for review. The corresponding pathology report must accompany the slides for review.

13.5.1.5 **Pathology Reports**

A copy of all pathology reports on each case should be submitted. This includes the following:

1. Final corresponding pathology and bone marrow reports (even if bone marrow is negative)
2. All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available)

3. Results of any genotypic studies (i.e., gene rearrangement studies)
4. Results of any cytogenetic (karyotypic and FISH) analysis

13.5.1.6 Pathology Data Collection Forms/COG Pathology Center

A separate pathology data collection form (Institutional Pathology Form) should be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis utilizing the 2016 WHO Lymphoma Classification⁷⁸ on the data collection form.

13.5.1.7 Transmittal Form

A specimen transmittal form must be submitted along with the pathology review materials.

13.5.1.8 Biopathology Center Address

All material submitted for retrospective central pathology review should be sent via regular mail or using your institutional courier account to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897

*The room number is required. Packages not listing the room number could be denied and returned to sender.

13.5.1.9 Paraffin Blocks and Cytologic Slides-Storage/Return

Paraffin blocks and cytologic slides will be retained at the COG Biopathology Center indefinitely, unless the institution requests their return.

13.5.1.10 Lymphoma Classification

Morphologic evaluation and classification of the study cases will utilize the criteria described in the 2016 WHO Lymphoma Classification.⁷⁸ Eligible pediatric lymphomas will be classified as precursor B-cell lymphoblastic lymphoma.

13.5.1.11 Review Pathologist

For any questions regarding the pathology protocol, please contact:

Rodney Miles, MD, PhD
University of Utah Department of Pathology
ARUP Laboratories
500 Chipeta Way 115-G04
Salt Lake City, UT 84108
Phone: (801) 584-5240
Fax: (801) 584-5124

Table 13.1: MATERIALS TO SEND FOR RETROSPECTIVE CENTRAL PATHOLOGY REVIEW

| | |
|--|--|
| H&E Stained Slides | <ul style="list-style-type: none">• 2 H&E stained slides from each block |
| Paraffin Blocks Send one of the following: | <ul style="list-style-type: none">• Surgical biopsy specimen: One paraffin block (formalin preferred)• Cytology cell block: One paraffin block (specify fixative)• If blocks cannot be sent, submit twenty unstained and unbaked sections (4 µm) from 1 representative block on salinized slides. |
| Cytology Slides Send the following: | <ul style="list-style-type: none">• One stained (Romanowsky stain) and• 10 unstained slides |
| Specimens Demonstrating Relapse | <ul style="list-style-type: none">• A recut slide (hematoxylin and eosin stain) from each of the paraffin blocks from each of these types of biopsy specimens• Corresponding pathology report |
| Pathology Reports Send all of the following | <ul style="list-style-type: none">• Final reports of biopsy and bone marrow specimens (even if negative)• All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available); also include copies of flow cytometry histograms (if available)• Results of any genotypic studies (i.e., gene rearrangement studies)• Results of any cytogenetic (karyotype and FISH) analysis |
| Collection Forms | <ul style="list-style-type: none">• Pathology Data Collection Form (Institutional Pathology Form)• Transmittal Form |

14 SPECIAL STUDIES SPECIMEN REQUIREMENTS

14.1 Minimal Residual Testing (MRD) by Flow Cytometry Days 8 and 29 - REQUIRED

REQUIRED for B-ALL patients on this study

Submit Day 8 (for all patients except DS NCI HR) blood and Day 29 (for all patients) bone marrow specimens to a COG-approved flow cytometry laboratory for MRD testing to facilitate end of Induction risk group assignment. If Day 8 and Day 29 specimens are not obtained and shipped to a COG-approved flow lab for MRD testing, the patient will not be eligible to continue on this trial following completion of Induction therapy. **These samples are absolutely essential.**

Timing: Due to the importance of MRD in determining risk group assignment, the Day 8 PB MRD sample should be drawn no more than one day early or late, but must be drawn prior to administration of Day 8 IT MTX or VCR. The Day 29 BM MRD sample no more than two days early or late, with a preference for early rather than late to avoid potentially missing a high MRD level.

A list of COG-approved labs can be found via the following link:
https://www.cogmembers.org/_files/admin/mrdflowlabs.pdf

Sites should contact the COG-approved labs to request sample processing and shipping instructions according to each institution's guidelines. Flow Cytometry MRD testing guidance for labs is provided in [APPENDIX XI](#).

14.2 MRD by High-Throughput Sequencing (HTS) in Bone Marrow at EOI – REQUIRED

The submission of a bone marrow sample for MRD testing by HTS is required at the end of Induction therapy for NCI SR B-ALL patients (DS and non-DS). Sites must order this test using the Adaptive Portal. See the Adaptive Portal Walk-Through Slides and Adaptive SOP for instructions for initial set-up of Adaptive Portal account, ordering high-throughput sequencing (HTS) MRD assessments, and interpreting HTS MRD results. Sites must set up accounts ahead of ordering their first HTS MRD assessment since set-up of Adaptive Portal account may take 24 hours or longer to activate.

NOTE: Although all patients risk-stratified as SR-Avg must have this sample sent to the COG ALL Molecular Reference Laboratory, those patients with Double Trisomies 4 and 10 who are determined to have EOI flow MRD 0.01-<0.1% do not need to have HTS testing ordered through the Adaptive Portal. These patients are considered to have sufficiently high EOI MRD and will therefore be randomized.

Please submit samples to the COG ALL Molecular Reference Laboratory as follows:

14.2.1 Specimen Details

- 3 mL (patients <10kg) or 5 mL (patients ≥ 10kg) of bone marrow at the end of Induction.

14.2.2 Sample Collection and Processing

- Collect 3 mL (patients <10kg) or 5 mL (patients ≥ 10kg) of bone marrow (BM) and transfer immediately into a 15 mL COG ALL SM tube.
- Mix well. Up to 5mL of BM can be placed in one 15 mL SM tube. If shipping media (SM) is not available, specimens may be transferred to large EDTA (lavender top) tubes.
- **Note:** for international sites, it is strongly encouraged that bone marrow samples are collected in COG shipping media to preserve the viability of the sample.
- If samples cannot be shipped on the day of collection, please store at 4°C until shipment on the next business day.

14.2.3 Sample labeling and Shipping

- Include the COG patient ID, patient name and date of birth, collection date, time point, and specimen type.
- **Do not** batch samples.
- Samples may be shipped Monday through Friday. If shipped on a Friday, mark Saturday delivery on the air bill and email the laboratory prior to shipment.
- Please include the RAVE transmittal form.
- Each sample should be prepared in accordance with IATA regulations.
- Ship samples via FedEx priority overnight. Utilize the COG Federal Express account found at:
https://www.cogmembers.org/_files/reference/FEDEXmemo.pdf.

For samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in the shipment.

14.2.4 Shipping Information for Specimens for COG ALL Molecular Reference Laboratory

Specimens for the COG ALL Molecular Reference Laboratory are to be collected in shipping media (SM) tubes which are prepared in the COG ALL Molecular Reference Lab and shipped in batches to each participating institution. The shipping media is in 15 mL conical tubes and contains RPMI and FBS with EDTA as the anticoagulant. Use tubes by expiration date.

Store shipping media tubes in a non-cycling -20°C freezer for prolonged storage. Tubes are stable in a -20° C freezer for 1 year after preparation date (see expiration date on tube). For short term storage, refrigerate shipping media tubes at 2-8° C for up to 3 months. Defrost frozen media and mix before adding blood or bone marrow.

To request prepared and pre-packaged sample shipping tubes, order tubes through the Biopathology Center Kit Management application (<https://ricapps.nationwidechildrens.org/KitManagement/>). Please be sure to select APEC14B1 for the protocol and “Shipping Media” for the kit type.

If you have questions about shipping media orders, please contact the COG ALL Molecular Reference Lab at (614) 722-2866.

Note: Institutions are strongly encouraged to make requests for sample tubes well in-advance of their first patient registration on the relevant therapeutic protocol; it will not be possible to expedite shipping because of prohibitive costs.

14.2.5 Contact Information

Laboratory Contact Information:

COG ALL Molecular Reference Laboratory
mglab@nationwidechildrens.org
Phone: (614) 722-2866
Fax: (614) 722-2887

Shipping Address:

COG ALL Molecular Reference Laboratory
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215

14.3 Biobanking for Future Research in Peripheral Blood at End of Induction – OPTIONAL (non-DS NCI SR B-ALL)

The submission of a peripheral blood sample is optional at the end of Induction therapy. Specimens will be shipped to the COG ALL Molecular Reference Lab (MRL). Please submit samples as follow:

14.3.1 Specimen Details

- Collect 3-5 mLs of peripheral blood (PB) at the following time-point:
- End of Induction

14.3.2 Sample Collection and Processing

- Collect 3-5 mLs of peripheral blood in a 5 mL EDTA (lavender top) tube.
- Mix well.
- If samples cannot be shipped on the day of collection, please store at 4°C until shipment on the next business day.

14.3.3 Sample labeling and Shipping

- Include the COG patient ID, patient name and date of birth, collection date, time point, and specimen type.
- **Do not** batch samples.
- Samples may be shipped Monday through Friday. If shipped on a Friday, mark Saturday delivery on the air bill and email the laboratory prior to shipment.
- Please include the RAVE transmittal form.
- Each sample should be prepared in accordance with IATA regulations.
- Ship samples via FedEx priority overnight. Utilize the COG Federal Express account found at:
https://www.cogmembers.org/_files/reference/FEDEXmemo.pdf.

- See [Section 14.2.4](#) for additional shipping information.

For samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in the shipment.

14.3.4 Contact Information

Laboratory Contact Information:

COG ALL Molecular Reference Laboratory
mglab@nationwidechildrens.org
Phone: (614) 722-2866
Fax: (614) 722-2887

Shipping Address:

COG ALL Molecular Reference Laboratory
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215

14.4 MRD by Flow Cytometry at End of Consolidation - REQUIRED for NCI SR B-ALL (with or without DS) with EOI flow MRD $\geq 0.1\%$ and NCI HR DS B-ALL with EOI flow MRD $\geq 0.01\%$

NOTE: For NCI SR B-ALL subjects (with or without DS) with end of Induction MRD by flow cytometry 0.01-0.099%, assessment of end of Consolidation MRD by flow cytometry is not required. However, if the treating clinician chooses to perform this optional assessment, samples may be sent to the University of Washington and costs for MRD assessment at this time point will also be covered by COG (samples should be processed as described in [Section 14.4](#)). All patients will also have the option of submitting material for Biobanking for Future Research (See [Section 14.5](#)).

14.4.1 BM Specimen Details

Collect 1-2 mLs of bone marrow (BM) at the end of Consolidation. See [APPENDIX XI](#) for additional details.

REQUIREMENTS FOR COLLECTION OF BM

- Following completion of Consolidation therapy, end of Consolidation bone marrow MRD will determine if eligible to continue on protocol therapy (See [Section 8.1](#)).
- The end of Consolidation marrow should occur as close to Day 56 as possible, but should be delayed until counts have recovered with an APC (Absolute Phagocyte Count) $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$. The end of Consolidation marrow should not be performed prior to Day 56 even if counts have recovered.
- If on Day 56, the counts have recovered with an APC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$, the bone marrow for end of Consolidation MRD should be performed on that day. A three day deviation is allowed, but any deviation that is greater than 3 days after count recovery must be discussed with the study chair.
- If on Day 56, the counts have not recovered (e.g., APC $< 500/\mu\text{L}$ or platelets $< 50,000/\mu\text{L}$), the bone marrow for end of Consolidation MRD should be delayed until APC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$. The bone marrow for end of Consolidation

MRD should be performed within 3 days of count recovery (APC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$). Any deviation that is greater than 3 days after count recovery must be discussed with the study chair. If counts have not recovered on Day 56, patients should have a CBC checked every 2-3 days (three times a week) at minimum until count recovery to minimize delay in obtaining the bone marrow.

- Patients who have not had count recovery (e.g., APC $\geq 500/\mu\text{L}$ and platelets $\geq 50,000/\mu\text{L}$) by Day 72 should undergo bone marrow to ensure they are not Consolidation failures.

Samples are to be shipped to Dr. Brent Wood at the University of Washington Flow Cytometry Laboratory. The AALL1731 Specimen Transmittal Form is to be submitted with each sample submitted to the COG Reference Laboratory. The specimen transmittal form information should always include the name and telephone number of a person designated by the PI to receive calls from the Reference Laboratory directors. The PI's FAX number must also be noted on each sample inclusion form. Because clinical recommendations will be made on these samples, **always include the patient's name, birth date and COG number on any sample submitted**. This is a CLIA requirement. University of Washington Flow Cytometry Lab may be unable to analyze specimens if adequate patient identifiers are not provided.

End of Consolidation bone marrow samples for the University of Washington Flow Cytometry Lab are to be collected in **green top sodium heparin** tubes. **Do not use** the 15 mL conical tubes (SM) containing EDTA/RPMI or large purple EDTA tubes at this time point.

Bone Marrow Collection Procedures:

- a. Collect 2 ml of BM from the 1st pull into a syringe and transfer the specimen immediately into a green top sodium heparin tube (commonly available in most hospitals). Collection of marrow volumes beyond 2 ml or use of marrow other than the 1st pull will result in hemodilution and may effect quantitation of MRD.
- b. Mix well.

14.4.2 Sample Shipping

Bone marrow samples for MRD studies will be shipped to:

University of Washington Flow Cytometry Reference Laboratory
Brent Wood, MD, PhD
Seattle Cancer Care Alliance
Hematopathology Laboratory, Room G7-800
825 Eastlake Ave. E.
Seattle, WA 98109-1028
Phone: 206-288-7060
FAX: 206-288-7127

All samples should be mailed by Federal Express Priority Overnight using the COG FedEx account:
https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

SEND ALL SAMPLES AT ROOM TEMPERATURE EXCEPT FOR INTERNATIONAL SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS – PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. IF SHIPPING DURING EXTREMELY HOT WEATHER, INCLUDE A COLD PACK (NOT AN ICE PACK).

SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS—PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST TWO PATIENT IDENTIFIERS, INCLUDING THE NAME AND THE COG NUMBER. IN ADDITION, AN AALL1731 SPECIMEN TRANSMITTAL FORM AVAILABLE IN RAVE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

Call Reference Laboratories only when shipping a sample to be delivered on Saturday. All Saturday deliveries must be marked “For Saturday Delivery” on the FedEx air bill. Saturday delivery is only available for fresh bone marrow.

14.5 Biobanking for Future Research in Bone Marrow at End of Consolidation – OPTIONAL (SR-High patients with EOI flow MRD $\geq 0.1\%$, and SR-High patients with EOI flow MRD $0.01\text{-}0.099\%$ who have BM assessed for MRD at EOC)

14.5.1 BM Specimen Details

Collect 3 mL (patients $<10\text{kg}$) or 5 mL (patients $\geq 10\text{kg}$) of bone marrow at the following time-point:

- End of Consolidation therapy

Sample Collection and Processing

Bone Marrow Collection Procedures for Reference Laboratories:

- a. Collect 3 mL (patients $<10\text{kg}$) or 5 mL (patients $\geq 10\text{kg}$) BM into a syringe and transfer the specimen immediately into the SM tube with RPMI/EDTA.
- b. Mix well. Up to 5 mL of BM can be placed in 1 SM tube. If you don't have SM tubes, you can place the BM into large purple EDTA tubes that are commonly available in most hospitals. However, the viability of the cells is greatly enhanced in the SM tubes.
- c. Use multiple syringes and tubes as necessary. Reposition the BM aspirate needle at least once during the diagnostic procedure to ensure the maximum quality of BM. **DO NOT SHIP SYRINGES.**

14.5.2 Specimen Labeling, Packaging and Shipping

Specimens labeling:

- Patient's full name (not initials)
- Patient's Date of birth
- COG number
- BPC number
- Sample time-point: End of Consolidation
- Specimen type (BM) on each tube

All specimen tubes for **optional studies** must include, at minimum, the patient's COG number and BPC number as patient identifiers.

Specimen Packaging:

Supplies for packaging/shipping for freshbone marrow are not provided. The following considerations should be made when preparing biospecimens for shipment:

- Sites must comply with IATA standards (www.iata.org) when shipping all samples.
- Send bone marrow at room temperature except for international samples that are expected to be delayed for more than 48 hours – place a cold pack (not ice pack) in shipment.
- If shipping bone marrow during extremely hot weather, include a cold pack (not an ice pack).
- When shipping during extremely cold weather, surround the samples with extra insulation to keep them from freezing.

Shipping:

Protocol-required fresh specimens must be sent directly at room temperature to the COG Reference Laboratory in SM. Every effort should be made to ship samples on the day that they are obtained to optimize cell viability and test results, however samples will be accepted if shipped the next day.

All samples should be mailed by Federal Express Priority Overnight using the COG FedEx account:

https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

Call or email the Reference Laboratories only when shipping a sample to be delivered on Saturday. All Saturday deliveries must be marked “For Saturday Delivery” on the FedEx air bill. Saturday delivery is only available for fresh bone marrow.

14.5.3 Contact Information

Laboratory Contact Information:

COG ALL Molecular Reference Laboratory
mglab@nationwidechildrens.org
Phone: (614) 722-2866
Fax: (614) 722-2887

Shipping Address:

COG ALL Molecular Reference Laboratory
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215

14.6 Immune Function in Children with Down Syndrome B-ALL – OPTIONAL (all DS patients)

This optional correlative biology study will identify factors responsible for infection-related mortality (IRM) in children with DS and B-ALL by performing functional immune profiling using high-dimensional mass cytometry (MC). We will compare functional immune profiles in DS patients with ALL who suffer Grade 4-5 infections during treatment versus DS patients who did not. Peripheral blood samples will be analyzed by MC using highly multiplexed 40-marker panels to quantify the abundance and activation states of monocytes, plasmacytoid dendritic cells, natural killer cells, and T-cell subsets; and to comprehensively profile cytokines from all innate and adaptive T-cells subsets. See [Section 15.1](#) for further details.

14.6.1 Specimen Details

Collect 6-10 mLs of peripheral blood (PB) at the following time-points:

- Pretreatment/Diagnosis
- Day 1 of Maintenance Cycle 2 (may be collected 4 weeks early or late)

Note: 4mL PB is acceptable for patients with a BSA < 0.6 m²

14.6.2 Sample Collection and Processing

- Collect peripheral blood in a green top sodium tube
- Obtain Maintenance Cycle 2 PB prior to steroid treatment
- Samples may be stored prior to shipment
- For baseline/pretreatment samples collected on Friday/Saturday/Sunday, shipment may be delayed until Monday. Store at 4°C.
- Please schedule the Maintenance sample to ensure collection and shipment Monday-Thursday

14.6.3 Sample Labeling and Shipping

Please label all tubes with the study number, COG patient ID, and BPC ID.

- Pre-treatment:
 - Label as “pre-PB”
 - Denote sample collection date/time
 - Denote chemotherapy start date
- Second sample:
 - Label as “Maintenance PB”
 - Denote sample collection date/time
 - If steroid is given prior to blood collection, specify date/time of dose of steroids
- Do not batch samples
- Pack samples with at least 2 ice packs in non-winter months to assure temperature stability. Wrap sample in absorbent cloth to keep from breaking.
- Contact lab before specimens are shipped
- Deliveries are accepted Monday-Friday
- DO NOT ship on Friday, weekends, or holidays

- Include a Specimen transmittal sheet with white blood count and blast percentage for pre-treatment samples. Refer to the Data Collection tab on the AALL1731 study page for the Specimen transmittal sheet.

Ship samples by Federal Express Priority Overnight delivery using the following:

FedEx account #: 296621072

Please be sure to add air bill comment: TCH CC# 6014

- Notify Gaye Jenkins **prior to shipment of the sample**. Please email the Fed-Ex tracking number if prior notification is not possible.
- If possible, do not ship samples for delivery on a weekend or holiday. Please contact the Horton lab for special instructions if samples are collected on a Friday

14.6.4 Contact Information

Laboratory Shipping Address:

Terzah Horton, MD, PhD
c/o Gaye Jenkins
1102 Bates, Suite 750.01
Houston, TX 77030

Laboratory Contact Information:

Gaye Jenkins
Email: gjenkin@txch.org
Phone: (832) 824-4676
Fax: (832) 825-1206

DS Immune Function Study questions:

AALL1731_DS immune function@texaschildrens.org

14.7 Biobanking for Future Research on CSF for B-ALL – OPTIONAL

14.7.1 CSF Specimen Details for non-DS B-ALL patients

After the first aliquot is reserved for cell count, per standard of care, collect leftover cerebral spinal fluid (CSF) at the following time-points, prior to the scheduled administration of intrathecal chemotherapy:

- End of Induction
- Final lumbar puncture of Consolidation
- Day 1 LP of Maintenance Cycle 1
- Final lumbar puncture of Maintenance

Sample Collection and Processing

Collect CSF into an empty, sterile tube. To minimize sample degradation between the time of collection and analysis, each sample should be placed on ice after collection. Centrifuge in a sterile 15 mL conical tube at 1,000-3,000 RPM at 4°C for 3-5 minutes within 60 minutes of collection to remove cellular elements. The supernatant should then be separated from any pellet and transferred to empty cryovial(s) of no more than 1 mL/tube. A total of 3-5 mL should be collected. Store the supernatant at -

70°C until for up to 1 month until it can be batch shipped on dry ice. For those institutions without access to -70°C storage, samples will be shipped same day.

14.7.2 Specimen Labeling, Packaging and Shipping

Specimens labeling:

- Patient's full name (not initials)
- Patient's Date of birth
- COG number
- BPC number
- Sample time-point:
 - Time-point 1 (end of Induction)
 - Time-point 2 (final LP of Consolidation)
 - Time-point 3 (first LP of Maintenance Cycle 1)
 - Time-point 4 (final LP of Maintenance)
- Specimen type (CSF) on each tube
- Samples may be batch shipped each month, but must be shipped overnight for mid-week arrival, frozen on dry ice.
- Do not ship frozen specimens on a Friday or the day before a holiday.

All specimen tubes for **optional studies** must include, at minimum, the patient's COG number and BPC number as patient identifiers.

Specimen Packaging:

Supplies for packaging/shipping frozen CSF are not provided. The following considerations should be made when preparing biospecimens for shipment:

- Sites must comply with IATA standards (www.iata.org) when shipping all samples.
- CSF must be shipped in an insulated box (not provided) with enough dry ice to keep samples frozen until arrival at the reference laboratory.

Shipping:

All samples should be mailed by Federal Express Priority Overnight using the COG FedEx account:

https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf

Call or email the Reference Laboratories only when shipping a sample to be delivered on Saturday. All Saturday deliveries must be marked "For Saturday Delivery" on the FedEx air bill. Frozen CSF samples must be shipped on Monday through Thursday only.

14.7.3 Contact Information

Laboratory Contact Information:

COG ALL Molecular Reference Laboratory

mglab@nationwidechildrens.org

Phone: (614) 722-2866

Fax: (614) 722-2887

Shipping Address:
COG ALL Molecular Reference Laboratory
Nationwide Children's Hospital
575 Children's Crossroads, Room WB2255
Columbus, OH 43215

14.8 Biobanking for Future Research for B-LL_y patients – OPTIONAL

14.8.1 Specimen Details for B-LL_y patients

Snap frozen tissue from biopsy at diagnosis, relapse (if it occurs), and of any residual or new masses at any time in therapy or follow-up. See below for collection and shipping instructions for biopsy samples.

14.8.2 Sample Collection and Processing of Biopsies

For every case, snap-frozen tissue is preferred. Wrap each aliquot of tissue in a piece of foil and snap freeze in vapor phase liquid nitrogen (do not submerge the tissue in the liquid nitrogen) or on dry ice.

- Place frozen tissue in zip lock bag.
- Using a waterproof marker, label the bag with the patient's COG patient ID, BPC number, specimen type (P for primary or M for metastatic) and date obtained.
- Store specimens at -70°C or colder until shipped.
- Include a transmittal form and the corresponding pathology report with each shipment of specimens.

Note: If snap-frozen tissue is not available, a representative tumor block or ten 5 µm unstained slides and two 50 µm tissue sections (scrolls) are requested. The 50 µm sections should be placed in a cryovial. Slides and the cryovial holding the scrolls must be labeled with the surgical pathology ID number and block number from the corresponding pathology report, in addition to the BPC number, specimen type (P for primary or M for metastatic) and collection date.

The Biopathology Center (BPC) will bank the tissue for future distribution and use, including the studies listed above.

14.8.3 Sample Labeling and Shipping

Specimen Procurement Kits for shipping frozen tumor tissue to the BPC for AALL1731 are provided upon request. To request a Specimen Procurement Kit, access the BPC Kit Management system: <https://ricapps.nationwidechildrens.org/KitManagement/>. Specimen procurement kits must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday. Shipping supplies are not provided for shipment of blocks or slides.

The single chambered kit is used to ship frozen tumor to the Biopathology Center.

1. Before frozen specimens are placed into the Specimen Procurement Kit, they first need to be placed in three layers of packaging.

- a. Place the specimens in individual zip lock bags (one bag per specimen type/time point).
 - b. Place the zip lock bags in the biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
 - c. Place the biohazard envelope inside the Tyvek envelope. Expel as much air as possible and seal securely.
2. Place the specimens inside the kit compartment with dry ice.
 - a. Layer the bottom of the compartment with dry ice until it is approximately one-third full.
 - b. Place the frozen specimens on top of the dry ice.
 - c. Cover the specimens with the dry ice until the compartment is almost completely full.
 3. Enclose the transmittal form(s) and any other required documents in a plastic bag and place inside the kit chamber.
 4. Place the foam cover on top to insulate specimens during shipment.
 5. Close the outer lid of the Specimen Procurement Kit and tape with filament or other durable sealing tape.
 6. Print a shipping label via the BPC Kit Management system. Attach the shipping label to the top of the kit.
 7. Complete the dry ice label (UN 1845). Stick the dry ice and Exempt Human Specimen labels to the side of the kit.

Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355.

Frozen or formalin-fixed and paraffin-embedded tissue specimens should only be shipped to the BPC on Monday-Thursday for Tuesday-Friday delivery. Blocks, slides, and scrolls should be sent via regular mail or using your institutional courier account.

14.8.4 Shipping Address

Ship specimens to:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865

14.9 Minimal Marrow Disease for B-LLy patients – Optional

14.9.1 Sample Collection

Bone marrow specimen will be obtained from B-LLy patients to assess disease involvement in the bone marrow at the following time points:

- Diagnosis

This sample will be shipped to ARUP Laboratories for analysis by Dr. Rodney Miles. A Specimen Transmittal Form, ARUP requisition, and a copy of the pathology report of the original biopsy is required for each sample submitted (the Specimen Transmittal Form and ARUP requisition are posted on the AALL1731 page of the COG members' website. The specimen transmittal form information should always include the name and telephone number of a person designated by the PI to receive calls from the Laboratory directors. The PI's Fax number must also be noted on each sample inclusion form. See [Appendix XIII](#) for additional instructions on sample collection and processing.

14.9.2 Bone Marrow Collection Procedures:

- a. Collect 2 mL (minimum 1 mL) BM into a syringe and transfer the specimen immediately into a large sodium heparin tube (green tube).
- b. Mix well.
- c. Sample should be maintained at ambient/room temperature or refrigerated. Samples should never be frozen.

14.9.3 Sample Shipping

- a. B-LLy bone marrow samples for MMD studies will be shipped to ARUP Laboratories on the same day as collection. For institutions that are ARUP clients, samples should be shipped using your hospital's ARUP courier system. Submit sample to your laboratory with the ARUP requisition. If your institution is not an ARUP client and/or does not have an ARUP courier system in place, please contact Trent Weight at ARUP Laboratories to arrange sample submission (ideally this should be done a few days prior to sample collection).

Trent Weight
Phone: 801-583-2787 ext. 2225
Email: trent.weight@aruplab.com.

- b. Include the ARUP requisition form, a specimen transmittal form with each specimen and include a copy of the pathology report of the original biopsy with the sample at diagnosis.
- c. Samples should be shipped at ambient/room temperature except as below. Samples should never be frozen.
- d. Samples can be shipped 7 days a week.

Ship to:

ARUP Laboratories
ATTN: CT Processing
500 Chipeta Way
Salt Lake City, UT 84108
Phone: (801) 584-5240
Fax: (801) 584-5124

SAMPLES THAT ARE EXPECTED TO BE DELAYED FOR MORE THAN 48 HOURS - PLACE A COLD PACK (NOT ICE PACK) IN SHIPMENT. ALL TUBES SHOULD BE LABELED WITH AT LEAST TWO PATIENT IDENTIFIERS, INCLUDING THE NAME AND THE COG NUMBER. IN ADDITION, THE ARUP REQUISITION AND A SPECIMEN TRANSMITTAL FORM AVAILABLE ON THE RAVE SHOULD ALWAYS BE SUBMITTED WITH EACH SAMPLE.

15 DS B-ALL IMMUNE FUNCTION STUDIES

15.1 Immune Function in DS B-ALL (OPTIONAL)

15.1.1 Objective

To define defects in innate and/or adaptive cell-mediated immunity that underlie the high infection-related mortality in DS children during ALL therapy.

15.1.2 Background and Rationale

Survival outcomes remain unsatisfactory for children with DS due to both higher rates of relapse and treatment-related mortality (TRM).³² TRM, chiefly due to infections, is 3.5- to 10-fold increased compared to the overall pediatric population with ALL (13% vs 0.89% Induction deaths for U.S. DS vs non-DS patients ($p=0.0008$); 21.6% vs 3.3% treatment-related mortality for U.K. patients ($p<0.00005$)^{32,44,79,80} and occurs in all phases of ALL treatment including Maintenance therapy. The microorganisms underlying grade 5 infections were bacterial (68%), fungal (20%) and viral (12%) suggesting a broad or multifaceted impairment of immune function in this group.⁴⁴ Although infection-related mortality (IRM) decreased when the regimens for DS children were de-intensified,^{79,80} we recently reported that rates remain significantly higher than for non-DS patients on the current U.S. trials (2.1% vs 0.67% Induction deaths, $p=0.017$).⁸¹

Children with DS not treated for leukemia have 30% increased mortality risk from sepsis⁸² but it is not evident which impairments of innate and adaptive immune function underlie this risk and are exacerbated by the immune- and myelosuppressive effect of ALL therapy. Early reports focused on abnormalities of the innate immune system in DS such as impaired neutrophil chemotaxis.⁸³ Flow cytometric enumeration subsequently revealed a decrease of total white cells, granulocytes, NK cells⁸⁴ and monocytes, but an increase of pro-inflammatory, non-classical CD14dimCD16+ monocytes⁸⁵ while increased NK cell numbers were found by others.⁸⁶ Decreased thymus size and mild to moderate lymphopenia of DS early on suggested concomitant abnormalities of adaptive immunity. Strikingly, the expansion of primary T and B lymphocytes during the first years of life is absent in children with DS. Numbers of CD3+CD4+ T helper, CD3+ CD8+ cytotoxic and TCRαβ+ T lymphocytes are decreased.⁸⁷ Among CD4+ T cell subsets, proportions of regulatory (CD25+CD127lowCD4+) T cells, Th1 and Th17 cells, defined by the stimulated production of IFNγ and IL-17, respectively, are significantly increased without evident functional deficit.⁸⁶ T cells subsets in DS recently were shown express higher levels of the inhibitory receptor PD1.⁸⁶ In addition, B lymphopenia persists in children with DS throughout childhood and 88% of children show B cell numbers in the peripheral blood below the 5th percentile.⁸⁷ IgG levels are typically in the normal range while IgM levels decrease in late childhood and IgG2 and IgG4 subclass deficiencies may appear.^{84,88}

The relevance of these findings to infection-related mortality (IRM) of DS patients during ALL therapy is unclear. Furthermore, these studies focused on only a few immune functions, precluding an integrated view of how diverse immune abnormalities might act independently or cooperatively to increase IRM. The observation that IRM in DS-ALL is associated with bacterial, fungal and viral infections,^{32,44,89} suggests globally defective Type 1 and/or Type 17 cell-mediated immune responses.⁹⁰ Despite these clues, the complex network of innate and adaptive

immune cell types has not been assessed to identify the relevant functional impairments that result in the observed excessive IRM of patients with DS and ALL.

To enable a highly efficient approach for deep functional immune profiling, we developed mass cytometry (MC), a multi-dimensional next-generation flow cytometry platform that can measure 40 cell markers per tube to reveal clinically relevant complexity in immune functions.^{91,92} Cells labeled with metal-tagged antibodies are introduced into a mass spectroscopy-coupled flow cytometer (CyTOF) to identify cell-associated metal tags. We have developed and validated 35-marker MC protocols and antibody panels to quantify secretion of pro- and anti-inflammatory cytokines from multiple naïve and effector memory T cell subsets in a single tube of peripheral blood mononuclear cells (PBMC).

To date, supportive care for children with DS enrolled on COG studies for SR and HR ALL has been modified empirically.⁹³ Analysis of the specific immune defect(s) in this group is essential for the development of evidence-based enhanced supportive care interventions that will improve overall survival of children with DS by preventing their excessive IRM during chemotherapy for ALL.

15.1.3 Study Design

We will perform functional immune profiling on peripheral blood (PB) samples in the following groups:

- DS-ALL cases who experienced severe (grade 4-5) infections during treatment
- DS-ALL controls who did not
- Non-DS ALL controls who did not

Samples for DS-ALL cases and controls will be collected from consenting participants enrolled on AALL1731. Samples for non-DS ALL controls will be collected on a separate, non-COG protocol. Each group will be frequency matched (1:2 cases:controls) on sex, race and ethnicity to reduce the likelihood of confounding effects.

Samples will be collected at two time points (see [Section 14.6](#) for additional details):

- Pretreatment/Diagnosis
- Day 1 of Maintenance Cycle 2 (\pm 4 weeks is acceptable)

Mononuclear cells (prepared by Ficoll centrifugation) will be cryopreserved for subsequent high dimensional immune profiling by MC. We have developed highly multiplexed MC panels to quantify abundance and activation states of classical, non-classical, and intermediate monocytes; conventional and plasmacytoid dendritic cells; NK cells; naïve and effector memory CD4 and CD8 T cells, and CD4+ FoxP3+ Treg cells. For Maintenance samples, we will also include CD31 to evaluate thymic production of naïve T cells during chronic treatment.⁸⁵ We will comprehensively profile production of inflammatory (IL-1 β , IFN γ , TNF α , IL-6, IL17, CCL4), anti-inflammatory (IL4, IL10), and other (IL2) cytokines from innate and adaptive T cell subsets.

15.1.4 Sample Size Considerations

All DS patients enrolling on AALL1731 are eligible for this study. Total estimated accrual over the duration of the study is 240, and we conservatively estimate that 70%

of patients will consent to participation and contribute adequate sample material, for an estimated sample size of 168. We anticipate a 20% incidence of grade 4-5 microbiologically documented infections, based on historical data from DS patients enrolled on AALL0932 and AALL1131, providing 34 DS cases and 134 DS controls. We plan to perform profiling on all available cases ($n=34$) and twice as many controls ($n=68$). Since this is an exploratory, hypothesis-generating study, we will use DiffCyt (described in section 15.1.5 below) to identify differentially abundant cell clusters that predict or classify cases and controls. DiffCyt utilizes the statistical methods originally developed for analysis of gene expression data. Therefore, we utilized the “check.power” function in the “ssizeRNA” R package to verify the power for this exploratory analysis.⁹⁴ The following parameters were used for our calculations: nGenes = 50 (in this case immune markers), m = 34 (sample size per group), mu = 10 (control group mean), disp = 0.1 (dispersion), fc = 1.5 (fold change), fdr = 0.05 (false discovery rate), sims = 10 (number of simulations). Given our experience with this type of data, we are allowing for a meaningful fold-change of 1.5 in our results and are basing the calculation on a dispersion factor of 0.10, which is equivalent to a coefficient of variation (CV) of 32%. This may be a slightly higher CV than we might expect for flow cytometry data based on published data⁹⁵; however, it allows a more conservative estimate of the power for this exploratory study. With smaller CVs, we would expect even better power to detect differences between groups. See Figure with range of dispersion factors from 0.05-0.20 (equivalent to CV ranging from 22%-45%). Given these parameters, we have 84% power to detect a 1.5-fold difference in abundance between the clusters, after correcting for multiple comparisons using the Benjamini-Hochberg method. As the calculator cannot handle unequal samples, the power is likely to be increased with 34 ‘cases’ and 68 ‘controls’ as proposed in our analysis plan. These sample sizes will be used for both the diagnosis and Maintenance time points, and at each time point these sample sizes will apply to comparisons of DS cases to both DS controls and non-DS controls.

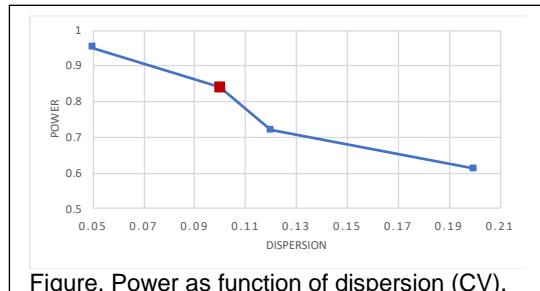


Figure. Power as function of dispersion (CV). Red square represents dispersion factor of 0.10.

15.1.5 Analysis Plan

We will use the FlowSom high resolution clustering approach to identify cellular subsets and/or activation states (endophenotypes) that distinguish cases from controls.⁹⁶ The FlowSOM clustering approach allows unbiased detection and quantification of common and rare subsets based on their similarities in high dimensional space. We will then utilize the “diffCyt” framework to identify those cell clusters that significantly differ between groups. FlowSom has been identified as among the top-performing open source algorithms for clustering data to identify cell subsets. DiffCyt has been validated for discovery of differential abundance of cell subsets or marker intensity in flow or mass cytometry data sets (<http://dx.doi.org/10.1101/349738>), using an R implementation of *edgeR* for mass cytometry data.

15.2 Host Genetic Susceptibility to Infection in DS B-ALL (OPTIONAL)

15.2.1 Background and Objectives

Recently, there has been growing awareness of the role of genetic factors affecting susceptibility to infection in childhood ALL.^{45,46} Variant alleles of genes involved in the immune response and genes affecting metabolism of immunosuppressive chemotherapeutic agents, have been implicated in the risk of severe infectious complications. The presence of a variant allele with adverse immunologic effects may be particularly profound when superimposed on these generalized immune defects of children with DS. Identifying such effects may enable specific targeted pharmacogenetic and/or immunotherapeutic interventions, such as individualization of drug dosing to prevent undue myelosuppression, or augmentation of a defective immune response.

15.2.2 Overview of Study Design

We plan to conduct a genome-wide assessment of variants associated with risk of severe infection using a case-control approach. All DS patients enrolling on AALL1731 will be eligible for participation. Following completion of protocol therapy, patients who experienced a grade 4-5 microbiologically documented infection will be categorized as cases, and those who did not will be categorized as controls. Peripheral blood or bone marrow obtained for banking will be used as a source of constitutional (germline) DNA. Genotyping data will be used to compare relative frequencies of single nucleotide polymorphisms (SNPs) between cases and controls.

15.2.3 Sample Size Considerations

All DS patients enrolling on AALL1731 are eligible for this study. Total estimated accrual over the duration of the study is 240, and we conservatively estimate that 90% of patients will consent to optional banking and contribute adequate remission sample specimens, for an estimated sample size of 216. We anticipate a 20% incidence of grade 4-5 microbiologically documented infections, based on historical data from DS patients enrolled on AALL0932 and AALL1131. To ensure robust and unbiased results, we conducted power calculations using Quanto version 1.2.4. Using $\alpha=5\times10^{-6}$, we have sufficient power ($1-\beta=0.80$) to detect the following odds ratios (ORs) assuming a range of minor allele frequencies (MAF): OR=4.9, MAF=20%; OR=4.3, MAF=30%; OR=4.2, MAF=40%. These effect sizes are consistent with previous GWAS of adverse outcomes among children with ALL and other malignancies.^{97,98}

15.2.4 Analysis Plan

We will conduct a genome-wide assessment using a case-control approach: those who develop grade 4-5 microbiologically documented infections (cases) compared to those who do not (controls). To ensure robust and unbiased results, we will employ a two-step iterative resampling procedure for internal validation of our findings that was successfully used in a recent GWAS of relapse in childhood ALL,⁹⁸ and recently expanded by Kang et al.⁹⁹ We will divide our population into a discovery and replication cohorts using a 70:30 split. In Step 1 (discovery), we will use multiple logistic regression models to calculate the OR, 95% confidence interval, and p-value evaluating the association between each SNP and grade 4-5 infections. Genotypes will be coded using an additive genetic model (i.e., SNPs will be categorized as 0, 1, or 2, based on the number of minor alleles). SNPs where $p<10^{-4}$ in the discovery

cohort will be moved forward for replication. In Step 2 (replication), a SNP will be considered validated if its genotype is associated with grade 4–5 infectious toxicities at $p<0.05$. This approach preserves a type 1 error rate per SNP of 5×10^{-6} . We will conduct 100 replications, resampling the 70:30 split in each replicate. SNPs significant ≥20 times in 100 replications are considered validated.⁹⁹ To reduce the likelihood of confounding by race/ethnicity, all models will be adjusted for genetic ancestry (based on top components from principal components analysis). Additionally, we will adjust for clinical factors significantly associated with outcome, including treatment protocol and sex.

16 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

Radiation therapy (RT) for patients on COG protocols can only be delivered at approved COG RT facilities.

Treatment Planning

CT-treatment planning: All patients will undergo CT treatment planning for this protocol when treated with cranial irradiation. CT treatment planning is optional for testicular irradiation. Slices no more than 0.5cm thick shall be taken throughout the extent of the irradiated volume.

Patient positioning

Reproducible setups are critical and the use of immobilization devices is strongly encouraged. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

Immobilization devices

Standard immobilization devices for the brain (eg facemask) and testes (eg vac-lock, alpha cradle, body mold) are to be used.

Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

16.1 Cranial Irradiation

Cranial irradiation will be given to Down-syndrome (DS)-High B-ALL patients with CNS3 leukemia at diagnosis. Cranial radiotherapy will be given concurrent with Maintenance therapy, and is to begin after Day 1, Cycle 1 of Maintenance therapy to avoid concurrent treatment with IT MTX. Radiotherapy should be completed by Day 29 of Maintenance. Refer to [Section 4.43](#).

In-room verification of spatial positioning

Two-dimensional or volumetric imaging may be used to verify correct patient positioning. Portal imaging using EPIDs is the most common two-dimensional method. Film is discouraged but is acceptable. For 3D photon treatments, a pair of images (usually orthogonal AP and lateral) is required to verify that the isocenter is in correct alignment relative to the treatment plan; these may be MV or kV images.

16.1.1 Equipment and Calibration

16.1.1.1 Modality

Photon beams with a nominal energy of 4 or 6 MV. Intensity-Modulated Radiation Therapy (IMRT) is not allowed.

16.1.1.2 Calibration

The calibrations of therapy units used in this protocol shall be verified by the IROC Houston QA Center.

16.1.2 Target Volume

16.1.2.1 Cranial Irradiation

The target volume consists of the entire brain and meninges.

Anterior: including the frontal lobe as well as the posterior halves of the globes of the eyes, with the optic disk and nerve.

Superior: to the vertex.

Posterior: to the occiput.

Inferior: caudal to the skull base and at least the level of the C1/C2 interspace.

16.1.3 Target Dose

16.1.3.1 Prescription Points

The prescription point in each target volume is at or near the center.

16.1.3.2 Dose Definition

The absorbed dose is specified in centigray (cGy)-to-muscle.

16.1.3.3 Tissue Heterogeneity

Calculations may take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities.

16.1.3.4 Prescribed Dose and Fractionation

Daily Dose: The daily dose to the prescription points for the cranial volume will be 180 cGy.

Total Dose:

Cranium: The total dose to the prescription point shall be 1800 cGy in 10 treatments.

Fractionation: All radiation fields shall be treated once each day; the treatment shall be given 5 days a week.

Treatment Interruptions: No corrections will be made for treatment interruptions less than 7 days. For any interruptions greater than 7 days, contact the study coordinator.

Dose Uniformity: The dose variations in each target volume shall be within +7%, -5% of the prescription-point dose.

16.1.4 Treatment Technique

16.1.4.1 Patient Position

The patient can be treated prone or supine with immobilization with a facemask.

16.1.4.2 Beam Configuration

The cranial volume is treated with 2 lateral or anterior oblique, equally weighted photon beams. The fields shall extend at least 1 cm beyond the periphery of the scalp.

16.1.4.3 Shielding

Blocks: Field-shaping shall be done with blocks which are at least 5 HVL thick. Multi-leaf collimators are also acceptable provided coverage is adequate.

Figure 16.1.4.3

Example of radiation simulation radiograph with cerrobend block design for cranial irradiation volume.



Lens sparing techniques are encouraged with 1 of 2 techniques:

- 1) Angling of the 2 lateral fields in the anterior direction (RAO/LAO) using the lateral canthus markers to “flatten” the beam edge. Shielding blocks are used to block the anterior halves of the eyes, the nose, and mouth.
- 2) Set the central axes of the horizontal cranial beams so that they are aligned to the lateral canthi (half-beam blocking technique). The anterior edges of the beams are defined by an external block or by an independently controlled collimator and meet at a point 1 cm anterior to the frontal lobe meninges. Shielding blocks cover the anterior halves of the eyes and protect the nose and mouth.

16.2 Testicular Irradiation

Testicular irradiation will be given to Down Syndrome (DS) patients with testicular leukemia at diagnosis that does not resolve completely by the end of Induction. Testicular radiotherapy is to start during Consolidation and must be completed before the end of this phase of therapy. Please see [Section 4.35](#) for more timing details.

16.2.1 Equipment and Calibration

16.2.1.1 Modality

Photon (4-6 MV) or electron beams are allowed. Selection of energy is determined by dose uniformity criterion, and with electrons, the lowest possible energy should be used to spare tissues outside target volume. IMRT is not allowed.

16.2.1.2 Calibration

Calibrations of therapy machines used in this protocol will be verified by the IROC Houston QA Center.

16.2.2 Target Volume

Clinical target volume (CTV) consists of the scrotum including the bilateral testes and gross tumor in the scrotal sac.

16.2.3 Target Dose

16.2.3.1 Prescription Point

Prescription point is at or near center of planning target volume for treatment with photons and at Dmax for treatment with electrons.

16.2.3.2 Dose definition

Absorbed dose is specified as centigrays (cGy)-to-muscle. Calculations may take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. However, a clinical set-up is also acceptable.

16.2.3.3 Prescribed Dose and Fractionation

Total dose to prescription point will be 2400 cGy in 12 fractions. Patient will be treated once a day with 200 cGy. The treatment shall be given 5 days a week.

16.2.3.4 Dose Uniformity

Variations of dose within planning target volume will be within +7%, -5% of dose to prescription point. The Uniformity requirement can be met with electron beam of appropriate energy provided bolus is used, which is simplest technique. Bolus may also be needed for photon beams to fulfill dose uniformity requirement.

16.2.3.5 Treatment Interruptions

No corrections will be made for treatment interruptions less than 7 days. For interruptions greater than 7 days, contact the study coordinator.

16.2.4 Treatment Technique

16.2.4.1 Patient Position

Patient will be treated in supine position with separation of the legs to allow exposure of the scrotum. Note: due to the cremasteric reflex, the position of the testes can change and rise superiorly. Attention is warranted to ensure they do not move out of the radiation field.

16.2.4.2 Field-shaping

Field shaping can be done with blocks of at least 5 HVL thick or multi-leaf collimators. With electron fields, 2 cm from scrotum to block edge is recommended.

16.2.5 Normal Tissue Sparing

Testes will be supported posteriorly and, if possible, extended caudally in order to minimize perineal irradiation. Field will not be angled towards perineum. The penis will be excluded from the field by fixing it to skin over symphysis pubis.

16.3 Quality Assurance Documentation

16.3.1 IROC RI Post Treatment Review

Patients receiving RT on this study will have a simple review of the treatment delivered. There is no on-treatment review in this study. There is no film review required. Within 1 week of the completion of radiotherapy, the following data will be submitted:

- “RT-2 Radiotherapy Total Dose Record” form.
- Copy of patient’s radiotherapy record, including prescription, and daily and cumulative doses.

16.3.2 Data may be emailed to: datasubmission@qarc.org or mailed to:

IROC Rhode Island
Building B, Suite 201
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Fax: 401-753-7601

16.3.3 Questions regarding the dose calculations or documentation should be directed to:

IROC Rhode Island
Phone: 401-753-7600
Email: physics@qarc.org

16.3.4 Questions regarding radiation therapy should be directed to:

Julie Bradley, MD
UF Health Proton Therapy Institute
University of Florida Health Science Center - Gainesville
2015 North Jefferson Street
Jacksonville, FL 32206

Phone: (904) 588-1441
Fax: (904) 588-1303
E-mail: jbradley@floridaproton.org

Benjamin Cooper, MD
Laura and Isaac Perlmutter Cancer Center
New York University Langone
160 East 34th Street, LL1
New York, New York 10016
Phone: (212) 731-5003
Fax: (212) 731-5512
E-mail: benjamin.cooper@nyumc.org

16.4 Definitions of Deviation in Protocol Performance

16.4.1 Variation Acceptable

Dose to prescription point differs from that in protocol between 6% and 10%.

16.4.2 Deviation Unacceptable

Dose to prescription point differs from that in protocol by more than 10%.

17 NEUROCOGNITION, HOUSEHOLD MATERIAL HARDSHIP, AND CAREGIVER BURDEN IN B-ALL

17.1 Neurocognition, Household Material Hardship and Caregiver Burden in NCI SR B-ALL – OPTIONAL (non-DS only)

17.1.1 Primary Objective

Among a prospectively acquired cohort of children with NCI SR B-ALL without DS and enrolled on AALL1731, we aim to:

Compare the change in neurocognitive functioning from baseline to end-of-therapy between children from poor families (defined as presence of household material hardship (HMH)) and non-poor families (absence of HMH) adjusting for treatment arm using the following measurements:

- 1) Cogstate computerized cognitive measures of attention and processing speed.
- 2) Parent-reported behavior and cognitive regulation (BRIEF2 or BRIEF-P, based on age).

Hypothesis: Children with HMH will experience greater decline in neurocognitive function across domains of attention, processing speed and executive function as measured by Cogstate Cognitive testing and parent-completed BRIEF2/BRIEF-P.

17.1.2 Secondary Objectives

Among children enrolled on the neurocognitive and household material hardship study, for the subset classified post Induction as SR-Avg or SR-High B-ALL we aim to:

- 17.1.2.1 Compare the demands and work limitations on caregivers of children with ALL receiving chemotherapy versus chemotherapy with the addition of blinatumomab and to compare the change in the demands and work limitations over time, measured by the Care of My Child with Cancer questionnaire and the Caregiver Work Limitations questionnaire during post-Induction therapy.
- 17.1.2.2 Describe the impact of baseline household material hardship (HMH) on caregiver demands during post-Induction therapy in families with children randomized to chemotherapy versus chemotherapy with the addition of blinatumomab.
- 17.1.2.3 Compare changes in HMH levels from baseline to beginning of Maintenance therapy in families with children randomized to chemotherapy versus chemotherapy with the addition of blinatumomab.

17.1.3 Exploratory Objective

Determine the prevalence of symptoms and change over the course of therapy of symptoms in children with ALL receiving chemotherapy with or without the addition of blinatumomab as measured by the Memorial Symptom Assessment Scale.

17.1.4 Background for the neurocognitive and HMH aim

One in five children in the U.S. lives in poverty,¹⁰⁰ and poor children in the U.S. are at higher risk of impaired cognitive function as compared to their non-poor

counterparts.⁵⁰ Neurocognitive deficits have been reported in 20-40% of childhood ALL survivors^{101,102} and are associated with inferior child quality-of-life⁵¹ and increased parental stress.⁵² Consequently, it is crucial to identify children at highest risk of treatment-related neurocognitive decline to allow for design and testing of strategies to reduce this outcome. Despite this, almost no data exist elucidating the impact of pre-existing poverty or treatment-induced poverty on neurocognitive outcomes in childhood leukemia survivors.

In the context of AALL06N1, we previously found that children with public insurance, a crude indicator of lower socioeconomic status, were at significantly increased risk of neurotoxicity (mean estimated IQ US Public Insurance = 93.4 vs. US Private or Military Insurance = 106.2; p < 0.001). These data suggest an important outcome disparity, but provide no target for intervention. As such, identifying targetable predictors and mechanistic pathways driving poverty-associated neurocognitive toxicity are essential. We hypothesize that children living in poverty at the time of their leukemia diagnosis are at risk of experiencing greater declines in neurocognitive function from baseline than their non-poor counterparts.

A majority of children with ALL treated on modern COG trials will be long-term survivors, and late effects of therapy including neurocognition are thus highly salient to this population. The premise of this proposed research is that those individuals at greatest risk of treatment-induced neurocognitive decline can be identified within the early months of leukemia therapy, when a proactive intervention might prevent permanent neurocognitive declines.

Rationale for selected approach and trial design

Poverty as a risk factor for treatment-related neurocognitive decline is a rational target for investigation. Epidemiologic data that demonstrate poor U.S. children without cancer experience inferior neurocognitive outcomes as compared to their non-poor counterparts.^{50,103} In typical developing children, both socioeconomic disadvantage and subjective social status impact executive function and school readiness.¹⁰⁴⁻¹⁰⁶ Children from impoverished backgrounds are also more likely to experience developmental delay, exhibit behavioral problems, and exhibit worse performance on cognitive and achievement tests than those from more socioeconomically advantaged backgrounds.¹⁰⁷ Strikingly, both early childhood poverty and later childhood changes in family poverty are independently associated with executive function.¹⁰⁸ These data suggest that young children with ALL who come from impoverished households may face dual risks for treatment-related neurocognitive decline in the setting of robust data demonstrating that poor pediatric cancer families experience greater financial hardship during therapy.¹⁰⁹

Poverty is linked to differences in brain structure and function.^{110,111} The relationship between poverty and neurocognitive development is multifaceted even in general pediatrics, and likely more complex among individuals with chronic health conditions.¹¹² There is evidence from both animal models and human research indicating that individuals living with low social status show differences in brain structure and function as a result of impairments in the development of stress regulatory systems.^{50,108,113} Investigators seeking to understand the biological underpinnings of this and other poverty-related health disparities have identified the

concepts of “allostatic load” and “toxic stress” referring to dysregulation of the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenomedullary system that results in chronic elevation of stress hormones, inflammatory cytokines and parasympathetic responses.^{114,115} Data suggest that plasticity of the early childhood brain makes it particularly sensitive to “toxic stress”, which may disrupt neuronal architecture and neuronal pruning, ultimately resulting in impaired neurocognitive function.¹¹⁴ Application of the toxic stress model to help elucidate physiological responses to stress that may underlie inferior health outcomes represents a key next step in advancing the science of outcome disparities.¹¹⁵

Figure 17.1 shows a conceptual model of how poverty may impact neurocognitive function.⁵⁰ Numerous domains of poverty may increase a child’s exposure to “toxic stress,” including material deprivation (e.g., limited food leading to undernutrition), behavioral stressors (e.g., single parent status leading to decreased parenting capacity in the home and decreased cognitive stimulation), and environmental exposures (e.g., increased exposure to lead or increased exposure to community violence triggering stress). A child’s neurocognitive outcomes may be associated with one or more of these domains of socioeconomic disadvantage^{112,116}—potentially mediated by underlying genetic susceptibility of the child.¹¹⁴ As childhood cancer *incidence* is not consistently higher in any one income group,¹¹⁷ the epidemiology of child poverty in the United States means that approximately 20% of children with newly diagnosed ALL will come from an impoverished home. We hypothesize that children living in disadvantage prior to diagnosis are more vulnerable to the additional neurotoxicities of chemotherapy treatment. This pre-existing vulnerability will put them at greater risk of treatment-related declines in neurocognitive function, above and beyond potential pre-diagnostic neurocognitive impairments.

We propose to investigate this hypothesis using a concrete measure of poverty, household material hardship (HMH), a dimension of poverty which both predicts child health outcomes and can be remedied by intervention.^{53-55,118,119} HMH is defined as unmet basic needs including food, heat, housing or transportation, and prior work by our group has identified HMH in 20% of pediatric cancer families at diagnosis and 30% after the initial six months of chemotherapy.⁵⁷ HMH is as widely prevalent as income poverty such that 20% of U.S. households with children are defined as food insecure, meaning that “their access to adequate food is limited by a lack of money and other resources.”¹²⁰ Critically, while children living in families with HMH experience higher rates of poor nutrition, injury, infectious disease and hospitalization,^{54,121,122} linking families with targeted “safety-net” programs ameliorates these health outcomes.^{53,55,118} More specifically, interventions targeting HMH from the clinical setting are feasible and effective in general pediatrics and internal medicine.¹¹⁹ As such, HMH represents a particularly appealing poverty measure for investigation because interventions already exist to modify HMH-associated outcomes.

Prior work by our group demonstrates that HMH is prevalent in the pediatric oncology population and that survey-based evaluation of HMH is feasible and acceptable to pediatric cancer families. In a longitudinal cohort study of 99 newly diagnosed pediatric oncology families (response rate 87%, retention rate 93%) we found that 20% of families report at least one pre-existing domain of HMH at the time of their child’s cancer diagnosis, and 30% do so by 6 months into chemotherapy despite existing psychosocial supports.⁵⁷ A subsequent retrospective medical record review of 413

children treated for newly diagnosed cancer at a large referral center found that 38% of families endorsed difficulty paying for food, heat, lights, rent or mortgage using a clinically administered survey at diagnosis.¹²³ In this cohort, 95% of families completed self-report questions assessing HMH and 94% reported household income in a face-to-face social work encounter supporting the feasibility and acceptability of evaluating such patient-reported measures. HMH investigation also appears feasible based on preliminary data from the ongoing multi-center Dana-Farber Cancer Institute ALL Consortium front-line trial for pediatric ALL (DFCI 16-001). Families consent to an embedded ancillary HMH study as an opt-in part of upfront consent to trial enrollment, and complete face-to-face surveys with a research assistant at 4-time points over the 2-years of therapy beginning in Induction. To date, 104 of 122 eligible families have enrolled in the HMH study (consent to participation 85%), and three families have withdrawn. Data review of HMH-enrolled families demonstrate 100% complete HMH data and 95% complete income data from baseline survey administration with a preliminary parent-reported HMH frequency of approximately 30% at time of trial enrollment.

Figure 17.1 Neurodevelopmental framework of the impact of SES on cognition

**How SES and chemotherapy impact brain development:
Impact of Poverty on Brain Development**

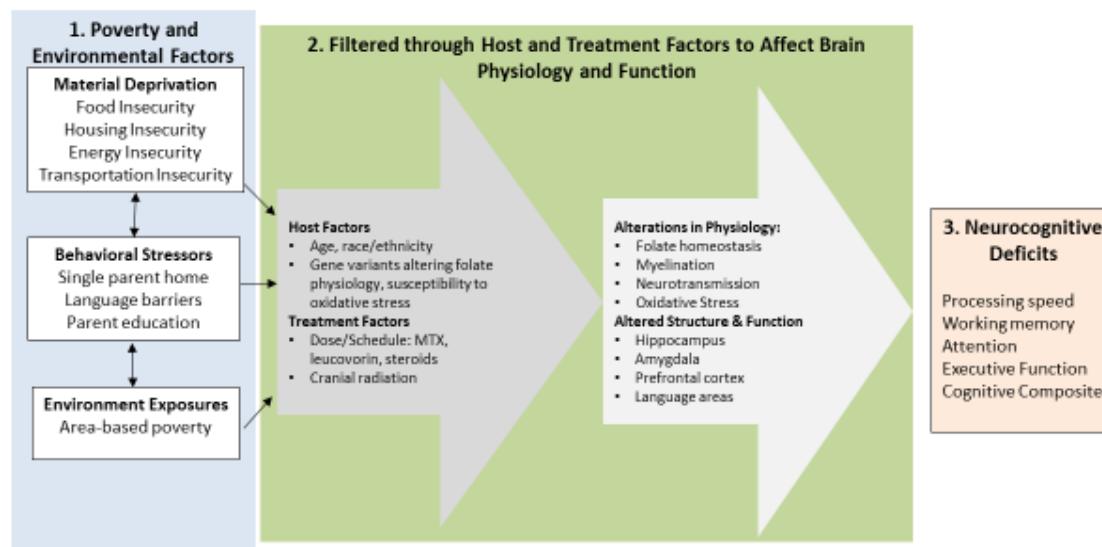


Figure 1. Conceptual Model of SES and Neurocognitive outcomes. Adapted from Johnson SB et al. *Pediatrics* 2016.

We have developed a brief HMH survey, which captures both our primary poverty measure of interest (HMH) as well as covariates detailed in the above model to allow for robust analysis of the relationship between HMH and neurocognitive decline in the context of pediatric ALL therapy. It is worth noting that family poverty measures have not historically been collected on pediatric ALL trials across the United States. Consequently, it is not known which measures of poverty (household income, HMH, geocoded area-level poverty) are most strongly associated with outcome, nor at what time-point in therapy a measure of poverty is pertinent to outcome.

Data from COG AALL06N1 identify health insurance as an independent predictor of neurocognitive outcome providing preliminary evidence of a relationship between poverty and neurocognitive outcomes in ALL survivors.¹²⁴ Modifiable measures of poverty, such as HMH, have not been investigated. We have previously demonstrated the feasibility of longitudinal neurocognitive assessment with minimal participant and institutional burden using Cogstate Cognitive testing. Embedded in AALL1131 was a DCP-supported longitudinal evaluation of neurocognition for patients aged 6-12 at diagnosis using Cogstate, a brief computerized battery. Testing is performed at five time-points for females and six for males. One hundred eighty participating COG institutions enrolled 479 patients on the neurocognitive study, and data collection rates at the six time-points range from 78 to 94%, with 85% of the consenting patients remaining on trial. Technical problems with the program have occurred in fewer than 2% of cases, and fewer than 2% of patients have been too ill to complete testing. Attrition from the parent ALL trial for all reasons (e.g., patient- or physician-initiated withdrawal or relapse) is 17%. Early results indicate that an increasing number of participants have abnormal scores on the computerized testing over the first two years after diagnosis. By the end of Maintenance 6, approximately 27% of children have scores < 1.5 SD below the mean on at least two Cogstate tasks, and this figure is more pronounced for the youngest children, for whom the percentage of abnormal scores is 37%. Consistent with data from survivor cohorts, the two domains with the highest rates of impairment are sustained attention (30%) and processing speed (29%). These data demonstrate that this monitoring battery is both (1) feasible and (2) able to detect changes in cognitive functioning as they evolve during therapy for ALL.

The current study will identify children at greatest risk of treatment-related neurocognitive decline by using: (1) Validated, reliable, measures of cognitive function (Cogstate and BRIEF2/BRIEF-P); (2) Robust baseline poverty evaluation including measures known to be associated with neurocognitive function in general pediatrics.

17.1.5 Background for the Caregiver Burden and Symptom Assessment Aims

Patient-reported outcomes (PROs) are necessary for understanding and improving cancer treatment-experiences, in particular for subjective outcomes such as symptom- or caregiver-burden.¹²⁵⁻¹²⁸ Systemic collection of PROs in pediatric oncology clinical trials can facilitate clinical care and anticipatory guidance by providing insight and experience from the perspective of patients and families that is not well captured through typical data collection on clinical trials. Caregiver strain is a key determinant of parental health-related quality of life (HRQoL).¹²⁹ Caregiver demands have not been assessed on a large-scale, prompting this study. Since caregiver and child well-being are reciprocal, understanding and alleviating caregiver burdens may translate into improved child health outcomes and quality of life.

This trial will evaluate the efficacy of blinatumomab delivered primarily in the outpatient setting as a 28-day continuous infusion. Though these infusions have been accomplished on a small scale, in the relapse setting, this will be the first large-scale use of this product in a newly diagnosed population. Accordingly, it is critical to assess the impact this prolonged infusion will have on caregiver strain to inform anticipatory guidance and intervention development if blinatumomab proves efficacious. Specifically, caregivers will be responsible for the care of their child with an accessed

central line and a drug infusion device for 28 days. They will also be responsible for monitoring and responding to both common therapy-related toxicities and the potentially unique toxicities associated with blinatumomab including cytokine release syndrome and drug-related neurotoxicity.

Studies that have included PROs to assess quality of life or symptom burden among children with ALL are limited to date.¹³⁰⁻¹³² Quality of life (QoL) was prospectively studied in two Children's Oncology Group studies, AALL0331 and AALL0932, both of which demonstrated considerable, and, for some children, persistent impairments in patient health-related QoL.¹³⁰⁻¹³² Little is known about the effects of blinatumomab on QoL and patient-reported symptoms. In a study of adult patients with relapsed or refractory ALL, patients randomized to receive blinatumomab compared favorably across all HRQoL dimensions evaluated compared to those receiving standard of care therapy.¹³³ Preliminary toxicity data from the ongoing COG study of blinatumomab after relapse (AALL1331) indicates that blinatumomab toxicity compares favorably with intensive conventional chemotherapy; however, patient/proxy-reported symptom burden and corresponding QoL are not being evaluated on that trial.

Socioeconomic status may be a critical covariate in the evaluation of caregiver burden, especially in the context of prolonged home medication administration. Approximately 20% of newly diagnosed pediatric ALL patients will come from an impoverished home. We propose to investigate the hypothesis that poverty status is associated with caregiver burden using a concrete measure of poverty, household material hardship (HMH), which is both associated with inferior child health outcomes and remediable with intervention.^{53-55,118,134} HMH is defined as unmet basic needs including food, utilities (heat, electricity), housing or transportation. Prior work has identified HMH in 20% of pediatric cancer families at diagnosis and 30% after the initial six months of chemotherapy.¹³⁵ Since HMH is a targetable domain of poverty, if families with HMH experience disproportionate burden, interventions to screen for and intervene upon HMH may ameliorate inequities in demands of therapy.

AALL1731 provides a unique opportunity to prospectively investigate the impact of blinatumomab on caregiver burden and on pediatric patient symptom experience, as well as to gain additional information about the burdens of conventional chemotherapy. Importantly, assessing family financial situation at baseline and serially during the trial will allow for an assessment as to how resources impact the burden associated with therapy and conversely, the impact that therapy has on resources. Understanding the unique burdens associated with a regimen containing blinatumomab may inform future interventions to mitigate caregiver demands and reduce symptom burden, thereby hopefully improving the quality of life for patients with ALL and their families.

Experience from recent COG studies suggest that collecting patient-reported outcomes is feasible. For AAML1031, 73-83% of families enrolled on the optional quality of life study completed assessments at each of the first 5 of 8 planned timepoints.⁵⁹ Similarly, quality of life data captured in the standard risk ALL study, AALL0932 demonstrated 88% completion at 2 months into therapy and 75% at 18 months into therapy.¹³²

17.1.6 Study Design

Eligibility for neurocognitive and HMH primary aim

Inclusion criteria:

1. Enrolled on AALL1731 as NCI SR B-ALL
2. Ages 1-<10 years at the time of enrollment
3. English, French or Spanish-speaking (languages in which Cogstate is available)
4. U.S. or Canadian site

Note: Children younger than age 4 years at diagnosis may enroll on the HMH neurocognitive study (including HMH data collection), but will not be evaluated with the Cogstate battery until the next assessment following their 4th birthday.

Exclusion criteria:

1. No known pre-existing neurodevelopmental disability (e.g., Down syndrome, Fragile X, William's syndrome, cognitive impairment) that precludes computer use
2. No known significant sensory impairment (e.g., visual) that precludes computer use

Eligibility for caregiver burden and symptoms assessment aims

Children enrolled on the neurocognitive/HMH study who are identified as having SR-Average and SR High disease post Induction will be eligible for the secondary aims related to caregiver burden and symptom assesment. An additional inclusion criteria is that caregivers must be able to read English or Spanish. Eligibility will be determined at the time of post induction risk group assignment and consent included in the post induction consent.

Rationale for eligibility criteria:

This study utilizes the Cogstate measure of neurocognitive function which is validated down to age 4. We will collect HMH data on enrollees ages 1 - <4 years at time of AALL1731 enrollment to maximize our opportunity for systematic collection of poverty data which will be used for both the primary (HMH and neurocognitive function) and secondary (caregiver burden) aims. All of these children will reach age 4 by the final time-point of neurocognitive testing. Given that younger age is a known risk factor for both treatment-related impact on neurocognitive function and socioeconomic-impact on neurocognitive function, including the youngest children in data collection to the best of our ability is of significant import. Neurocognitive testing using Cogstate and BRIEF2/BRIEF-P will be performed beginning at age 4 (whether at time of AALL1731 enrollment or during therapy). Testing of children is performed on a computer; thus neurodevelopmental or visual limitations, which preclude computer use, would make participation infeasible. Similarly, Cogstate is available in English, Spanish and French only.

Consent:

Patients who meet the above eligibility requirements will be given the option to participate in this study as an opt-in part of the Induction consent to AALL1731. Families will be provided with an opportunity for opt-in consent to (1) longitudinal HMH survey evaluation, and (2) longitudinal neurocognitive testing as part of upfront

Induction consent to AALL1731. This approach will allow for collection of baseline data during Induction therapy, as close to time of diagnosis as possible. This procedure has been successfully used in DFCI 16-001, with an 85% participation rate to both an opt-in HMH survey study and opt-in Neurocognitive Function study. This procedure has been used successfully in AALL1131, resulting in a 70% participation rate in neurocognitive testing for eligible patients.

The subset of patients that at end induction meet the criteria for SR-Average and SR-High disease and who will be offered participation in the blinatumomab randomization will also be offered participation in the secondary caregiver burden and symptoms assessment aims. An additional inclusion criteria is that caregivers must be able to read English or Spanish. Consent for participation in the caregiver burden secondary aims will occur at the time of the post-Induction therapy consent.

Required Observations for neurocognitive and HMH aim:

The required observations for participants in this ancillary poverty and neurocognitive outcome study are included in the AALL1731 delivery maps. Longitudinal assessment of neurocognitive function and HMH will be collected at a total of 4 time-points as detailed below in Table 17.1.1.

Table 17.1.1 Required Observations (HMH and neurocognitive testing)

| Time-point | Measures | Treatment Phase |
|-----------------|--|--|
| 1 (baseline) | <ul style="list-style-type: none">• HMH (baseline)• Cogstate*• BRIEF2/BRIEF-P* | Induction <ul style="list-style-type: none">• Must be administered prior to Induction Day 29 LP |
| 2 | <ul style="list-style-type: none">• HMH (follow-up)• Cogstate*• BRIEF2/BRIEF-P * | Beginning Maintenance <ul style="list-style-type: none">• Administer Day 1 of Maintenance Cycle 1• Must be administered \pm 4 weeks from Maintenance Cycle 2 |
| 3 | <ul style="list-style-type: none">• HMH (follow-up)• Cogstate*• BRIEF2/BRIEF-P * | End of Therapy <ul style="list-style-type: none">• Administer at 1st off-therapy visit or at start of final planned cycle of Maintenance chemotherapy• Must be administered \pm 8 weeks from end of therapy |
| 4 | <ul style="list-style-type: none">• HMH (follow-up)• Cogstate*• BRIEF2/BRIEF-P * | 1-Year Off-Therapy <ul style="list-style-type: none">• Administer at 1-year off-therapy visit• Must be administered \pm 4 months of 1 year off therapy |

*Children ages 4 years and older only.

Required Observations for caregiver burden and child symptoms aims: Longitudinal assessment caregiver burden and child symptoms will be conducted at a total of 4 time points during prescribed therapy as detailed in the table below:

Table 17.1.2 Required observations (for patients participating in the caregiver burden and symptom secondary aims)

| Time-point | Measures | Treatment Phase |
|-----------------|---|---|
| 1 (baseline) | <ul style="list-style-type: none"> • Care of My Child with Cancer • Caregiver Workplace Limitations • Memorial Symptom Assessment Scale* | SR-Avg and SR-High: Day 1 of Consolidation (+14 days) |
| 2 | <ul style="list-style-type: none"> • Care of My Child with Cancer • Caregiver Workplace Limitations • Memorial Symptom Assessment Scale* | SR-Avg Arm A: Day 21 Interim Maintenance I (± 14 days) SR-High Arm C: Day 29 Interim Maintenance I (± 14 days) SR-Avg Arm B and SR-High Arm D: Day 15 Blinatumomab block 1 (± 14 days) |
| 3 | <ul style="list-style-type: none"> • Care of My Child with Cancer • Caregiver Workplace Limitations • Memorial Symptom Assessment Scale* | SR-Avg Arm A and SR-High Arm C: Day 29 Delayed Intensification (± 14 days) SR-Avg Arm B and SR-High Arm D: Day 15 Blinatumomab Block 2 (± 14 days) |
| 4 | <ul style="list-style-type: none"> • Care of My Child with Cancer • Caregiver Workplace Limitations • Memorial Symptom Assessment Scale* | SR-Avg and SR-High: Day 29 Maintenance Cycle 1 (± 28 days) |

*For patients < 2 years of age at the time point for assessment no MSAS will be completed. For those ages ≥ 2 and < 7 at the time of assessment parent/caregivers will complete proxy symptom assessments using the MSAS proxy measure modified from the MSAS 10-18. For patients ages ≥ 7 years of age at the time of assessment the patients will complete the MSAS 7-12 and the parent/caregivers will complete the proxy measure.

17.1.7 Rationale for assessment timing

Day 1 of Consolidation will serve as a baseline and assess demands and symptoms associated with Induction therapy common to all patients. The second and third time points will occur while patients on the SR-Average B-ALL and SR-High B-ALL experimental arms (Arms B and D) are receiving blinatumomab. Patients on the control arms will be receiving a standard block of chemotherapy. These time points will provide the opportunity to compare caregiver burden/limitations and patient symptoms during either a block of standard chemotherapy or a block of blinatumomab therapy. It is acknowledged that blinatumomab is given in addition to standard post-Induction chemotherapy, replacing instead 2 months of maintenance. The fourth time point will again serve as a time point when patients

on both the control arms and the experimental arms will be receiving identical chemotherapy during Interim Maintenance II, and will serve as the primary comparison for long-term caregiver burden and work limitations between the two treatment arms.

17.1.8 Data Collection

Data Capture: Neurocognition and HMH

All study assessments will correspond to scheduled clinic visits or inpatient hospitalizations when at all possible. Both HMH survey administration and neurocognitive testing may be performed at the same visit if convenient (not required). It is recommended, but not required, that Cogstate testing be avoided when a child is NPO for procedures and within 24 hours of anesthesia or conscious sedation. Each assessment will be administered by a clinical research assistant (CRA) (or nurse, psychologist or other pediatric oncology professional who completes an online training in the administration of Cogstate). Both HMH surveys (parent) and Cogstate testing (child) will be administered in-person by the designated site personnel; BRIEF2/BRIEF-P forms will be provided to the parent for completion.

- **HMH:** Survey is administered face-to-face (read-aloud) with the parent/guardian to overcome barriers of literacy. The baseline HMH (T1) survey takes approximately 15-20 minutes, and the follow-up HMH (T2-T4) takes approximately 10 minutes. There is a U.S. version (Baseline and Follow-up) and a Canadian version (baseline and follow-up). Surveys may be administered with an interpreter and are available in English, Spanish (U.S. version) and English and French (Canadian version).
- **Neurocognitive testing:** Children will complete a proctored 25-30 minute computerized Cogstate assessment; concurrently, the child's parent/guardian will complete a brief survey of executive function (BRIEF2/BRIEF-P), which takes 10-15 minutes. This measure is currently available in English and Spanish only. Sites will be notified when a French version is available (enrolled French-speaking families will complete all other study measures).

HMH surveys will be administered to the family by local site personnel. Completed surveys will be reviewed by the CRA for completeness, and surveys scanned as PDFs and transferred to the central site (DFCI) via secure email (HMHneurocog_AALL1731@DFCI.HARVARD.EDU) for central data entry into the RAVE CRF. Families who do not complete a survey at a particular time-point for any reason will continue to participate in remaining survey time-points. Patients who discontinue therapy on AALL1731 will not receive further survey assessments after they come off protocol therapy.

BRIEF2/BRIEF-P questionnaires will be self-completed by caregivers via a paper form. Completed questionnaires will be reviewed by the CRA for completeness, and questionnaires scanned as PDFs and transferred to the central site (DFCI) via secure email (HMHneurocog_AALL1731@DFCI.HARVARD.EDU) for central data entry into the RAVE CRF.

Cogstate is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 4-90 years. The software

can be installed on most computers or tablet systems and can be proctored by designated site personnel (e.g. CRA) after completing minimal training. Data are automatically scored and stored.

Data Capture: caregiver burden and symptom assessment aim

For all participants who are eligible and provide consent for the caregiver burden and symptom assessment, the appropriate questionnaires based on the age of the patient will be downloaded from the COG protocol web site by the institutional CRA. The assessments will be provided to the family for completion and collected by the CRA at the appropriate time points described above. Completed forms will be reviewed by the CRA for completeness, and surveys scanned as PDFs and transferred to the central site (DFCI) via secure email (HMHneurocog_AALL1731@DFCI.HARVARD.EDU) for central data entry into the RAVE CRF. SR-Average risk patients who are found to have HTS EOI MRD which is undetectable will not complete questionnaires beyond time point 1 as they will not be eligible for randomization to blinatumomab. Families who do not submit a questionnaire (parental or child form) at a particular time point for any reason will still continue to participate in the remaining questionnaire time points. Patients who discontinue therapy on AALL1731 will not receive assessments at time points after they go off protocol therapy.

The data on household material hardship will be captured as part of the neurocognitive function and poverty secondary aim.

17.1.9 Study Measures for neurocognitive and HMH aim

1. Poverty Predictors

Household Material Hardship (HMH): Baseline HMH (T1, Induction) will be utilized as the primary predictor in all analyses. In accordance with previous research, families will be defined as having HMH if they report at least one of four concrete needs: (1) *Food insecurity*: Validated 2-item food insecurity screen.¹³⁶ (2) *Housing Insecurity*: Standardized 5-item screen.¹³⁷ (3) *Energy Insecurity*: Standardized 4-item screen.¹³⁷ (4) *Transportation Insecurity*: Standardized 2-item screen. Families are considered to have insecurity in a domain if they screen positive to at least one item. HMH as a binary present/absent predictor variable will be utilized in all analyses. An exploratory analysis scoring HMH as a categorical variable (defined as the number of unmet concrete resource needs, range 0-4) will be performed *a priori*.¹³⁷

HMH survey instrument: The HMH surveys constitute abbreviated versions of the 101-item Oncology EIS survey, which has been utilized in two prior studies with high willingness to participate and low participant burden.^{57,135} The baseline HMH survey (administered in Induction, T1 only) takes 15-20 minutes to complete and includes measures across the following domains: 1) Demographics¹³⁸⁻¹⁴⁰; 2) HMH^{136,137}; 3) Income and Financial Strain; 4) Social supports¹⁴¹; 5) Resilience;¹⁴² 6) Household Chaos;¹⁴³ 7) Parent anxiety¹⁴⁴ and 8) Everyday discrimination.¹⁴⁵ The Longitudinal HMH follow-up survey (administered at T2, T3 and T4) takes 10-minutes to complete and includes

measures across the following domains: 1) Brief Demographics¹³⁸⁻¹⁴⁰; 2) HMH;^{136,137} 3) Income and Financial Strain; and 4) Parent anxiety.¹⁴⁴

Collected baseline social determinant covariates will include the following: Parent-reported race, ethnicity and primary language collected per U.S. Health and Human Services guidelines,¹⁴⁰ parental health literacy utilizing a validated 1-item screen,¹³⁹ parental educational attainment, parental age, household composition, and child insurance coverage. In addition, we will collect multi-dimensional poverty data including family income as a percent of Federal Poverty Level (FPL) and area-based socioeconomic measures (ABSM). FPL will be calculated using reported annual household income and household size according to the U.S. Health and Human Services Poverty Guidelines for the year the survey is administered.^{146,147} Families are considered to be low-income at an annual household income of <200% FPL.¹⁴⁸ For exploratory analyses, household income as percent FPL will be stratified *a priori* into low-income (<200% FPL) and non-low-income ($\geq 200\%$ FPL) in concert with published definitions of low-income families in the United States.¹⁴⁸ ABSM is assessed using geocoded residential address and zip code (at T1) linked to U.S. Census Bureau data from the American Community Survey. Our primary ABSM will be zip-code linked percent of families in poverty, which is a Census defined binary variable of “high-poverty” ($\geq 20\%$ of residents in a zip code living at or below the poverty threshold) and “low-poverty” zip code (<20% of residents below the poverty threshold) in concert with prior publications.¹⁴⁹ We will explore residential address-linked ABSM as defined by Krieger et al.¹⁴⁹

Clinical and Treatment Data: COG data elements to be a priori included in analysis will include the following: date of diagnosis, CNS status, end of Induction MRD, final risk group, treatment arm and randomization, date of therapy completion, EFS, and OS.

2. Neurocognitive Outcomes

Our primary outcome measurement will be difference in change in neurocognitive function as evaluated by attention and processing speed, and parent-reported executive function from T1 (Induction) to T3 (end-of-therapy). Neurocognitive outcomes will be measured using Cogstate (attention and processing speed), a performance based cognitive battery currently included in the front-line COG high risk trial (AALL1131) and the BRIEF2, a parent-report measure of executive function. Change in neurocognitive function for our primary aim will be evaluated from baseline (T1) to end-of-therapy (T3, end of Maintenance). Participants will complete neurocognitive testing as detailed at the 4 time-points previously described. The required observations will require 30 minutes or fewer, depending on the age of the patient (i.e., younger patients require less time).

Cogstate Computerized Assessment (child-completed): Cogstate is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 4-90 years. All tasks were developed specifically for use in clinical trials as computerized adaptations of traditional neuropsychological measures. For this study, we will use 5 tasks in the

following domains: (1) visual learning; (2) processing speed; (3) visual attention; (4) working memory, and (5) executive function. These tasks were selected because they measure the neurocognitive functions identified in previous research as being most susceptible to decline in the pediatric ALL population. Of note, the youngest children in our study (i.e., ages 4-5) will only complete the processing speed and sustained attention tasks, but will complete the other tasks in the battery when they turn 6 years of age or greater. The entire battery is estimated to take approximately 15 to 25 minutes.

Behavior Rating Inventory of Executive Function – Second Edition (BRIEF2) (parent-completed): The BRIEF2 is a widely used assessment of executive functioning for children aged 5-18 years; a preschool version (BRIEF-P) is available for children aged 3-6, though will only be administered to children age 4 (those age 5 and older will complete BRIEF-2). The parent-report version consists of 63 items which map onto 2 broad areas: behavioral regulation and metacognition, as well as 2 validity scales. The Behavioral Regulation domain is further divided into 3 clinical subscales: Inhibit, Shift, and Emotional Control, whereas the Cognition domain is divided into 5 clinical subscales: Initiate (i.e., beginning a task), Working Memory (i.e., holding information), Plan/Organize (i.e., anticipating future events and developing appropriate strategies), Organization of Materials (i.e., maintaining order in memory), and Monitor. Parents are asked to consider the frequency with which each item has been a problem over the last 6 months, responding on a 3-point Likert scale consisting of “never,” “sometimes,” and “often.” Items were developed to be ecologically-valid behavioral correlates to presumed neurocognitive difficulties with executive functioning; thus, this measure was selected to provide parent reported outcomes of problems related to attention, memory, and executive function that occur in everyday life.

17.1.10 Study Measures for caregiver burden and symptom assessment aims

Care of My Child with Cancer [150,151](#)

This is a validated measure that assesses the amount of time required and the difficulty or effort associated with providing care to a child with cancer. The instrument uses a 5-point Likert-type scale to assess amount of time spent on 28 caregiving tasks (None to >5 hours/week) and rate the amount of effort/difficulty (none to a great deal). Instructions have been modified from the original measure to ask the caregiver to think of the most challenging week in the past month when answering.^{[187](#)} The majority of items form 2 subscales: Emotional Caregiving (13 items) and Physical Caregiving (7 items). Total and subscale scores are calculated. Individual item scores are the square root of the time score multiplied by the effort score. The total score is the sum of individual items and can range from 28 to 140. Scores can range from 13 to 140 for the Emotional Caregiving subscale and from 7 to 35 for the Physical Caregiving subscale. Higher scores indicate higher caregiver demands. Care of My Child with Cancer has evidenced high internal consistency with alpha coefficients > 0.9 for the total score, 0.9 for the Emotional Caregiving subscale and 0.79 for the Physical Caregiving subscale. It has also shown good construct validity.

Caregiver Work Limitations Questionnaire [152](#)

This is a 23-item validated instrument, which assesses the impact of caregiving for an ill family member on the caregiver's work performance and productivity over a 4-week recall period. There are 4 subscales for the questionnaire: time management, physical tasks, mental and interpersonal tasks, and output tasks. In addition, there is an algorithm to convert subscale scores into an at-work productivity loss summary score. Scores range from 0 to 100 (limited none of the time through limited all of the time, respectively). Scale reliability was noted with alpha coefficients >0.9 for all subscales.

Memorial Symptoms Assessment Scale (MSAS) [153-155](#)

The MSAS was originally designed for adults and has been extensively validated demonstrating high internal consistency ($\alpha>0.8$). It measures frequency, severity, and distress caused by a number of physical and psychological symptoms. There are two child versions, one for ages 10-18 (MSAS 10-18: 30 items), and another for 7-12 years (MSAS 7-12: 8 items), which have also undergone validation, showing similar internal consistency. A modified version of the MSAS 10-18 serves as a parent proxy measure for children of all ages, including those as young as 2 years old (completed by parents on the child's behalf). The instrument item response options use Likert scales to assess physical symptoms (pain, fatigue, drowsiness, nausea, anorexia, cough, diarrhea, vomiting, itching, skin issues, constipation, dysphagia, dry mouth, numbness, sweating, dyspnea, and dysuria), and psychological symptoms (irritability, sleep disturbance, nervousness, sadness, worrying, difficulty concentrating, and image issues). Three subscales are calculated: 1) physical symptoms, 2) psychological symptoms and 3) global symptom distress as well as a total score. Total and sub-scores are calculated as the average of relevant symptoms, with higher scores representing higher symptom burden.

Table 17.1.3

| Patient age | Measures | | |
|--|-------------------------|-------------------------------------|--|
| | years | Care of My Child with Cancer | Caregiver Workplace Limitations |
| >1 and <2 | Parent only | Parent only | N/A |
| ≥2 and <7 | Parent only | Parent only | Parent only |
| ≥7 | Parent only | Parent only | Parent and patient |
| Estimated time for completion | 28 items 5-7 minutes | 29 items 5-7 minutes | 8 items-patient 30 items-parent 5-10 minutes |
| Total time for completion at each time point: 20-25 minutes | | | |

17.1.11 Accrual and Sample Size Justification

Our target consented accrual to achieve the necessary evaluable samples for both the primary (HMH/neurocognitive outcome) and secondary (Caregiver Burden) aims is N=1030 accounting for study attrition. Target accrual is feasible in the context of AALL1731 based on the following trial details. On AALL1731, the expected number of SR patients per year without DS who will reach EOI is 1062 (5310 total over 5 years). Of these, we estimate approximately 50% will be eligible

for the primary aim based on age (>4 years), language, and lack of pre-existing neurocognitive deficits, leaving N=531 eligible annually for the poverty neurocognitive aim. We anticipate that 70% of these eligible patients will consent to participate (N=372 annually), and accounting for 15% attrition, expect N=316 annually to be evaluable for the primary aim. As detailed below, N=720 evaluable are needed for the HMH/neurocognitive aim and thus we require N=847 eligible and consented to this aim and will fully accrue in about 2.3 years.

The Caregiver Burden secondary aim requires that subjects be randomization eligible. Of the N=847 patients consented for the HMH/neurocognitive aim, we estimate that N=360 will be randomization eligible (accounting for SR-Favorable, EOI HTS MRD undetectable, and poor EOC MRDs for SR-High). After accounting for an estimated 20% attrition, this leaves N=288 (144/group) that would be available and evaluable for this aim. The aim requires N=350 (175/group), and thus an additional N=62 evaluable patients are required. This additional enrollment will come from those that are ages 1 to less than 4 at diagnosis, who will be consented on the HMH/neurocognitive study, but not be eligible for analysis due to their age. In order to obtain N=62 evaluable, we will consent a total of N=183 1 to 4 year olds. This gives the required sample size after accounting for randomization eligibility and an attrition rate of 20%. Since the additional number required for the secondary aim is small and the enrollment for the 1-4 year olds is concurrent, the accrual is only predicted to take 0.6 years at full pace study accrual, and will not extend the accrual of HMH/neurocognitive study aim at all. When N=183 eligible 1-4 year olds are consented, this portion of the study accrual will end.

Children with outcome measures relevant to the primary HMH/neurocognitive aim (e.g., age \geq 4 years with T1 neurocognitive measures and HMH measures) are included in the following target accrual and power calculation. With the expected proportion of poor children in this cohort of 30% whose change in neurocognitive function will be compared to the 70% proportion of non-poor children, we require an evaluable total sample size of N=720 (an estimated N=216 poor and N=504 non-poor) to analyze HMH as a factor predicting change for the specified clinically relevant difference in mean change of 2.5 or higher for the outcomes (Cogstate and BRIEF2) as detailed below in the power calculation.

17.1.12 Statistical Analysis Plan for neurocognitive and HMH aim

We will utilize linear regression to analyze differences in expected pre-treatment to post-treatment change scores. The expected standard deviation for the standardized outcome measures is 10 at both the pre-treatment and post-treatment time points. Pre and Post treatment scores are expected to be correlated at levels of at least $\rho=0.4$. At $\rho=0.4$, the expected sd for individual change scores would be 10.95 (and would be less for higher correlation values). HMH status is included as a binary present/absent primary predictor variable in all analyses. At a two-sided 0.05 significance level and estimating a pre-treatment and post-treatment correlation >0.4 , this will provide the desired 80% power to detect a clinically significant difference in mean difference of 2 or higher in Cogstate and BRIEF2 changes between the HMH status groups. We will consider the following as potential confounders in multivariable analyses: Final ALL risk group, CNS status at

diagnosis, age at diagnosis, sex, randomization arm. We will additionally plan to *a priori* conduct exploratory analyses of other poverty measures (income, insurance status) and our primary outcome. Finally, given the expected significant overlap in minority status and poverty status, we will perform exploratory stratified analyses by racial/ethnic minority status and poverty variables.

17.1.13 Statistical analysis for caregiver burden and symptom assessment aims

Objective: To compare the demands and work limitations on caregivers of children receiving ALL chemotherapy versus chemotherapy with the addition of blinatumomab and the change in the demands and work limitations over time, as measured by the Care of My Child with Cancer questionnaire and the Caregiver Work Limitations questionnaire.

Outcomes of interest: (i) Mean Total score from the Care of My Child with Cancer questionnaire; (ii) At-Work Productivity Loss summary score from the Caregiver Work Limitations questionnaire.

Secondary outcomes: (i) Emotional Caregiving and Physical Caregiving Subscales for the Care of My Child with Cancer Questionnaire; (ii) Time Management, Physical Tasks, Mental and Interpersonal Tasks, and Output Tasks subscales from Caregiver Work Limitations questionnaire.

Time point for primary comparison: Time point 4 will be used to assess long-term caregiver burden and work limitations between the 2 treatment groups, using the baseline (Time point 1) as a covariate.

The trajectory and magnitude of caregiver burden and work limitations at each time point (including time points 2 and 3) will be examined to assess if there are short-term increases in caregiver burden and work limitations during blinatumomab courses compared with the chemotherapy only arm.

Analysis plan: The mean total score from the Care of My Child with Cancer questionnaire and At-Work Productivity Loss summary score from the Caregiver Work Limitations questionnaire at time point 4 will be compared between randomization groups using time point 1 as a covariate in an Analysis of Covariance (ANCOVA) analysis. Each of the two primary outcomes will be tested at the alpha=0.05 significance level and powered to have 80% power to detect a difference of 0.3 standard deviations of difference in the means between the groups.

1. To describe the impact of baseline household material hardship (HMH) on caregiver demands during post-Induction therapy in families with children randomized to chemotherapy versus chemotherapy with the addition of blinatumomab.
2. To compare changes in HMH from baseline to beginning of Maintenance therapy in families with children randomized to chemotherapy versus chemotherapy with the addition of blinatumomab.

Analysis Plan: An HMH score will be calculated based on the number of concrete domains (0-4 domains of HMH: food, housing, utilities, transportation) for which a family has insecurity. Families are considered to have insecurity in a domain if they

screen positive for at least one item in that domain. HMH domain counts will be further categorized into an HMH insecurity level with ‘No insecurity’ (domain count=0), ‘Some insecurity’ (domain count 1 to 2), and ‘severe insecurity’ (domain count 3 to 4), similar to categories used in prior research.¹³⁷

To describe the impact of baseline HMH on caregiver demands, analysis of covariance regression will be used with baseline HMH and the interaction effects of baseline HMH and treatment assignment being used as predictors of caregiver demands at time point 3, controlling for baseline reported caregiving demand, patient age, caregiver marital status, and caregiver education. Time point 3 was selected for this objective as this time point is the last time point where patients enrolled on the different arms are receiving different therapy.

To compare changes in HMH from baseline to beginning of Maintenance therapy between randomized arms, the HMH score will be utilized to analyze the relationship between receipt of blinatumomab and change in HMH over time. For each family, the difference between the number of HMH domains in which a family screens positive at baseline versus start of Maintenance will be categorized as improved (change score <0), unchanged (change score=0), or worsened (change score >0). For each arm (blinatumomab versus not), the proportion of families with worsened HMH at the start of Maintenance will be estimated along with a 90% exact CI. Additionally, ordered logistic regression models will be used to estimate odds ratio associated with randomization grouping for comparing ‘worsened’ versus ‘unchanged’ or ‘improved’, and ‘worsened’ or ‘unchanged’ vs ‘improved’. If any zero or low count cells are present, categories will be combined and standard logistic regression will be performed.

- 1) To compare the prevalence of symptoms in children with ALL receiving chemotherapy versus chemotherapy with the addition of blinatumomab as measured by the Memorial Symptom Assessment Scale.
- 2) To compare change over the course of therapy of symptoms in children with ALL receiving chemotherapy versus chemotherapy with the addition of blinatumomab as measured by the Memorial Symptom Assessment Scale.

Analysis Plan: For each group (those receiving blinatumomab and those not receiving blinatumomab), total MSAS scores, total sub-domain scores, and individual symptom scores will be calculated separately. Median and range of the scores will be tabulated. Because patients in both groups will receive standard therapy (plus/minus blinatumomab), we will not compare symptom experiences between groups. Rather, the purpose of these descriptive analyses is to provide new data regarding the symptom experience of either regimen.

17.1.14 Contact

Please address questions to: HMHneurocog_AALL1731@dfci.harvard.edu.

17.2 Longitudinal Assessment of Neurocognitive, Functional, and Quality of Life Outcomes in Patients with Down Syndrome and Acute Lymphoblastic Leukemia – OPTIONAL (DS only)

17.2.1 Objective

To describe the impact of ALL and its therapy on neurocognitive, functional, and quality of life outcomes in patients with NCI SR and NCI HR DS B-ALL.

17.2.2 Background and Rationale

Contemporary therapy protocols for ALL aim to reduce treatment late effects while maintaining cure rates of greater than 90% for children from the general population (i.e., without DS) with standard risk disease.¹⁵⁶ Modifications to therapy have resulted in lowered risk for acute and long-term neurotoxicity with no adverse impact on survival.¹⁵⁶ However, survivors treated with contemporary frontline therapy (i.e., without cranial radiation) continue to demonstrate neurocognitive problems following therapy, most commonly in the areas of attention, processing speed, and executive function.^{51,157,158} These difficulties have clinically meaningful implications, including lower academic achievement, reduced rates of college graduation, and lower quality of life.^{159,160} As such, neurocognitive monitoring is recommended as standard of care for childhood cancer survivors treated with CNS-directed therapy.¹⁶¹ Findings from neurocognitive studies in survivors have helped researchers identify risk factors for poorer outcomes and informed cognitive intervention studies that demonstrate efficacy for ameliorating existing neurocognitive difficulties.¹⁶²

We know very little about the impact of cancer treatment on neurodevelopment in children with DS, as patients with preexisting neurodevelopmental conditions have been systematically excluded from neurocognitive studies in childhood cancer.^{17,48,157,158,163-169} There is an urgent and unmet need to understand the impact of ALL and its treatment on neurocognitive outcomes in DS-leukemia survivors.

To date, one study has examined neurocognitive outcomes in 26 survivors of DS-leukemia (AML and ALL), using performance-based measures that were developed and standardized for use in higher functioning populations.¹⁷⁰ The authors found that children with DS-ALL performed significantly worse than controls (age similar children with DS and no ALL) on measures of neurocognitive skills, academic achievement, and adaptive function, providing a foundational step towards understanding the impact of disease and treatment in a neurodevelopmentally vulnerable population. However, the utility and interpretation of the results were limited by a significant proportion of the DS-leukemia cohort being unable to complete the assessment measures, and by a high frequency of floor effects (i.e., individuals were assigned the lowest age-standardized score because the raw score fell outside of the normative range), with children under 10 years having the most difficulty. These findings highlight the substantial challenges of using traditional neurocognitive measures with lower functioning populations. The limited sensitivity of these performance based measures is especially apparent in studies that aim to quantify change over time.

Children with preexisting neurodevelopmental conditions, including DS, are significantly more likely to demonstrate new impairments following acquired brain injury when compared to children without preexisting conditions.^{171,172} Results from studies of long-

term survivors of childhood ALL suggest that genetic predispositions to neurocognitive impairment may interact with treatment exposure to increase risk.¹⁷³ These data suggest that preexisting neurodevelopmental and genetic conditions may significantly contribute to functional outcomes in long-term survivors. Extrapolating from these findings, we hypothesize that children with DS may be particularly vulnerable to treatment-related acute neurotoxicity, as well as longer-term changes in neurocognitive functioning.

In summary, children with DS have been systematically excluded from most neurocognitive studies in childhood cancer. Practically, this means that we know very little about neurocognitive outcomes in these survivors with preexisting neurodevelopmental vulnerability and increased risk for leukemia and treatment toxicity. Although intellectual disability is inherent to the cognitive phenotype in DS, individuals continue to acquire knowledge and learn new skills at a rate that is slower than their chronologically age-matched peers. Many adults with DS live independently, marry, and are gainfully employed. It is incumbent on clinicians and researchers to provide these patients and families with opportunities for improved outcomes similar to that which has been afforded to childhood leukemia survivors without DS. Outcome data from a large, uniformly treated, cooperative group study cohort are needed to guide modifications to therapy, inform supportive care guidelines (e.g., rehabilitative therapies and educational programming), and to provide families with evidence-based information about neurodevelopmental outcomes, in a manner similar to that which has been afforded to the non-DS ALL population.

This study is the first to systematically and prospectively assess neurocognitive, functional, and quality of life outcomes in a sizeable cohort of children with DS-ALL treated on a cooperative group protocol, thus addressing a substantial gap in knowledge about outcomes in this neurodevelopmentally and medically vulnerable population. Outcomes will be measured by parent questionnaires that have documented clinical utility in children and adolescents with DS without a cancer history.¹⁷⁴⁻¹⁷⁶ Collecting caregiver-reported outcomes is feasible in COG, as evidenced by the successful integration of neurocognitive and psychological outcome studies such as ALTE07C1. Collection of data at serial timepoints will provide insights into the impact of ALL therapy on neurocognitive, functional, and quality of life outcomes throughout the arc of treatment, including the early intensive phases, Maintenance, and post-therapy. In addition to generating benchmark data on neurocognitive function and quality of life in the DS-ALL population, this study will also provide a unique opportunity to examine the effects of blinatumomab in this population. Blinatumomab has been used in patients with DS-ALL without evidence of unexpected toxicity or decreased efficacy,^{30,36} but these reports are based on small numbers and require further confirmation in a larger study. Further, data on two specific features associated with blinatumomab will be of particular interest for the DS population: (1) the frequency and severity of neurotoxicity and (2) the impact of delivering a continuous 28-day IV infusion on quality of life and participation in rehabilitation and early intervention services.

Outcomes from this study have the potential to substantially influence frontline therapy and survivorship care by providing clinicians and researchers with a mechanism for quantifying the acute and long-term impact of treatment on neurocognitive and functional outcomes, informing guidelines for supportive care during therapy (e.g., rehabilitative services and school programming), and providing families with anticipatory guidance regarding neurodevelopmental progression following treatment.

17.2.3 Study Overview

Participation in the DS Neurocognitive Study will be offered to patients with Down syndrome enrolled on AALL1731 and identified as having NCI SR or NCI HR B-ALL. Eligible and consented patients must also have a parent/guardian who is able to read English, Spanish, or French. Families who consent to this optional study will complete assessments during regularly scheduled clinic visits. The estimated time to complete the assessment is 45-60 minutes. Assessments will be completed at three time points according to the schedule in Table 17.2.1. Caregivers (parents or legal guardians) will complete standardized ratings of executive function, behavior, adaptive skills, and quality of life (Table 17.2.2). Outcomes will be assessed using caregiver ratings in order to facilitate data collection in the cooperative group environment and in consideration of the limited utility of performance-based measures in populations with intellectual disability. In addition to collection of caregiver ratings, this study will collect data on participation in school and rehabilitation programs using a study-specific form; as well as standard demographic, clinical and treatment data submitted as part of AALL1731 (including but not limited to number of hospitalization days, treatment arm, age at diagnosis, and socioeconomic status as assessed by zip code and insurance status).

17.2.4 Assessments and Questionnaires

Timing of Assessments

Longitudinal assessment will be conducted at three time points (Table 17.2.1). Assessments may be performed within 4 weeks before or after the specified time points. To reduce participant burden, all study assessments coincide with regularly scheduled clinic visits. For each assessment, caregivers (parents/legal guardians) will complete standardized rating forms to provide information on the patient's neurocognitive, behavioral, adaptive function, and quality of life. Caregivers will also provide information about the patient's current participation in school and community-based activities (e.g., rehabilitation). Ratings may be administered by a clinical research assistant, nurse, psychologist, or any other study staff available in the pediatric oncology clinic who completes a brief, online training.

Table 17.2.1. Assessment Schedule for DS-ALL Neurocognitive Study

| Time point Number | Treatment phase |
|-------------------|--|
| 1 | Maintenance Cycle 1 Day 29 (\pm 4 weeks) |
| 2 | Maintenance Cycle 5 Day 29 (\pm 4 weeks) |
| 3 | One Year after End of Therapy (\pm 4 weeks) |

Rationale for Assessment Timing

Time points were selected in consideration of the psychosocial standard of care recommendation in pediatric oncology, which calls for monitoring and assessment of neuropsychological outcomes intermittently during and after therapy.^{161,177} Time point 1, Maintenance Cycle 1, is designed to capture data reflecting the impact of the intensive treatment phases that occur prior to Maintenance. Time point 2, one year later, indicates patient status during Maintenance therapy. Finally, Time point 3, one year after end of therapy, serves as a measure of patient status when the acute effects of therapy are past.

Assessment Instruments

Caregivers will complete standardized ratings of the patient's executive function, behavior adaptive skills, and quality of life (Table 17.2.2). Executive functions are higher-order

cognitive abilities that are necessary for goal-directed behavior, problem solving, and the application of learned skills to everyday life. These skills are disproportionately impaired in individuals with DS without leukemia, are considered “at-risk” domains in childhood leukemia survivors, and are associated with functional outcomes, including adaptive skills and behavior. We will collect information on patient involvement in rehabilitative programming and school, to further clarify the day-to-day impact of ALL and its treatment. These data may be used as covariates in planned analyses of risk and resiliency factors for outcomes.

Table 17.2.2. DS-ALL neurocognitive, functional and quality of life assessment measures

| Domain | Measure | Age specific forms |
|--------------------|---|--|
| Executive Function | Behavior Rating Inventory of Executive Function, Parent Rating Forms (BRIEF) | BRIEF-P: 2:6 to 4:11 BRIEF-2: 5:0 and 18:11 BRIEF-A-Informant: 19:0 and up |
| Behavior | Behavior Assessment System for Children, Third Edition, Parent Rating System (BASC-3 PRS) | BASC-3-PRS: <ul style="list-style-type: none"> • Preschool: 2:0 to 5:11 • Child: 6:0 to 11:11 • Adolescent: 12:0 to 21:11 |
| Adaptive Skills | Adaptive Behavior Assessment System, Third Edition, Parent Rating Forms (ABAS-3) | ABAS-3 Parent Ratings: <ul style="list-style-type: none"> • Parent/Primary Caregiver Form - Ages 0:0 to 4:11 • Parent/Primary Caregiver Form - Ages 5:0 to 21:11 • Adult Form 22:0 and up |
| Quality of Life | Pediatric Quality of Life Inventory, Generic Core Scales 4.0, Parent Report (PedsQL) | PedsQL: <ul style="list-style-type: none"> • Toddler: 2:0 to 4:11 • Young Children: 5:0 to 7:11 • Children: 8:0 to 12:11 • Teens: 13:0 to 18:11 • Young Adult: 19:0 and up |
| Daily Activity | Study specific questionnaire | All ages complete the same questionnaire |

Ages are reported in years: months. Measures are completed by caregivers (parent/legal guardian) at each study time point. The specific version of each measure is dependent on the chronological age of the DS-ALL patient at the study time point. Total time to complete all questionnaires is around 45-60 minutes. All measures are administered at all study time points.

17.2.4.1 Behavior Rating Inventory of Executive Function, Preschool, Second Edition, and Adult-Informant (BRIEF-P, BRIEF-2 and BRIEF-Adult Informant)^{[178-181](#)}

The BRIEF forms are parent-completed measures of executive function behaviors in the home environment. Executive functions include goal-directed behaviors, such as the ability to plan, organize, sustain and change performance in response to feedback. The BRIEF questionnaires consists of items from which clinical scales and broad indices of executive function are derived. Items were developed to be ecologically-valid behavioral correlates to presumed neurocognitive difficulties with executive functioning; thus, this measure was selected to provide parent and patient-reported outcomes of problems related to attention, memory, and executive function that occur in everyday life. Psychometric properties of this measure are strong using normative samples weighted to match ethnic and sex proportions in the US population. Scores are age and sex standardized, with a mean of 50 and a

standard deviation of 10; higher scores indicate greater difficulties. Age appropriate versions will be used in this study according to Table 17.2.2.

17.2.4.2 **Behavior Assessment System for Children, Third Edition, Parent Rating Scales (BASC-3-PRS, Preschool, Child, Adolescent)¹⁸²**

The BASC-3 parent ratings contain items that describe the behaviors, thoughts, and emotions of children and adolescents. The BASC-3 contains nine clinical scales (Hyperactivity, Aggression, Conduct Problems, Anxiety, Depression, Somatization, Atypicality, Withdrawal, and Attention Problems), five adaptive scales (Adaptability, Social Skills, Leadership, Activities of Daily Living, and Functional Communication) and five composite scales (Internalizing, Externalizing, Behavior Symptoms Index, Adaptive Functioning, and Total Problems). The BASC-3 also includes three validity indices (F – negative response bias; L – positive response bias; and V – nonsensical statements) and two response set indices (Consistency Index and Response Pattern Index). Reliability, content validity, and construct validity have been well established for this measure. Scores are age standardized, with the mean of 50 and a standard deviation of 10. Higher scores indicate more problems on clinical scales. Higher scores indicate better adaptive functioning on adaptive scales. Age appropriate versions will be used in this study according to Table 17.2.2.

17.2.4.3 **Adaptive Behavior Assessment System, Third Edition, Parent/Caregiver Rating Scales (ABAS-3)¹⁸³**

The parent-report form of the ABAS-3 will be used for the assessment of adaptive skills in individuals from birth to 89 years of age. Separate scale scores are available for 11 skill areas, as well as for 3 adaptive domains (Conceptual, Social, and Practical) and an overall adaptive domain (General Adaptive Composite; GAC). The internal consistency ranges from 0.91 to 0.99 for the adaptive domains and the GAC. Domain and composite scores are age-standardized, with a mean of 100 and a standard deviation of 15. Skill area scores are age-standardized, with a mean of 10 and a standard deviation of 3. Higher scores indicate more independent functioning. Construct, convergent, and discriminant validity have also been established for this measure. Age appropriate versions will be used in this study according to Table 17.2.2.

17.2.4.4 **Pediatric Quality of Life Inventory, Generic 4.0, Parent Rating Forms (PedsQL; Toddlers, Young Children, Children, Teens, and Young Adult)¹⁸⁴**

The PedsQL 4.0 is a modular approach to measuring health-related quality of life in healthy children and adolescents as well as in those with acute and chronic health conditions. The Generic Version has separate parent-report forms based on patient age. The questionnaire yields domain scores for Physical, Emotional, Social, and School Functioning as well as summary scores for Total Quality of Life, Physical Health, and Psychosocial Health. Higher scores equal better quality of life. Reliability and validity have been established for this measure. Age appropriate versions will be used in this study according to Table 17.2.2.

17.2.4.5 **Information on Daily Activities**

The parent/guardian will also be asked to complete a study-specific form that includes items regarding patient participation in school and rehabilitation.

17.2.5 Data Collection

For all participants who provide consent for this ancillary study, the appropriate questionnaires based on the age of the patient will be provided to the specific site via a centrally located CRA. The assessments will be administered to the family by trained clinic personnel or institutional COG CRAs at the time points described above. Training will be completed via a brief online module that will be made available to study staff by the central site. Completed forms will be reviewed by the CRA for completeness and transferred to the central site for scoring and data entry. Please use the study email (AALL1731_DownSyndrome_neurocog@stjude.org) for inquiries regarding training, study procedures, study materials, and data transmission. Responses will be entered through the RAVE system by the central site and the original forms retained at the central institution and secured according to research standards. Families that do not submit a questionnaire at a particular time point for any reason will still continue to be offered participation in the remaining questionnaire time points. Patients who discontinue therapy on AALL1731 will not receive assessments at time points after they go off protocol therapy.

17.2.6 Statistical Plan

17.2.6.1 **Sample Size Considerations**

We will attempt to recruit all eligible patients for this novel study of neurocognitive, functional, and quality of life outcomes in DS ALL. Total estimated accrual over the duration of AALL1731 is around 240 DS ALL patients: DS SR-Fav: 3/year for post-Induction = ~15 total; DS SR-Avg (randomization eligible): 15/year = ~75 total; DS-HIGH: 30/year = ~150 total. We conservatively estimate that 70% of patients will meet sub-study eligibility criteria, consent to participation, and remain on protocol therapy, based on prior experiences with clinical research studies in the DS population, for an estimated overall sample size of 168 (DS SR-Fav = 10; DS SR-Avg = 52; DS-HIGH = 105).

17.2.6.2 **Planned Analysis**

This study is the first to systematically and prospectively assess neurocognitive, functional, and quality of life in children with DS-ALL, thus addressing a substantial gap in knowledge about outcomes in a neurodevelopmentally and medically vulnerable population that has previously been systematically excluded from a large body of research on neurocognitive outcomes in childhood ALL survivors. Accordingly, the primary aim of this study is to characterize the longitudinal trajectory of outcomes in DS-ALL. Thus, this study will provide benchmark data that may be used to guide modification to treatment and supportive care, as well as educate families about expected outcomes. Where available, data from cross-sectional studies in age-similar DS populations will be used as a baseline for comparison to the outcomes observed in children with DS-ALL at the time points assessed on this study. [174-176,185,186](#)

Primary Aim: To describe the impact of ALL and its therapy on neurocognitive, functional, and quality of life outcomes in patients with DS-ALL.

Primary outcomes of interest are detailed in Table 17.2.3. We will use descriptive statistics to characterize participants on relevant demographic and clinical variables. Interval data distributions will be inspected and transformed as needed

to ensure the appropriate use of parametric statistics. We will use regression or t-tests to check whether outcomes differ based on demographic or clinical variables, and adjust all analyses accordingly. Standardized scores and raw scores will be used in analyses. Standardized scores will be compared to available normative data using continuous and categorical methods; for example, a one sample t-test will be used for mean comparisons and the frequency of impairments will be compared using exact test by binomial distribution or other methods as appropriate. Consistent with widely recognized standards in clinical practice and with prior neurocognitive studies in DS, at-risk scores will be defined as scores that are >1.0 standard deviation outside of expectations and problem scores will be defined as scores ≥ 1.3 standard deviation outside of expectations. Univariate and multivariable regression models will be used to assess the effect of demographic and clinical variables on outcomes. We will conduct similar analyses with secondary (e.g., subscales on rating measures).

Table 17.2.3. Outcomes of Interest

| Domain (Measure) | Outcome Score |
|------------------------------|---|
| Executive Function (BRIEF) | <ul style="list-style-type: none">• Global Executive Composite• Metacognitive Index• Behavior Regulation Index |
| Behavior (BASC-3) | <ul style="list-style-type: none">• Externalizing Problems Composite• Internalizing Problems Composite• Behavior Symptoms Composite• Adaptive Skills Composite |
| Adaptive Functioning (ABAS3) | <ul style="list-style-type: none">• General Adaptive Composite• Conceptual Composite• Social Composite• Practical Composite |
| Quality of Life (PedsQL) | <ul style="list-style-type: none">• Global Functioning• Physical Functioning• Emotional Functioning• Social Functioning• School Functioning |

If feasible based on sample size, we will use t-tests or regression to compare outcomes between DS-SR (Avg and Fav combined, total n = 63) and DS-HR group (n = 105), to assess the impact of the higher intensity treatment phases administered to the DS-HR group. A total sample size of 168 (DS-SR-combined = 63; DS-HR = 105) will provide 80% power to detect effect sizes of $d \geq 0.50$ (alpha = 0.025, two-tailed). If feasible based on sample size, we may also examine the impact of blinatumomab on outcomes for DS patients, by comparing DS patients who did not receive blinatumomab (DS-SR-Fav [n=11] and those DS-SR-Avg patients randomized to the control arm [n=26], for a total of 37) to those DS patients randomized to receive blinatumomab (n=26) and DS-High patients [n=105]. Mean comparisons with this sample size (131 treated with blinatumomab, 37 treated without blinatumomab) will provide 79% power to detect effect sizes of $d \geq 0.57$ (alpha = 0.025, 2-tailed). Thus, both comparisons will have adequate power to detect medium to large effect sizes, which are most likely to be clinically meaningful.

There are no published data to guide the anticipated effect size for these comparisons. Effect sizes in studies comparing outcomes between cohorts of healthy individuals with DS and typically developing individuals matched for mental age range from medium to large, as follows: adaptive functioning, $d = 1.46$; and executive functioning, $d = 0.71-1.77$.¹⁸⁷ Effect sizes in studies comparing outcomes between healthy DS participants to chronologically age-based normative expectations a range from medium to large, as follows: behavior, $d = 0.42 - 0.80$.¹⁷⁴

17.2.7 Contact

Please address questions to: AALL1731_DownSyndrome_neurocog@stjude.org

18 B-Ly REQUIRED IMAGING STUDIES AND RESPONSE ASSESSMENT

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable (except where explicitly prohibited within the protocol).

18.1 DISEASE PARAMETERS

18.1.1 Measurable disease

A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extra-nodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

18.1.2 Non-measured disease

All other lesions (including nodal, extra-nodal, and assessable disease) should be followed as non-measured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

18.1.3 Target lesions

For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

18.2 METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks prior to the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

18.2.1 Clinical lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

18.2.2 Conventional CT and MRI

Extent of disease at diagnosis will be established by CT or MRI in conjunction with PET (strongly recommended) and morphologic evaluation of bone marrow (BM) if involved at diagnosis. With growing concerns about the risks of cumulative ionizing radiation exposure to children from CT, MRI could be considered as an alternative to CT for evaluating non-pulmonary disease sites. e.g., assessment of abdominal/pelvic disease. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the response guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Pulse sequences should include at a minimum, axial and coronal fat-saturated FFRFSE-T2, coronal T1 and axial and coronal post-gadolinium fat-saturated T1 weighted imaging. Body scans should be performed with breath-hold scanning techniques, if possible.

18.2.3 PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for International Pediatric Non-Hodgkin Lymphoma Staging System measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. However, PET/CT is strongly recommended as the primary modality for staging and response evaluation.

18.2.4 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

18.3 EVALUATIONS

18.3.1 Diagnosis Staging

- Bilateral bone marrow biopsies and aspirates
- PET scan is strongly recommended.
- CT or MRI of the neck, chest, abdomen and pelvis
- CXR
- Bone scan for patients with bone symptoms
- MRI of brain/spine if neurologic symptoms
- Diagnostic LP with evaluation of CSF

18.3.2 Induction Day 29

- PET scan is strongly recommended as primary modality to assess response
- If PET not available, repeat CT or MRI of areas of active disease at diagnosis
- Bone scan for patients with baseline study
- Diagnostic LP with evaluation of CSF

18.3.3 End of Consolidation (Only for patients not in a CR at the end of Induction)

- PET scan if positive at end of Induction, OR
- Repeat CT or MRI of active sites of disease at EOI, OR

A PET scan is highly recommended but not required at diagnosis, at the end of Induction, and, if there are residual masses and/or FDG avidity, at the end of Consolidation. Of note, if a PET scan is obtained at baseline, PET imaging should be continued with subsequent response assessment until patient no longer has PET-avid disease. For patients who had a PET at diagnosis, a PET can be used instead of a regular CT or MRI to follow disease response.

18.4 RESPONSE CRITERIA

These criteria are derived from published international consensus guidelines [18862.63](#)

18.4.1 COMPLETE RESPONSE (CR) for B-LY PATIENTS

Defined as disappearance of all detectable clinical evidence of disease from all sites. For patients with a previous positive PET scan, PET scan must be negative.
OR

Resolution of all detectable masses. Lymph nodes must have decreased to ≤ 1.5 cm. This will be determined by physical exam and CT or MRI.

Bone marrow must be M1 by morphology (< 5% blasts).

CSF status must be CNS1.

For PET positive lesions at diagnosis:

A post-treatment residual mass of any size is considered a CR as long as it is PET negative (Deauville ≤ 3) on follow-up scan. A negative PET is required in patients with post-treatment residual masses in order to be considered CR. Patients with post-treatment residual masses must be followed by PET and remain PET negative to be considered CR.

Bone lesions that remain positive by MRI or PET will be considered CR if there is resolution of all surrounding soft tissue component by the end of Consolidation. There must be no new lesions.

18.4.2 PARTIAL RESPONSE (PR) for B-LLy PATIENTS

In patients with a positive PET scan prior to therapy, the post-treatment PET must be positive in at least one previously involved site. If all lesions are PET negative, see description of CR (above).

At least a 50% decrease in the sum of the product of diameters (SPD) of the lesions of up to six of the largest dominant nodes or nodal masses. Splenic and hepatic nodules must decrease by at least 50% in their SPD. No new lesions.

18.4.3 STABLE DISEASE (SD) for B-LLy PATIENTS

Failure to qualify for a PR or PD. No new lesions.

In patients with a positive PET scan prior to therapy, the PET must be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

18.4.4 RELAPSE/PROGRESSIVE DISEASE (PD) for B-LLy PATIENTS

Greater than 50% increase in the size of any lesions or appearance of new lesion(s) more than 1.5 cm in any axis.

In patients with a positive PET scan prior to therapy, lesions suspected of relapse must be PET positive.

Positive bone marrow (using ALL relapse definitions, see [Section 3.3.5](#)) or CNS3 disease.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (<https://ctepcore.nci.nih.gov/iam>). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (<https://ctepcore.nci.nih.gov/rcr>). Documentation requirements per registration type are outlined in the table below.

| Documentation Required | IVR | NPIVR | AP | A |
|---|-----|-------|----|---|
| FDA Form 1572 | ✓ | ✓ | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | |
| NCI Biosketch (education, training, employment, license, and certification) | ✓ | ✓ | ✓ | |
| HSP/GCP training | ✓ | ✓ | ✓ | |
| Agent Shipment Form (if applicable) | ✓ | | | |
| CV (optional) | ✓ | ✓ | ✓ | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR **Help Desk** by email at RCRHelpDesk@nih.gov.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements For AALL1731 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at <https://www.ctsu.org/RSS/RTFProviderAssociation>, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab
→ Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

APPENDIX II: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY (for children from 7 through 12 years of age with B-ALL)

A study to compare the addition of Blinatumomab in combination with chemotherapy in patients diagnosed with standard risk B-cell Acute Lymphoblastic Leukemia (B-ALL), Down syndrome B-cell Acute Lymphoblastic Leukemia (B-ALL) and localized B-cell Lymphoblastic Lymphoma (B-LLy)

1. We have been talking with you about your B-cell Acute Lymphoblastic Leukemia or B-ALL. B-ALL is a type of cancer that grows in the bone marrow. The bone marrow is inside your bones. It is where your blood is made. After doing tests, we have found that you have this type of cancer.
2. We are asking you to take part in a research study because you have Standard-Risk B-ALL. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat B-ALL. We will do this by trying different ways to treat B-ALL and seeing which one works better. By doing this study, we are hoping that we can figure out the best way to treat B-ALL while also reducing the bad effects of the anti-cancer drugs.
3. Children who are part of this study will receive a treatment called chemotherapy. Chemotherapy medicines that kill cancer cells. Children who are part of this study will get the usual treatment doctors use for B-ALL. Some of the children will get less chemotherapy and some will get more depending on how much they need to treat their B-ALL. Also, some children will get an extra medicine in addition to the usual treatment for B-ALL. We don't know if this medicine will help treat your B-ALL, this is why we're doing this study. Whether or not you get the extra medicine is decided by chance, like flipping a coin.
4. You will also have regular blood tests and several bone marrow tests and spinal taps (a way to collect fluid from your spine) during your treatment. These tests help doctors in deciding the most appropriate treatment for your B-ALL. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.
5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible and with less bad effects, but we don't know for sure if there is any benefit to being part of this study.
6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." You might have more risks if you receive the extra medicine in addition to the usual chemotherapy. Common risks caused by the extra medicine are anemia, diarrhea, nausea, tiredness, fever, bruising, bleeding, and headache. Anemia is having less blood in your body. This can make you feel tired and sick, and you might need to get a blood transfusion. Also, usually boys with B-ALL receive one more year of chemotherapy, but on this study they will receive the same amount of chemotherapy as girls. This is because we hope that there will be less bad effects, but it is possible that the treatment won't work as well.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
8. We are asking your permission to collect additional blood, bone marrow, and spinal fluid for special studies. These studies will help us better understand B-ALL and how it responds to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. We also might ask for your permission to collect some extra information from you. We want to find out how your life has been affected by cancer and its treatment. We will look at how you are feeling physically and emotionally during your cancer treatment. We will also look at how you are able to do your normal day-to-day activities, and we will ask you questions and perform some examinations on you 3-6 times during treatment. You can still take part in this study even if you don't allow us to collect these extra samples and tests for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY
(for children from 7 through 12 years of age with B-LLy)**

A study to compare the addition of Blinatumomab in combination with chemotherapy in patients diagnosed with standard risk B-cell Acute Lymphoblastic Leukemia (B-ALL), Down syndrome B-cell Acute Lymphoblastic Leukemia (B-ALL) and localized B-cell Lymphoblastic Lymphoma (B-LLy)

1. We have been talking with you about your localized B-cell Lymphoblastic Lymphoma or B-LLy. B-LLy is a type of cancer that grows in the lymph system. The lymph system is made up of lymph nodes and other tissue throughout the body, and it helps fight infections and keep the body healthy. After doing tests, we have found that you have this type of cancer and it is only located in one particular area in the body.
2. We are asking you to take part in a research study because you have B-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat B-LLy. We will do this by trying different ways to treat B-LLy and seeing which one works better. By doing this study, we are hoping that we can figure out the best way to treat B-LLy while also reducing the bad effects of the anti-cancer drugs.
3. Children who are part of this study will receive a treatment called chemotherapy. Chemotherapy is medicines that kill cancer cells. Children who are part of this study will get the usual treatment doctors use for B-ALL, which is a similar type of cancer. This medicine has helped treat children with B-ALL, but we don't know if this medicine will help treat your B-LLy, this is why we're doing this study.
4. You will also have regular blood tests, bone marrow tests, spinal taps (a way to collect fluid from your spine), and scans during your treatment. These tests help doctors in deciding the most appropriate treatment for your B-LLy. The bone marrow tests and spinal taps may hurt some, but medicines will be given to keep it from hurting too much.
5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible and with less bad effects, but we don't know for sure if there is any benefit of being part of this study.
6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risk to you from this study is that the treatment might not work well. Other things may happen to you that we don't yet know about.
7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.
8. We are asking your permission to collect additional blood, bone marrow, and tumor tissue for special studies. These studies will help us better understand B-LLy and how it responds to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect these extra samples for research.

INFORMATION SHEET REGARDING RESEARCH STUDY (for teens from 13 through 17 years of age with B-LLy)

A study to compare the addition of Blinatumomab in combination with chemotherapy in patients diagnosed with standard risk B-cell Acute Lymphoblastic Leukemia (B-ALL), Down syndrome B-cell Acute Lymphoblastic Leukemia (B-ALL) and localized B-cell Lymphoblastic Lymphoma (B-LLy)

1. We have been talking with you about your localized B-cell Lymphoblastic Lymphoma or B-LLy. B-LLy is a cancer of the lymph system and other lymph tissue throughout the body. Lymph tissues make and store infection fighting white blood cells called lymphocytes. These cells become cancerous when a person has B-LLy. Your B-LLy is localized because your lymphoma is restricted to one particular area of the body or a particular system in the body.
2. We are asking you to take part in a research study because you have B-LLy. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about how to treat B-LLy. We will do this by trying different ways to treat B-LLy and seeing which one works better. By doing this study, we are hoping that we can figure out the best way to treat B-LLy while also reducing the bad effects of the anti-cancer drugs.
3. Children and teens who are part of this study will receive a treatment called chemotherapy. Chemotherapy is medicines that kill cancer cells. Children and teens who are part of this study will get the usual treatment doctors use for B-cell Acute Lymphoblastic Leukemia or B-ALL, which is a similar type of cancer that affects the bone marrow. This treatment has been effective in treating children and teens with B-ALL, but we don't know if this medicine will help treat your B-LLy, this is why we're doing this study.
4. You will also have regular blood tests, bone marrow tests, spinal taps (a way to collect fluid from your spine), and scans performed throughout the duration of therapy to see how your B-LLy is responding to treatment. These tests help doctors in deciding the most appropriate treatment for your B-LLy. The bone marrow tests and spinal taps may be painful, but medicines will be given to keep it from hurting too much.
5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is getting rid of the cancer for as long as possible and with less bad effects, but we don't know for sure if there is any benefit of being part of this study.
6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risk to you from this study is that the treatment might not work well. Other side effects may happen to you that we don't yet know about.
7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can inform you about. Make sure to ask your doctors any questions that you have.
8. We are asking your permission to collect additional blood, bone marrow, and tumor tissue for special studies. These studies will help us better understand B-LLy and how it responds to treatment. These samples would be taken when other standard blood tests are being performed, so there would be no extra procedures. You can still take part in this study even if you don't allow us to collect these extra samples for research.

APPENDIX III: MERCAPTOPURINE DOSING TABLE

Note: The Mercaptopurine dosing nomograms in this appendix only apply to the tablet formulation.

MERCAPTOPURINE 25 mg/m²

| Body Surface Area (m ²)* | Daily Dose (d) for 7 days (1 tablet = 50 mg) | Cumulative Weekly Dose |
|--------------------------------------|---|------------------------|
| 0.36 - 0.49 | ½ tab / d x 3 | 75 mg/wk |
| 0.50 - 0.64 | ½ tab / d x 4 | 100 mg/wk |
| 0.65 - 0.78 | ½ tab / d x 5 | 125 mg/wk |
| 0.79 - 0.92 | ½ tab / d x 6 | 150 mg/wk |
| 0.93 – 1.07 | ½ tab / d x 7 | 175 mg/wk |
| 1.08 – 1.21 | 1 tab / d x 1; ½ tab / d x 6 | 200 mg/wk |
| 1.22 – 1.35 | 1 tab / d x 2; ½ tab / d x 5 | 225 mg/wk |
| 1.36 – 1.49 | 1 tab / d x 3; ½ tab / d x 4 | 250 mg/wk |
| 1.50 – 1.64 | 1 tab / d x 4; ½ tab / d x 3 | 275 mg/wk |
| 1.65 – 1.78 | 1 tab / d x 5; ½ tab / d x 2 | 300 mg/wk |
| 1.79 – 1.92 | 1 tab / d x 6; ½ tab / d x 1 | 325 mg/wk |
| 1.93 – 2.07 | 1 tab / d x 7 | 350 mg/wk |
| 2.08 – 2.21 | 1½ tab / d x 1; 1 tab / d x 6 | 375 mg/wk |
| 2.22 - 2.35 | 1½ tab / d x 2; 1 tab / d x 5 | 400 mg/wk |
| 2.36 – 2.49 | 1½ tab / d x 3; 1 tab / d x 4 | 425 mg/wk |
| 2.50 – 2.64 | 1½ tab / d x 4; 1 tab / d x 3 | 450 mg/wk |
| 2.65 – 2.78 | 1½ tab / d x 5; 1 tab / d x 2 | 475 mg/wk |
| 2.79 – 2.92 | 1½ tab / d x 6; 1 tab / d x 1 | 500 mg/wk |
| 2.93 – 3.00* | 1½ tab / d x 7 | 525 mg/wk |

*Patients exceeding a BSA of 3.00 m² should have their MP doses calculated on actual BSA with no maximum dose.

MERCAPTOPURINE 60 mg/m²

| Body Surface Area (m ²)* | Daily Dose (d) for 7 days (1 tablet = 50 mg) | Cumulative Weekly Dose |
|--------------------------------------|---|------------------------|
| 0.33 - 0.38 | ½ tab / d x 6 | 150 mg/wk |
| 0.39 - 0.44 | ½ tab / d x 7 | 175 mg/wk |
| 0.45 - 0.50 | ½ tab / d x 6; 1 tab / d x 1 | 200 mg/wk |
| 0.51 - 0.56 | ½ tab / d x 5; 1 tab / d x 2 | 225 mg/wk |
| 0.57 - 0.62 | ½ tab / d x 4; 1 tab / d x 3 | 250 mg/wk |
| 0.63 - 0.68 | 1 tab / d x 4; ½ tab / d x 3 | 275 mg/wk |
| 0.69 - 0.74 | 1 tab / d x 5; ½ tab / d x 2 | 300 mg/wk |
| 0.75 - 0.80 | 1 tab / d x 6; ½ tab / d x 1 | 325 mg/wk |
| 0.81 - 0.86 | 1 tab / d x 7 | 350 mg/wk |
| 0.87 - 0.92 | 1 tab / d x 6; 1½ tab / d x 1 | 375 mg/wk |
| 0.93 - 0.98 | 1 tab / d x 5; 1½ tab / d x 2 | 400 mg/wk |
| 0.99 - 1.04 | 1 tab / d x 4; 1½ tab / d x 3 | 425 mg/wk |
| 1.05 - 1.10 | 1½ tab / d x 4; 1 tab / d x 3 | 450 mg/wk |
| 1.11 - 1.16 | 1½ tab / d x 5; 1 tab / d x 2 | 475 mg/wk |
| 1.17 - 1.22 | 1½ tab / d x 6; 1 tab / d x 1 | 500 mg/wk |
| 1.23 - 1.27 | 1½ tab / d x 7 | 525 mg/wk |
| 1.28 - 1.33 | 1½ tab / d x 6; 2 tab / d x 1 | 550 mg/wk |
| 1.34 - 1.39 | 1½ tab / d x 5; 2 tab / d x 2 | 575 mg/wk |
| 1.40 - 1.45 | 1½ tab / d x 4; 2 tab / d x 3 | 600 mg/wk |
| 1.46 - 1.51 | 2 tab / d x 4; 1½ tab / d x 3 | 625 mg/wk |
| 1.52 - 1.57 | 2 tab / d x 5; 1½ tab / d x 2 | 650 mg/wk |
| 1.58 - 1.63 | 2 tab / d x 6; 1½ tab / d x 1 | 675 mg/wk |
| 1.64 - 1.69 | 2 tab / d x 7 | 700 mg/wk |
| 1.70 - 1.75 | 2 tab / d x 6; 2½ tab / d x 1 | 725 mg/wk |
| 1.76 - 1.81 | 2 tab / d x 5; 2½ tab / d x 2 | 750 mg/wk |
| 1.82 - 1.87 | 2 tab / d x 4; 2½ tab / d x 3 | 775 mg/wk |
| 1.88 - 1.93 | 2½ tab / d x 4; 2 tab / d x 3 | 800 mg/wk |
| 1.94 - 1.99 | 2½ tab / d x 5; 2 tab / d x 2 | 825 mg/wk |
| 2.00 - 2.05 | 2½ tab / d x 6; 2 tab / d x 1 | 850 mg/wk |
| 2.06 - 2.11 | 2½ tab / d x 7 | 875 mg/wk |
| 2.12 - 2.17 | 2½ tab / d x 6; 3 tab / d x 1 | 900 mg/wk |
| 2.18 - 2.23 | 2½ tab / d x 5; 3 tab / d x 2 | 925 mg/wk |
| 2.24 - 2.29 | 2½ tab / d x 4; 3 tab / d x 3 | 950 mg/wk |
| 2.30 - 2.35 | 3 tab / d x 4; 2½ tab / d x 3 | 975 mg/wk |
| 2.36 - 2.41 | 3 tab / d x 5; 2½ tab / d x 2 | 1000 mg/wk |
| 2.42 - 2.47 | 3 tab / d x 6; 2½ tab / d x 1 | 1025 mg/wk |
| 2.48 - 2.52 | 3 tab / d x 7 | 1050 mg/wk |

| Body Surface Area (m ²)* | Daily Dose (d) for 7 days (1 tablet = 50 mg) | Cumulative Weekly Dose |
|--------------------------------------|---|------------------------|
| 2.53 - 2.58 | 3 tab/ d x 6; 3½ tab / d x 1 | 1075 mg/wk |
| 2.59 - 2.64 | 3 tab/ d x 5; 3½ tab / d x 2 | 1100 mg/wk |
| 2.65 - 2.70 | 3 tab/ d x 4; 3½ tab / d x 3 | 1125 mg/wk |
| 2.71 - 2.76 | 3½ tab/ d x 4; 3 tab / d x 3 | 1150 mg/wk |
| 2.77 - 2.82 | 3½ tab/ d x 5; 3 tab / d x 2 | 1175 mg/wk |
| 2.83 - 2.88 | 3½ tab/ d x 6; 3 tab / d x 1 | 1200 mg/wk |
| 2.89 - 2.94 | 3½ tab/ d x 7 | 1225 mg/wk |
| 2.95 - 3.00 | 3½ tab/ d x 6; 4 tab / d x 1 | 1250 mg/wk |

*Patients exceeding a BSA of 3.00 m² should have their MP doses calculated on actual BSA with no maximum dose.

MERCAPTOPURINE 75 mg/m²

| Body Surface Area (m²)* | Daily Dose (d) for 7 days (1 tablet = 50 mg) | Cumulative Weekly Dose |
|---|---|-------------------------------|
| 0.36 - 0.40 | ½ tab / d x 6; 1 tab / d x 1 | 200 mg/wk |
| 0.41 - 0.45 | ½ tab / d x 5; 1 tab / d x 2 | 225 mg/wk |
| 0.46 - 0.49 | ½ tab / d x 4; 1 tab / d x 3 | 250 mg/wk |
| 0.50 - 0.54 | 1 tab / d x 4; ½ tab / d x 3 | 275 mg/wk |
| 0.55 - 0.59 | 1 tab / d x 5; ½ tab / d x 2 | 300 mg/wk |
| 0.60 - 0.64 | 1 tab / d x 6; ½ tab / d x 1 | 325 mg/wk |
| 0.65 - 0.69 | 1 tab / day | 350 mg/wk |
| 0.70 - 0.73 | 1 tab / d x 6; 1½ tab / d x 1 | 375 mg/wk |
| 0.74 - 0.78 | 1 tab / d x 5; 1½ tab / d x 2 | 400 mg/wk |
| 0.79 - 0.83 | 1 tab / d x 4; 1½ tab / d x 3 | 425 mg/wk |
| 0.84 - 0.88 | 1½ tab / d x 4; 1 tab / d x 3 | 450 mg/wk |
| 0.89 - 0.92 | 1½ tab / d x 5; 1 tab / d x 2 | 475 mg/wk |
| 0.93 - 0.97 | 1½ tab / d x 6; 1 tab / d x 1 | 500 mg/wk |
| 0.98 - 1.02 | 1½ tab / day | 525 mg/wk |
| 1.03 - 1.07 | 1½ tab / d x 6; 2 tab / d x 1 | 550 mg/wk |
| 1.08 - 1.11 | 1½ tab / d x 5; 2 tab / d x 2 | 575 mg/wk |
| 1.12 - 1.16 | 1½ tab / d x 4; 2 tab / d x 3 | 600 mg/wk |
| 1.17 - 1.21 | 2 tab / d x 4; 1½ tab / d x 3 | 625 mg/wk |
| 1.22 - 1.26 | 2 tab / d x 5; 1½ tab / d x 2 | 650 mg/wk |
| 1.27 - 1.30 | 2 tab / d x 6; 1½ tab / d x 1 | 675 mg/wk |
| 1.31 - 1.35 | 2 tab / day | 700 mg/wk |
| 1.36 - 1.40 | 2 tab / d x 6; 2½ tab / d x 1 | 725 mg/wk |
| 1.41 - 1.45 | 2 tab / d x 5; 2½ tab / d x 2 | 750 mg/wk |
| 1.46 - 1.49 | 2 tab / d x 4; 2½ tab / d x 3 | 775 mg/wk |
| 1.50 - 1.54 | 2½ tab / d x 4; 2 tab / d x 3 | 800 mg/wk |
| 1.55 - 1.59 | 2½ tab / d x 5; 2 tab / d x 2 | 825 mg/wk |
| 1.60 - 1.64 | 2½ tab / d x 6; 2 tab / d x 1 | 850 mg/wk |
| 1.65 - 1.69 | 2½ tab / d | 875 mg/wk |
| 1.70 - 1.73 | 2½ tab / d x 6; 3 tab / d x 1 | 900 mg/wk |
| 1.74 - 1.78 | 2½ tab / d x 5; 3 tab / d x 2 | 925 mg/wk |
| 1.79 - 1.83 | 2½ tab / d x 4; 3 tab / d x 3 | 950 mg/wk |
| 1.84 - 1.88 | 3 tab / d x 4; 2½ tab / d x 3 | 975 mg/wk |
| 1.89 - 1.92 | 3 tab / d x 5; 2½ tab / d x 2 | 1000 mg/wk |
| 1.93 - 1.97 | 3 tab / d x 6; 2½ tab / d x 1 | 1025 mg/wk |
| 1.98 - 2.02 | 3 tab / d x 7 | 1050 mg/wk |
| 2.03 - 2.07 | 3 tab / d x 6; 3½ tab / d x 1 | 1075 mg/wk |
| 2.08 - 2.11 | 3 tab / d x 5; 3½ tab / d x 2 | 1100 mg/wk |
| 2.12 - 2.16 | 3 tab / d x 4; 3½ tab / d x 3 | 1125 mg/wk |
| 2.17 - 2.21 | 3½ tab / d x 4; 3 tab / d x 3 | 1150 mg/wk |
| 2.22 - 2.26 | 3½ tab / d x 5; 3 tab / d x 2 | 1175 mg/wk |
| 2.27 - 2.30 | 3½ tab / d x 6; 3 tab / d x 1 | 1200 mg/wk |
| 2.31 - 2.35 | 3½ tab / d x 7 | 1225 mg/wk |
| 2.36 - 2.40 | 3½ tab / d x 6; 4 tab / d x 1 | 1250 mg/wk |
| 2.41 - 2.45 | 3½ tab / d x 5; 4 tab / d x 2 | 1275 mg/wk |

| | | |
|-------------|------------------------------|------------|
| 2.46 – 2.49 | 3½ tab/ d x 4; 4 tab / d x 3 | 1300 mg/wk |
| 2.50 – 2.54 | 4 tab/ d x 4; 3½ tab / d x 3 | 1325 mg/wk |
| 2.55 – 2.59 | 4 tab/ d x 5; 3½ tab / d x 2 | 1350 mg/wk |
| 2.60 – 2.64 | 4 tab/ d x 6; 3½ tab / d x 1 | 1375 mg/wk |
| 2.65 – 2.69 | 4 tab/ d x 7 | 1400 mg/wk |
| 2.70 – 2.73 | 4 tab/ d x 6; 4½ tab / d x 1 | 1425 mg/wk |
| 2.74 – 2.78 | 4 tab/ d x 5; 4½ tab / d x 2 | 1450 mg/wk |
| 2.79 – 2.83 | 4 tab/ d x 4; 4½ tab / d x 3 | 1475 mg/wk |
| 2.84 – 2.88 | 4½ tab/ d x 4; 4 tab / d x 3 | 1500 mg/wk |
| 2.89 – 2.92 | 4½ tab/ d x 5; 4 tab / d x 2 | 1525 mg/wk |
| 2.93 – 2.97 | 4½ tab/ d x 6; 4 tab / d x 1 | 1550 mg/wk |
| 2.98 – 3.00 | 4½ tab/ d x 7 | 1575 mg/wk |

*Patients exceeding a BSA of 3.00 m² should have their MP doses calculated on actual BSA with no maximum dose.

APPENDIX IV: THIOGUANINE DOSING TABLE**THIOGUANINE 60 mg/m²**

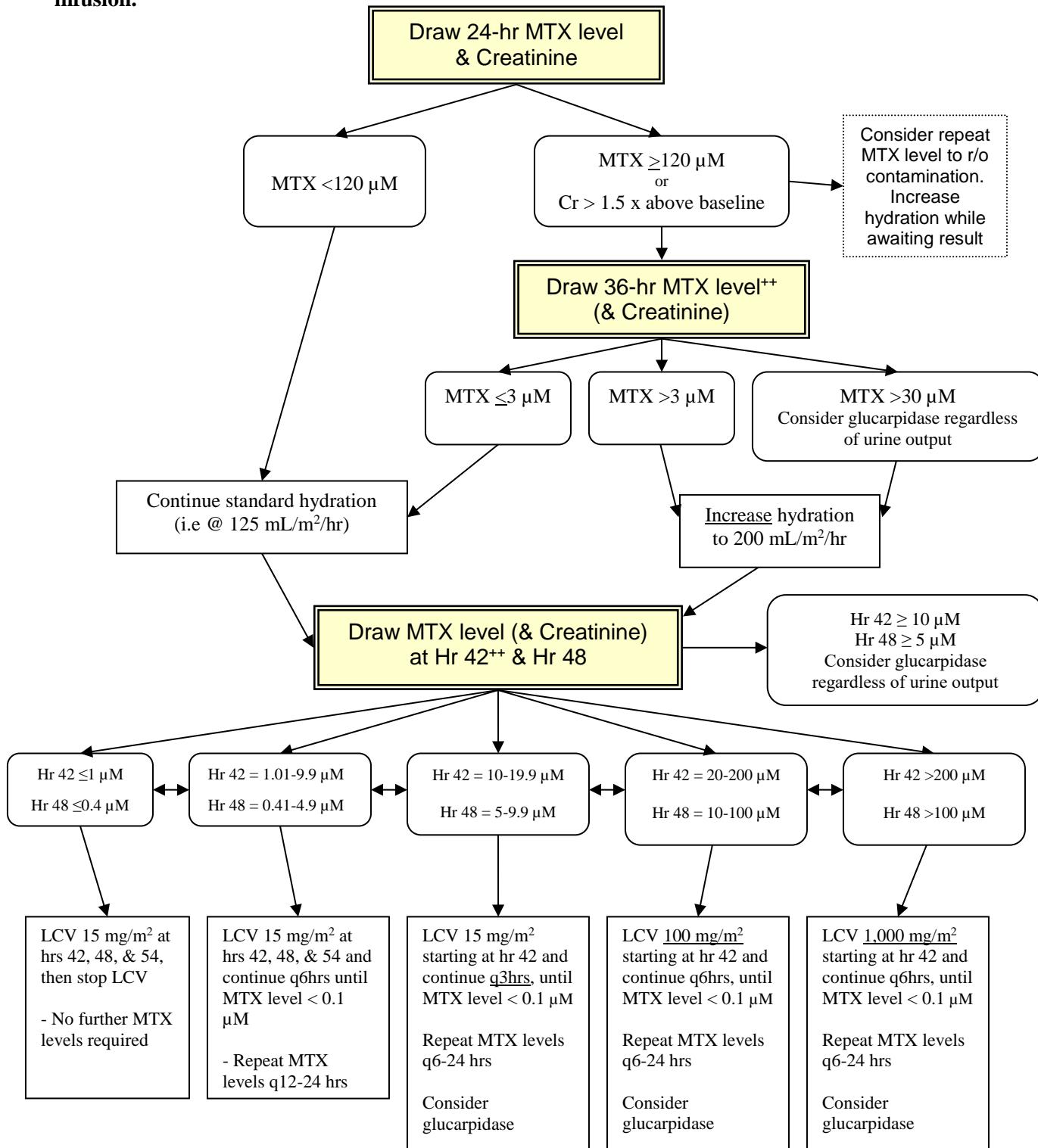
| Body Surface Area (m²)* | Daily Dose (d) for 7 days (1 tablet = 40 mg) | Cumulative Weekly Dose |
|---|---|-------------------------------|
| 0.31 - 0.35 | ½ tab / d x 7 | 140 mg/wk |
| 0.36 - 0.40 | ½ tab / d x 6; 1 tab / d x 1 | 160 mg/wk |
| 0.41 - 0.45 | ½ tab / d x 5; 1 tab / d x 2 | 180 mg/wk |
| 0.46 - 0.49 | ½ tab / d x 4; 1 tab / d x 3 | 200 mg/wk |
| 0.50 - 0.54 | 1 tab / d x 4; ½ tab / d x 3 | 220 mg/wk |
| 0.55 - 0.59 | 1 tab / d x 5; ½ tab / d x 2 | 240 mg/wk |
| 0.60 - 0.64 | 1 tab / d x 6; ½ tab / d x 1 | 260 mg/wk |
| 0.65 - 0.69 | 1 tab / day | 280 mg/wk |
| 0.70 - 0.73 | 1 tab / d x 6; 1½ tab / d x 1 | 300 mg/wk |
| 0.74 - 0.78 | 1 tab / d x 5; 1½ tab / d x 2 | 320 mg/wk |
| 0.79 - 0.83 | 1 tab / d x 4; 1½ tab / d x 3 | 340 mg/wk |
| 0.84 - 0.88 | 1½ tab / d x 4; 1 tab / d x 3 | 360 mg/wk |
| 0.89 - 0.92 | 1½ tab / d x 5; 1 tab / d x 2 | 380 mg/wk |
| 0.93 - 0.97 | 1½ tab / d x 6; 1 tab / d x 1 | 400 mg/wk |
| 0.98 - 1.02 | 1½ tab / day | 420 mg/wk |
| 1.03 - 1.07 | 1½ tab / d x 6; 2 tab / d x 1 | 440 mg/wk |
| 1.08 - 1.11 | 1½ tab / d x 5; 2 tab / d x 2 | 460 mg/wk |
| 1.12 - 1.16 | 1½ tab / d x 4; 2 tab / d x 3 | 480 mg/wk |
| 1.17 - 1.21 | 2 tab / d x 4; 1½ tab / d x 3 | 500 mg/wk |
| 1.22 - 1.26 | 2 tab / d x 5; 1½ tab / d x 2 | 520 mg/wk |
| 1.27 - 1.30 | 2 tab / d x 6; 1½ tab / d x 1 | 540 mg/wk |
| 1.31 - 1.35 | 2 tab / day | 560 mg/wk |
| 1.36 - 1.40 | 2 tab / d x 6; 2½ tab / d x 1 | 580 mg/wk |
| 1.41 - 1.45 | 2 tab / d x 5; 2½ tab / d x 2 | 600 mg/wk |
| 1.46 - 1.49 | 2 tab / d x 4; 2½ tab / d x 3 | 620 mg/wk |
| 1.50 - 1.54 | 2½ tab / d x 4; 2 tab / d x 3 | 640 mg/wk |
| 1.55 - 1.59 | 2½ tab / d x 5; 2 tab / d x 2 | 660 mg/wk |
| 1.60 - 1.64 | 2½ tab / d x 6; 2 tab / d x 1 | 680 mg/wk |
| 1.65 - 1.69 | 2½ tab / d | 700 mg/wk |
| 1.70 - 1.73 | 2½ tab / d x 6; 3 tab / d x 1 | 720 mg/wk |
| 1.74 - 1.78 | 2½ tab / d x 5; 3 tab / d x 2 | 740 mg/wk |
| 1.79 - 1.83 | 2½ tab / d x 4; 3 tab / d x 3 | 760 mg/wk |
| 1.84 - 1.88 | 3 tab / d x 4; 2½ tab / d x 3 | 780 mg/wk |
| 1.89 - 1.92 | 3 tab / d x 5; 2½ tab / d x 2 | 800 mg/wk |
| 1.93 - 1.97 | 3 tab / d x 6; 2½ tab / d x 1 | 820 mg/wk |
| 1.98 - 2.02 | 3 tab / d x 7 | 840 mg/wk |
| 2.03 - 2.07 | 3 tab / d x 6; 3½ tab / d x 1 | 860 mg/wk |
| 2.08 - 2.11 | 3 tab / d x 5; 3½ tab / d x 2 | 880 mg/wk |
| 2.12 - 2.16 | 3 tab / d x 4; 3½ tab / d x 3 | 900 mg/wk |
| 2.17 - 2.21 | 3½ tab / d x 4; 3 tab / d x 3 | 920 mg/wk |
| 2.22 - 2.26 | 3½ tab / d x 5; 3 tab / d x 2 | 940 mg/wk |
| 2.27 - 2.30 | 3½ tab / d x 6; 3 tab / d x 1 | 960 mg/wk |

| | | |
|-------------|-------------------------------|------------|
| 2.31 – 2.35 | 3½ tab / d x 7 | 980 mg/wk |
| 2.36 – 2.40 | 3½ tab / d x 6; 4 tab / d x 1 | 1000 mg/wk |
| 2.41 – 2.45 | 3½ tab / d x 5; 4 tab / d x 2 | 1020 mg/wk |
| 2.46 – 2.49 | 3½ tab / d x 4; 4 tab / d x 3 | 1040 mg/wk |
| 2.50 – 2.54 | 4 tab / d x 4; 3½ tab / d x 3 | 1060 mg/wk |
| 2.55 – 2.59 | 4 tab / d x 5; 3½ tab / d x 2 | 1080 mg/wk |
| 2.60 – 2.64 | 4 tab / d x 6; 3½ tab / d x 1 | 1100 mg/wk |
| 2.65 – 2.69 | 4 tab / d x 7 | 1120 mg/wk |
| 2.70 – 2.73 | 4 tab / d x 6; 4½ tab / d x 1 | 1140 mg/wk |
| 2.74 – 2.78 | 4 tab / d x 5; 4½ tab / d x 2 | 1160 mg/wk |
| 2.79 – 2.83 | 4 tab / d x 4; 4½ tab / d x 3 | 1180 mg/wk |
| 2.84 – 2.88 | 4½ tab / d x 4; 4 tab / d x 3 | 1200 mg/wk |
| 2.89 – 2.92 | 4½ tab / d x 5; 4 tab / d x 2 | 1220 mg/wk |
| 2.93 – 2.97 | 4½ tab / d x 6; 4 tab / d x 1 | 1240 mg/wk |
| 2.98 – 3.00 | 4½ tab / d x 7 | 1260 mg/wk |

*Patients exceeding a BSA of 3.00 m² should have their TG doses calculated on actual BSA with no maximum dose.

APPENDIX V-A: HIGH DOSE METHOTREXATE

Please refer to [Section 5.7.2](#) for complete details; all levels are timed from the start of the HDMTX infusion.

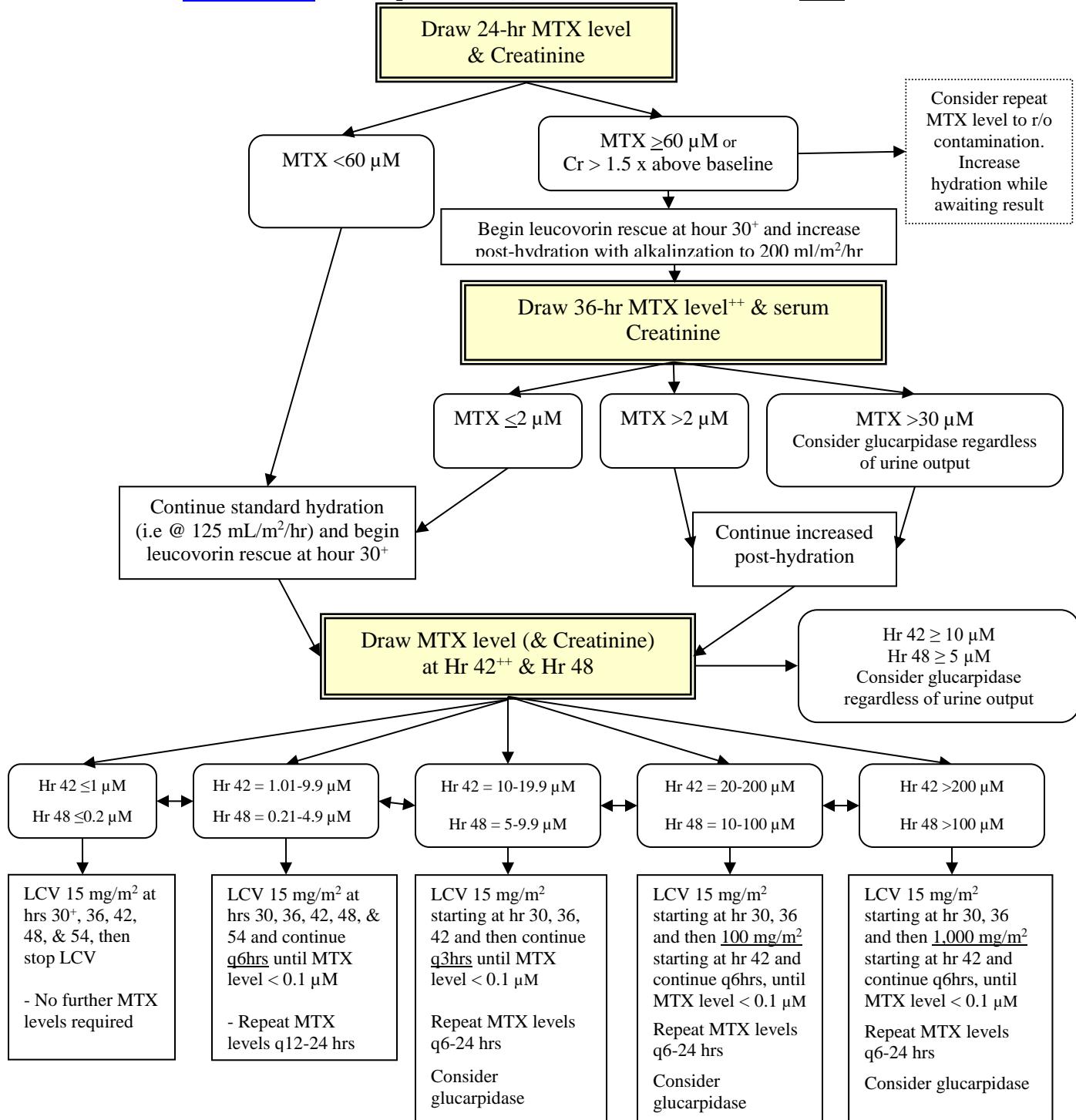


⁺⁺ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤ 0.4 μM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX V-B: INTERMEDIATE DOSE METHOTREXATE FLOW CHART

Down syndrome patients ONLY

Please refer to [Section 5.7.1](#) for complete details; all levels are timed from the start of the ID MTX infusion.



⁺ If the first cycle of ID MTX is tolerated, defined as no delayed clearance, no treatment delay due to myelosuppression, no mucositis of Grade 2 or higher, and no nephrotoxicity (pre-treatment serum creatinine >1.5x baseline or GFR creatinine clearance < 65 mL/minute/1.73m²), subsequent cycles of ID MTX should be followed by leucovorin 15 mg/m² PO/IV q 6h beginning 36 hrs after the start of the infusion for a minimum of 4 doses if 48 hour plasma MTX is < 0.2 μM.

⁺⁺ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤ 0.2 μM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX VI: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects, and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Some drugs, food, and supplements may interact with cyclophosphamide. Examples include:

| Drugs that may interact with cyclophosphamide |
|--|
| <ul style="list-style-type: none">• Allopurinol• Chloramphenicol• Cyclosporine• Digoxin• Etanercept• Hydrochlorothiazide• Indomethacin• Nevirapine• Pentostatin• Warfarin |

| Food and supplements that may interact with cyclophosphamide |
|--|
| <ul style="list-style-type: none">• St. John's Wort• Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants" |

Some drugs, food, and supplements may interact with cytarabine (by vein). Examples include:

| Drugs that may interact with cytarabine |
|--|
| <ul style="list-style-type: none">• Clozapine, digoxin, flucytosine, leflunomide |

| Food and supplements that may interact with cytarabine |
|---|
| <ul style="list-style-type: none">• Echinacea |

Some drugs, food, and supplements may interact with dexamethasone. Examples include:

| Drugs that may interact with dexamethasone |
|---|
| <ul style="list-style-type: none">• Antibiotics<ul style="list-style-type: none">○ Ciprofloxacin, levofloxacin, moxifloxacin, clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin• Antidepressants and antipsychotics<ul style="list-style-type: none">○ Aripiprazole, bupropion, citalopram, clozapine, escitalopram, fluvoxamine, ilurasidone, nefazodone, quetiapine• Antifungals<ul style="list-style-type: none">○ Caspofungin, fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole |

- Arthritis medications
 - Leflunomide, tofacitinib
- Anti-rejection medications
 - Cyclosporine, sirolimus, tacrolimus
- Antiretrovirals and antivirals
 - Atazanavir, boceprevir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, rilpivirine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
- Anti-seizure medications
 - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
 - Amiodarone, amlodipine, dronedarone, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Some oral contraceptives or birth control medications
- Many other drugs, including the following:
 - Aprepitant, artemether/lumefantane, aspirin, deferasirox, ibuprofen, ivacaftor, lomitapide, mifepristone, natalizumab, nimodipine, praziquantel, warfarin

Food and supplements that may interact with dexamethasone

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

Some drugs, food, and supplements may interact with mercaptopurine. Examples include:

Drugs that may interact with mercaptopurine*

- Arthritis medications: leflunomide, tofacitinib
- Other medications, such as allopurinol, azathioprine, clozapine, febuxostat, natalizumab, olsalazine, sulfasalazine, warfarin

Food and supplements that may interact with mercaptopurine**

- Echinacea

Some drugs, food, and supplements may interact with pegaspargase. Examples include:

Drugs that may interact with pegaspargase

- Leflunomide, natalizumab, tofacitinib

Food and supplements that may interact with pegaspargase

- Echinacea

Some drugs, food, and supplements may interact with predniSO(LO)ne. Examples include:

Drugs that may interact with predniSO(LO)ne

- Arthritis medications
 - Leflunomide, tofacitinib
- Antiretrovirals and antivirals
 - Boceprevir, ritonavir, telaprevir
- Anti-seizure medications
 - Phenobarbital, phenytoin, primidone
- Growth hormones
- Heart medications
 - Diltiazem, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Some oral contraceptives or birth control medications
- Many other drugs, including the following:
 - Aprepitant, aripiprazole, aspirin, cyclosporine, deferasirox, ibuprofen, itraconazole, mifepristone, natalizumab, rifampin, warfarin

Food and supplements that may interact with predniSO(LO)ne

- Echinacea

Some drugs, food, and supplements may interact with thioguanine. Examples include:

Drugs that may interact with thioguanine

- Arthritis medications: leflunomide, tofacitinib
- Other medications, such as allopurinol, clozapine, natalizumab, olsalazine, sulfasalazine

Food and supplements that may interact with thioguanine**

- Echinacea

Some drugs, food, and supplements may interact with vinCRISTine. Examples include:

Drugs that may interact with vinCRISTine*

- Antibiotics
 - Clarithromycin, erythromycin, naftillin, rifabutin, rifampin, telithromycin
- Antidepressants and antipsychotics
 - Aripiprazole, nefazodone, trazodone
- Antifungals
 - Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- Arthritis medications
 - Leflunomide, tocilizumab, tofacitinib
- Anti-rejection medications
 - Cyclosporine, tacrolimus
- Antiretrovirals and antivirals

- Atazanavir, boceprevir, darunavir, delavirdine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir
- Anti-seizure medications
 - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
 - Amiodarone, digoxin, dronedarone, propranolol, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
 - Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vinCRISTine

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

APPENDIX VII: STAGING CLASSIFICATION OF CHILDHOOD NON-HODGKIN LYMPHOMA

Modified from Murphy [Seminars in Oncology (1908) 7; 332-339]

| Stage | Criteria for the extent of disease |
|---------------------|--|
| Localized | |
| I | |
| | A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen. |
| II | A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tumour, usually in the ileocaecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected. |
| Disseminated | |
| III | Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intra-thoracic tumours (mediastinal, pleural, thymic). All extensive primary intra-abdominal disease. All paraspinal or epidural tumours, regardless of other tumour sites(s). |
| IV | Any of the above with initial CNS and/or bone marrow involvement. |

Enumeration of Number of Regions of Nodal Involvement

Each of these twenty regions is counted separately for purposes of determining number of sites of involvement.

Peripheral Regions

- Right neck; cervical, supraclavicular, occipital, and pre-auricular
- Left neck; cervical, supraclavicular, occipital, and pre-auricular
- Right infraclavicular
- Left infraclavicular
- Right axilla and pectoral

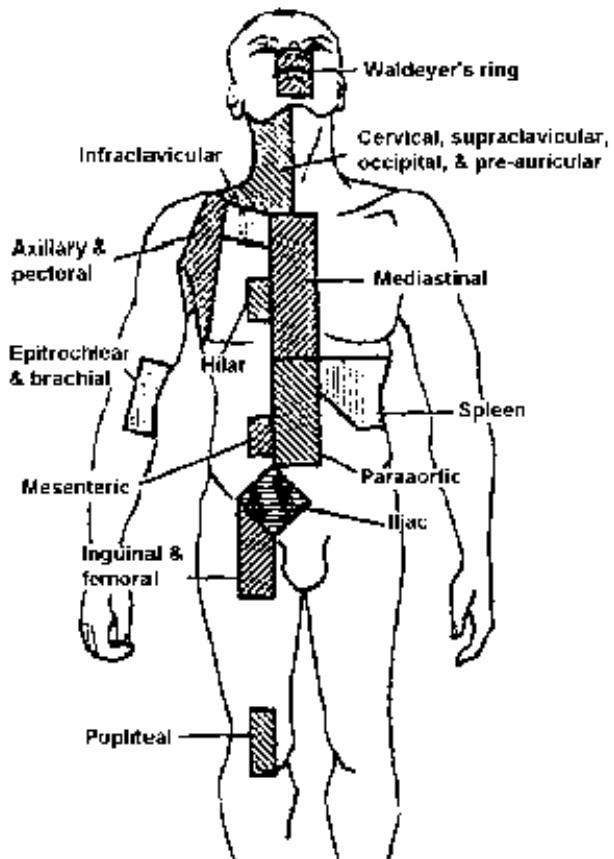
Left axilla and pectoral
Right epitrochlear and brachial
Left epitrochlear and brachial

Central Regions

Waldeyer's ring (including base of tongue)
Mediastinum (including paratracheal)
Hilar
Mesenteric
Paraaoortic (including retrocrural, portal and celiac)
Splenic/splenic hilar

Lower Regions

Right iliac
Left iliac
Right inguinal and femoral
Left inguinal and femoral
Right popliteal
Left popliteal



Anatomical Regions for the Staging Lymphoma

APPENDIX VIII: CPY3A4 SUBSTRATES, INHIBITORS AND INDUCERS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

| CYP3A4 substrates | Strong Inhibitors ¹ | Moderate Inhibitors | Strong Inducers | Moderate Inducers |
|---|--|---|---|--|
| acalabrutinib ⁵ alfentanil ^{4,5} amiodarone ⁴ aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib ⁵ budesonide ⁵ buspirone ⁵ cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib ⁵ conivaptan ⁵ copanlisib crizotinib cyclosporine ⁴ dabrafenib dapsone darifenacin ⁵ darunavir ⁵ dasatinib ⁵ dexamethasone ² diazepam dihydroergotamine docetaxel DOXOrubicin dronedarone ⁵ eletriptan ⁵ eplerenone ⁵ ergotamine ⁴ erlotinib estrogens etoposide everolimus ⁵ fentanyl ⁴ gefitinib haloperidol ibrutinib ⁵ idelalisib imatinib indinavir ⁵ irinotecan isavuconazole ⁵ itraconazole | atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit ³ grapefruit juice ³ idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole | aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit ³ grapefruit juice ³ imatinib isavuconazole mifepristone nilotinib verapamil | barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort | bosentan dabrafenib efavirenz etravirine modafinil naftcilin rifapentine |

| | | | | |
|---------------------------|--|--|--|--|
| ivacaftor | | | | |
| ketoconazole | | | | |
| lansoprazole | | | | |
| lapatinib | | | | |
| losartan | | | | |
| lovastatin ⁵ | | | | |
| lurasidone ⁵ | | | | |
| macrolide antibiotics | | | | |
| maraviroc ⁵ | | | | |
| medroxyprogesterone | | | | |
| methadone | | | | |
| midazolam ⁵ | | | | |
| midostaurin ⁵ | | | | |
| modafinil | | | | |
| nefazodone | | | | |
| nilotinib | | | | |
| olaparib | | | | |
| ondansetron | | | | |
| osimertinib | | | | |
| paclitaxel | | | | |
| palbociclib | | | | |
| pazopanib | | | | |
| quetiapine ⁵ | | | | |
| quinidine ⁴ | | | | |
| regorafenib | | | | |
| romidepsin | | | | |
| saquinavir ⁵ | | | | |
| sildenafil ⁵ | | | | |
| simvastatin ⁵ | | | | |
| sirolimus ^{4,5} | | | | |
| sonidegib | | | | |
| sunitinib | | | | |
| tacrolimus ^{4,5} | | | | |
| tamoxifen | | | | |
| telaprevir | | | | |
| temsirolimus | | | | |
| teniposide | | | | |
| tetracycline | | | | |
| tipranavir ⁵ | | | | |
| tolvaptan ⁵ | | | | |
| triazolam ⁵ | | | | |
| trimethoprim | | | | |
| vardenafil ⁵ | | | | |
| vemurafenib | | | | |
| venetoclax ⁵ | | | | |
| vinca alkaloids | | | | |
| zolpidem | | | | |

¹ Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.

²Refer to [Section 6.5](#) and [Section 6.11](#) regarding use of corticosteroids.

³The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.

⁴Narrow therapeutic range substrates

⁵Sensitive substrates (drugs that demonstrate an increase in AUC of ≥ 5 -fold with strong inhibitors)

APPENDIX IX: SUPPORTIVE CARE GUIDELINES

I. General Guidelines

Aggressive supportive care improves outcome. The following guidelines are intended to give general direction for optimal patient care and to encourage uniformity in the treatment of this study population. Notify Study Chair of any unexpected or unusually severe complications. Please also see the COG Supportive Care Guidelines at: <https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines>. Guidelines for DS patients are included below.

Blood Components

Blood products should be irradiated and leukodepleted following current FDA guidelines found at:

<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM320641.pdf>

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at: <http://www.scc.ca/en/standardsdb/standards/19234>

Red Blood Cells (RBC)

Transfusion with RBC is indicated to correct severe or symptomatic anemia or acute blood loss. In the setting of extreme hyperleukocytosis investigators should be mindful that peripheral red blood cells (PRBC) may contribute to hyperviscosity.

Platelets

Transfusion with platelets is indicated to correct bleeding manifestations and may be indicated for severe thrombocytopenia without bleeding particularly prior to an invasive procedure.

Infection Prophylaxis

Pneumocystis jiroveci

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 5 mg/kg/day divided BID 2-3 sequential days per week. For patients allergic to or experiencing excessive myelosuppression with TMP/SMX, alternative prophylaxis with dapsone, aerosolized pentamidine, atovaquone or IV pentamidine may be considered.

Antifungals

Azole antifungal agents (i.e., fluconazole, posaconazole, itraconazole, voriconazole, or isavuconazole [isavuconazonium sulfate]) given concurrently with vinCRISTine may increase the risk of neurotoxicity. Caution is advised if azole antifungals are used.

Treatment of Established or Presumed Infections

Fever with Neutropenia

For patients with ANC < 500/ μ L or expected to fall to this level within the next 48 hours and an oral-equivalent temperature $\geq 38.3^{\circ}\text{C}$ once or between 38.0°C and 38.3°C twice

within 12 hours, empiric broad spectrum antibiotics should be instituted after obtaining appropriate cultures. Patients who present with severe sepsis should have empiric antibiotic coverage widened to include resistant Gram-negative, Gram-positive, and anaerobic bacteria.

The risk of bacteremia and infectious mortality is higher during Induction and during profound neutropenia. The specific choice of antibiotics to be used in empiric treatment of febrile neutropenia is dependent on each institution's experience regarding the type of infecting organisms, and their antibiotic sensitivity patterns.

For prolonged fever and neutropenia (≥ 96 hours), empiric antifungal therapy with either caspofungin or liposomal amphotericin B should be given during periods of anticipated prolonged neutropenia including Induction. Other antifungal agents may be considered based on institutional standards.

Also, please see the COG Fever and Neutropenia Guidelines at:
https://childrensoncologygroup.org/downloads/COG_SC_FN_Guideline_Document_Dec_2017.pdf

Primary Varicella Infection (Chickenpox) or Reactivation (zoster)

Patients should be treated promptly with IV acyclovir, and monitored closely for the development of invasive systemic disease.

Empiric Management of Pulmonary Infiltrates

Pulmonary infiltrates should be evaluated in the context of the patient's clinical and laboratory profile as well as institutional infection patterns. If the patient is not neutropenic, and the pulmonary lesions on CT scan are not particularly suggestive of a fungal infection, consider using broad spectrum antibiotics. If the patient develops progressively worsening clinical or laboratory features, or if, the pulmonary lesions on CT scan are suggestive of a fungal infection (Aspergillus, Mucor), then more aggressive diagnostic measures should be undertaken. Pulmonary infiltrates may be evaluated with bronchoscopy and biopsy, lavage or open lung biopsy. If a procedure cannot be tolerated, and/or if there is high clinical suspicion consider beginning empiric fungal treatment. It is advisable to seek an infectious disease consult under these circumstances. If fungal pulmonary disease is documented, surveillance radiographic imaging studies of the sinuses, abdomen/pelvis and brain and ocular exams are indicated. Surgical excision of pulmonary lesions should be considered at the discretion of the treating physician. Treatment of fungal infections with amphotericin B and/or other antifungal agents will be at the discretion of the treating physician. **Azole antifungal agents (i.e., fluconazole, posaconazole, itraconazole, voriconazole, isavuconazole) given concurrently with vinCRISTine may INCREASE the risk of neurotoxicity. Caution is advised if azole antifungals are used.**

Management of Mucositis/Perirectal Cellulitis

Mucositis should be managed with IV hydration and hyperalimentation if indicated, effective analgesia, broad-spectrum gram-positive and gram-negative antibiotic therapy and empiric antiviral and antifungal therapy as indicated. Management of perirectal cellulitis should include broad-spectrum antibiotic therapy with dual gram-negative coverage as well as anaerobic coverage (i.e., ceftazidime or cefepime + aminoglycoside +

metronidazole; or piperacillin-tazobactam + aminoglycoside), Sitz baths, a strong barrier technique and effective analgesia.

Prevention and Management of Chemotherapy induced Nausea and Vomiting (CINV)

Please refer to the COG Endorsed guidelines on prevention and management of CINV at: https://childrensoncologygroup.org/downloads/COG_SC_CINV_Guidelines_Document_Feb_2018.pdf.

The routine use of steroids as antiemetics, including dexamethasone, is discouraged but may be appropriate in select patients with demonstrated intolerance to higher-dose chemotherapeutic agents.

Use of myeloid growth factors

The routine use of filgrastim or biosimilar products is not generally recommended, but may be used at the discretion of the investigator in situations of serious infection with neutropenia.

Osteonecrosis (ON)

Osteonecrosis (also referred to as avascular necrosis) may develop during or following therapy and often involves multiple joints over time. ON is not limited to weight bearing joints; common sites include hip, knee, ankle, heel, shoulder and elbow. Symptoms and exam findings may include joint pain, joint stiffness, limited range of motion (e.g., pain with internal rotation of the hip), limited mobility or ambulation, and/or gait abnormalities. Diagnostic imaging is indicated in any patient with suggestive findings. MRI is superior in sensitivity and specificity to other modalities, especially with early bone changes. Patients with negative studies, but who have persisting, progressive, or recurrent symptoms, should be re-imaged.

For modifications of ALL therapy, see [Section 5.9](#).

GI Protection

While patients are on steroid therapy, consider using an H2 blocker or proton pump inhibitor.

II. Guidelines for Induction

Acute Tumor Lysis Syndrome

Patients with ALL at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested initial studies, obtained prior to initiating antileukemia therapy, may include a complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorus, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

The risk for serious acute tumor lysis syndrome (TLS) is usually restricted to the first 72 hours after initiation of therapy; however, it may spontaneously occur prior to treatment. To manage the metabolic derangements caused by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following steps should be initiated:

- Begin allopurinol at a dose of 300 mg/m²/day or 10 mg/kg/day (maximum 800 mg/day) in 2 - 3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some patients, such as those with oliguria or severe renal dysfunction, or in those with marked hyperuricemia, it may be also be appropriate to use rasburicase. Note that rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Hydrate at 2,400-3,000 mL/m²/day to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced. Potassium should not be added to the hydration fluids.
- Urine alkalinization is NOT necessary for TLS prophylaxis. There is paucity of evidence demonstrating benefit of urine alkalinization and it can potentially lead to calcium phosphate precipitation and/or metabolic acidosis.

Diagnostic Lumbar Puncture

As there are data suggesting that traumatic diagnostic lumbar punctures may have an adverse effect on prognosis, consider interventions to minimize the chances of a traumatic diagnostic lumbar puncture (LP). These interventions may include:

1. Correcting any coagulopathy or thrombocytopenia present prior to the diagnostic LP.
2. Performing the diagnostic LP while the patient is in a controlled environment such as under moderate or deep sedation.
3. Administering intrathecal cytarabine at the time of the diagnostic lumbar puncture.
4. Having the diagnostic lumbar puncture performed by an experienced provider.

Induction – Infectious Complications

Since the Induction phase is associated with a higher rate of toxicity, investigators are cautioned to pay close attention to a number of factors during the early phases of treatment. Patients may experience profound myelosuppression and immune suppression during this time. Since steroids may mask fever, as well as other components of the systemic inflammatory response during Induction, the warning signs of septic shock may be associated with very mild and subtle symptoms. Caregivers must also be made aware that patients may experience very rapid clinical deterioration. This suggests the need for a supportive care network that can recognize and respond to sudden changes in a patient's condition. In addition it should be noted that serious toxic events can have an intestinal etiology. Patients with subtle GI symptoms should be monitored very closely.

III. **Patients with Down syndrome (DS)**

Patients with DS B-ALL and DS B-LLY have a significantly increased risk of morbidity and treatment-related mortality in most published series. Therefore, they require a diligent and conservative approach to supportive care. Infectious complications during times of neutropenia are of greatest concern. Infections in children with Down syndrome may be sudden in onset and progress rapidly mandating close surveillance and aggressive intervention or treatment.

Due to their unique risks, the following are recommended for patients with Down syndrome:

- **Hospitalization:** It is strongly recommended that children with Down syndrome be monitored in the hospital during Induction, Consolidation (if HR), and Delayed Intensification until they show signs of bone marrow recovery and, are afebrile and clinically stable. If a patient experiences profound myelosuppression at any other time, there should also be a very low threshold for hospitalization and inpatient management until there is evidence of bone marrow recovery.
- **Antibacterial prophylaxis** against Gram-positive and Gram-negative organisms (e.g., Levofloxacin) may be considered during periods of severe myelosuppression until patients meet criteria for discharge or get switched to broad-spectrum intravenous antibiotics per institutional guidelines if a patient develops febrile neutropenia while receiving prophylactic antibiotics.
- **Antifungal prophylaxis** may also be considered during periods of myelosuppression. Options include an echinocandin such as caspofungin or micafungin, or an azole. Investigators should be cautious however as **azole antifungal agents (i.e., fluconazole, posaconazole, itraconazole, voriconazole, isavuconazole)** given concurrently with vinCRIStine may increase the risk of neurotoxicity.
- **IgG replacement:** IgG levels should be monitored monthly and strong consideration given to IVIG therapy for levels less than 400 mg/dL. IgG levels and route of IVIG administration should be recorded on study CRF.

Children with DS B-ALL and DS B-LLy may not develop fever in response to infection, even with sepsis, particularly when they are receiving steroids. Therefore extra vigilance is needed, with a lower threshold for drawing cultures and starting antibiotics, even for subtle changes in clinical status. Aggressively manage episodes of fever ($\geq 100.5^{\circ}\text{F}/38.0^{\circ}\text{C}$) during Induction, Consolidation (if HR), and Delayed Intensification or when the patient is neutropenic with an ANC $\leq 1,000/\mu\text{L}$. The risk of life threatening infection is high, so these patients should be hospitalized with immediate institution of broad spectrum IV antibiotics adjusted appropriately for local patterns of antibiotic resistance. Adequate coverage for gram-negative and gram-positive organisms including viridans streptococci is recommended. Broad spectrum antibiotics, once started, should continue until evidence of bone marrow recovery. In the absence of response after 3 – 5 days, antifungal therapy should be strongly considered. Stress-dose steroids and/or filgrastim or biosimilar should be considered in DS B-ALL and DS B-LLy patients with fever and neutropenia who are very ill or not responding appropriately to antibiotic therapy.

APPENDIX X-A: CLINICAL SITE MANAGEMENT OF OUT PATIENT TREATMENT USING CTEP-SUPPLIED BLINATUMOMAB

- PREPARED IV INFUSION BAGS MAY NOT BE CHANGED BY THE STUDY SUBJECT
- PREPARED INFUSION BAGS OR INTACT VIALS MUST NOT BE TRANSPORTED TO ANOTHER LOCATION BY THE STUDY SUBJECT

AGENT PREPARATION AND ADMINISTRATION OPTIONS

- Prepare all out-patient infusion bags at the registering/treating institution. Study subjects should return to the registering/treating institution for all infusion bag changes.
- For study subjects that cannot return to the registering/treating institution for infusion bag exchanges, the next preference would be for **another institution that is participating on the trial and is closer to the subject's home take over** responsibility for the study subject's protocol participation. In such cases, transfer of the subject's protocol registration to another participating investigator and institution should be considered.
- If transferring the subject's protocol registration to another participating investigator and trial site within the institution is not feasible, use of **a local outpatient infusion center** could be considered.
 - a. First preference would be for all infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container to the local out-patient infusion center.
 - b. The prepared infusion bags are stored at the local outpatient infusion center. The infusion center would perform each infusion bag change.
 - c. If the local outpatient infusion center will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the local outpatient infusion center, with infusion bags prepared and administered by the local outpatient infusion center staff.
 - d. In either case, the local outpatient infusion center would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).
 - e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the local infusion center by registering/treating institution or local infusion center staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the local infusion center via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container.
- If an outpatient infusion center is not an option, use of a **home health care service** provider can be considered.

Note: If a home health care agency is being considered to prepare and change the blinatumomab infusion bag, the drug company that provides blinatumomab will provide drug but will NOT cover the costs associated with a home health care agency providing these services.

- a. The first preference would be for all outpatient infusion bags to be prepared by the registering/treating institution and shipped via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container to the servicing home health care agency.
 - b. The prepared infusion bags are stored by the home health care agency and each individual infusion bag transported to the subject's home by the home health care service nursing staff under refrigerated storage conditions for each infusion bag change.
 - c. If home health care agency will not administer prepared infusion bags admixed by the registering/treating institution, the registering/treating institution may provide intact vials of blinatumomab to the home health care agency, with infusion bags prepared and administered by the home health care agency staff.
 - d. In either case, the home health care agency would be managed as a satellite pharmacy of the registering/treating institution (see evaluation criteria below).
 - e. If physical transport of intact vials of blinatumomab from the registering/treating institution to the home health care agency by registering/treating institution or home health care agency staff is not possible, CTEP will allow shipment of the vials from the registering/treating institution to the home health care agency via overnight courier delivery service in a 2° to 8°C pre-qualified shipping container.
- If all options above are not feasible, shipping the prepared infusion bags directly to patient's home via overnight courier delivery service for administration by home healthcare agency staff is acceptable.
 - a. The prepared infusion bags are to be shipped in a 2° to 8°C pre-qualified shipping container containing one infusion bag per box. Example 1, if you are making 2 x 48 hour infusion bags, each infusion bag will be shipped in a separate 2° to 8°C pre-qualified shipping container. Example 2, if you are making a 2 x 96 hour infusion bags, each infusion bag will be shipped in a separate 2° to 8°C pre-qualified shipping container. The infusion of the 2nd 96 hour bag must be completed within 8 days (192 hrs) of preparation to avoid exceeding the expiration date. The number of infusion bags that may be prepared and shipped is dependent on the duration the shipping container used is qualified to maintain 2° to 8°C temperature.
 - b. Patients should NOT open the shipping container upon arrival. Shipping containers are to be stored in a secured area away from reach of children or pets.
 - c. Shipping containers must only be opened by the home health care service staff at the time of the infusion bag change. Only one shipping container should be opened at a time. If cold-chain management of the prepared infusion bag has been interrupted by opening of the shipping container or storage of the prepared infusion bag in the shipping container exceeds the duration of the qualified time the container will maintain 2° to 8°C temperature, the infusion bag should not be used.

The home health care service staff should immediately contact the registering/treating institution site pharmacy as indicated on the shipment form. Within 1 business day, the registering/treating institution site should send an email to the COG Industry Sponsored Trials office at istprogram@childrensoncologylgroup.org with a copy to PMB/CTEP at PMBafterhours@mail.nih.gov to report all such occurrences of prepared, unusable infusion bags shipped to a patient's home.

- d. Form documenting the time of packaging in the shipping container, duration of time the container will maintain 2° to 8°C temperature and verification that cold-chain management was maintained prior to administration must be included in each shipping container and returned to registering/treating institution for documentation purposes. ([See Appendix X-B](#))
- e. Home health care service staff is to use GCP guidelines.

EVALUATION OF POTENTIAL SATELLITE PHARMACY SITES

When the registering/treating institution is considering use of a local infusion center or home health care agency as a satellite pharmacy, the following must be assessed by the registering/treating institution in relation to the suitability of the local infusion center or home health care agency:

- Ability to appropriately store (temperature and security) the intact agent vials and/or prepared infusion bags.
- Ability to provide documentation of controlled and monitored temperature storage conditions while the IND agent is in the local infusion center or home health care agency possession.
- Availability of appropriately trained staff to prepare doses in compliance with USP <797> guidelines and the protocol, to label infusion bags according to the protocol instructions and to store agent doses under appropriate controlled temperature conditions.
- For home health care agency services, the ability to transport each prepared dose individually to the subject's home under appropriate controlled storage conditions or the ability to assess and confirm that cold-chain management of prepared infusion bags shipped to the subject's home is maintained prior to administration.
- Availability of appropriately trained staff to administer the prepared doses and perform the infusion bag changes according to the protocol.
- Methods for proper disposal of the waste, empty vials, IV bags, etc. are in place.
- Plan for return of unused intact vials to the registering/treating institution is in place.
- Source documentation to confirm agent administration must be maintained by the local infusion center or home health care agency and must be provided to the registering/treating institution for incorporation into the patient's medical/research records and for audit purposes.
- Plan for handling missed doses is in place.
- Agent accountability must be maintained via use of the NCI Drug Accountability Record Form (DARF). The originating site must keep a Control DARF and the local infusion center or home health care agency would be required to maintain a Satellite DARF if receiving and storing supplies of intact vials or receiving and storing infusion bags prepared by the registering/treating institution. Maintenance of a Satellite DARF is not required by home health care agency staff for prepared infusions bags shipped to the subject's home.
- The DARF must be provided to the registering/treating institution for record keeping purposes and audits.
- Documentation of IRB coverage for the protocol must be maintained. The IRB of record for the site must be informed that the study subject may receive therapy administered by a non-research site (i.e., the local infusion center or home health care agency).

APPENDIX X-B: SHIPMENT OF BLINATUMOMAB IV BAG FROM SITE/PHARMACY TO PATIENT'S HOME

To be completed by Site/Pharmacy:

| From: (Investigator Name, Address) | To Patient: (Patient Initials, Study ID No) _____ Patient Initials Study ID Number | Protocol No.: |
|------------------------------------|---|---------------|
| | | |

Prepare shipment of IV bag at 2°C to 8°C in validated/pre-qualified insulated shipper as per manufacturer instructions (see shipping container instructions). Please take care to use the applicable instructions for summer or winter package preparation, respectively.

| IV Bag number | Date of packaging [DD/MMM/YYYY] | Time of packaging [hh:mm] | packed by (initials) |
|---------------|------------------------------------|------------------------------|-------------------------|
| | | | |

Please tick the boxes and fill in the information below when preparing the IV bag shipment!

- | |
|--|
| <input type="checkbox"/> Validated/pre-qualified shipping container duration of time 2°C to 8°C temperature is maintained: _____ hours |
| <input type="checkbox"/> Cooling elements for provided box used according to manufacturer's instruction |

Confirmed by: _____
(print name, signature) _____ (date)

To be completed by Ambulant/Home Care Service Provider:

Shipment box unopened and content intact? YES NO **IF NO, please comment_**
_____Date and time shipment box opened: _____
(date) _____ (time)Confirmed by: _____
(print name, signature) Amb. Care Service _____ (date)

Note: If content is not intact, please do not use IV bag and inform site immediately!
If time box opened minus time of packaging exceeds the time duration the shipping container maintains 2°C to 8°C, please do not use IV bag and inform site immediately!

CONFIDENTIAL

APPENDIX XI: PROCEDURES FOR FLOW CYTOMETRY LABORATORIES SUGGESTED FOR AALL1731**Laboratory Director: Brent Wood MD, PhD (University of Washington, Seattle, WA)**

The University of Washington, Seattle Flow Cytometry Laboratory listed above is certified by the College of American Pathologists (CAP) and CLIA for the performance of clinical and immunophenotyping assays. In accordance, the laboratory maintains rigid sample handling, testing, and patient confidentiality standards, and participates in external proficiency programs. In past COG protocols, this laboratory was one of two reference laboratories performing minimal residual disease (MRD) analyses. With decentralization to COG-approved flow laboratories, the following is provided to local institutions for reference.

FLOW CYTOMETRIC TESTING FOR MRD ON DAYS 8 AND 29 OF INDUCTION

- Specimens from patients treated for B-ALL will be assessed by flow cytometry for MRD using the validated 6 color COG B-ALL MRD assay supplemented by a validated 8 color reagent combination (CART tube) to reduce dependence on CD19 for B-ALL MRD detection.
- The COG B-ALL MRD assay consists of two 6-color reagent cocktails containing antibodies against CD9, CD10, CD13/33, CD19, CD20, CD34, CD38, CD45 and CD58. A third reagent cocktail containing CD45, CD19 and SYTO16, a nucleic acid binding dye, is used to define the nucleated cell denominator. A supplemental CART tube consists of an 8-color reagent cocktail containing antibodies against CD10, CD20, CD22, CD24, CD34, CD38, CD45 and CD66b may be used for assessment of CD22 expression, which is not a therapeutic intervention planned for patients enrolled on AALL1731.
- Bone marrow specimens from patients with B-ALL will be labeled by a stain-lyse-wash method at saturating antibody concentrations using the reagent panels described above. In order to have adequate cell numbers to achieve a sensitivity of 0.01%, a sufficient number of cells will be labeled to allow a minimum of 750,000 cells to be acquired through the flow cytometer. Clusters of events that are distinct from positions occupied by normal cells will be sought on dual-parameter displays for each antigenic combination. Generally, alterations in the intensity of expression of the antigens listed above or changes in light scatter properties relative to expression of any of these markers have been most useful for discriminating normal and leukemic populations. The assay allows the consistent recognition of abnormal populations at a level of sensitivity of 1/10,000; in practice, well defined clusters can be recognized when they constitute as few as 10 cells, so that in many cases sensitivity is better than 1/10,000. Cases in which additional reagent panels were found to be more informative may be tested with those panels.

MRD TESTING AT END OF CONSOLIDATION (EOC):

NOTE: The EOC BM MRD assessment is a REQUIRED observation for NCI SR patients with end of Induction flow MRD $\geq 0.1\%$, and for NCI HR DS B-ALL with EOI MRD $\geq 0.01\%$, to the extent of requiring intensified therapy on the SR-High arm for non-DS and the DS-High arm for DS patients.

Should treating clinicians choose to perform this assessment for NCI SR B-ALL patients with EOI BM flow MRD 0.01-0.099%, MRD results should be submitted. All patients will also have the option of submitting material for Biobanking for Future Research (See [Section 14.5](#)).

The local institution should send a sample of the EOC BM aspiration directly to the University of Washington's COG-approved Flow Cytometry Reference Laboratory in accordance with the instructions in [Section 14.4](#). **If this specimen is not sent, the patient will be ineligible to receive post-Consolidation therapy on study.**

Due to the importance of accurate MRD enumeration for risk-stratification, institutions are encouraged to send the first pull of bone marrow for MRD evaluations whenever possible. If for some reason no specimen will be sent, the study coordinator should be notified.

Reporting:

Results of MRD testing on the EOC BM will be communicated to each local institution by the Flow Cytometry Reference Laboratory via Medidata Rave.

APPENDIX XII: PROCEDURES FOR HIGH-THROUGHPUT SEQUENCING METHOD OF MRD ANALYSIS

DNA will be isolated from bone marrow (BM) sent from COG Leukemia Molecular Reference Laboratory and Biospecimen Bank at Nationwide Children's Hospital (NWC) in Columbus, Ohio to the CLIA/Cap certified laboratory of Adaptive Biotechnologies, Seattle, Washington for IgH clonality and MRD assays using the QIAmp DNA mini kit. DNA extracted from peripheral blood (PB) at NWC will be sent to Adaptive Biotechnologies. Routinely 400 ng of genomic DNA/locus analyzed is used for the identification of dominant sequences in the sample of interest and, in general the IgH (V(D)J/ DJ) are studied in patients with B-cell precursor ALL. Therefore approximately 1 (one) microgram of genomic DNA should be set aside for this purpose from the initial diagnostic samples. Dominant sequence(s) roughly correlated with the blast count of the diagnostic specimens are defined using the following guidance:

1. >3% of all like sequences for the locus under study
2. >0.2% of the total nucleated cell number in the diagnostic specimen
3. A discontinuous distribution of clonal sequences (e.g., the dominant sequence must have no more than five sequences found in the next decile of sequence frequency beneath it)
4. > 40 estimated templates for any given dominant sequence

Once the dominant sequence(s) is identified it is available for tracking in subsequent samples from the same patient. Upon receipt of genomic DNA extracted from a subsequent bone marrow or peripheral blood sample from any given patient for whom a dominant sequence(s) has been identified a complete repertoire of the Ig is performed but, in addition, the specific sequence(s) previously identified in the diagnostic specimen is specifically searched for and quantitated.

Specimens:

Bone Marrow: For each time point 3-5 mL of BM should be obtained in a SM tube or purple top (EDTA) tube.

All SR-Avg patients will have frozen a BM pellet from diagnostic BM sample sent for clonality and a frozen BM pellet from the EOI BM sample sent for HTS-MRD (REQUIRED).

SR-High patients with EOI MRD $\geq 0.01\%$ by flow cytometry will have a frozen BM pellet from the diagnostic BM sample sent for clonality and frozen BM pellets from the EOI and EOC BM samples sent for HTS-MRD (OPTIONAL)

Peripheral blood (PB): 3-5 mL PB in purple top (EDTA)

SR-Avg and SR-High patients will have DNA extracted from the EOI PB sample at the COG Leukemia Molecular Reference Laboratory at Nationwide Children's and sent to Adaptive Biotechnologies for HTS-MRD (OPTIONAL)

Specimen Acquisition: Clinical samples will be sent to the COG Leukemia Molecular Reference Laboratory and Biospecimen Bank at Nationwide Children's Hospital (NWC) in Columbus, Ohio.

This CAP/CLIA-certified laboratory is run by Drs. Julie Gastier-Foster and Shalini Reshma. Frozen BM pellets and/or DNA extracted from PB will then be batched at the central COG laboratory and sent to Adaptive Biotechnologies (Seattle, WA) for high-throughput sequencing analysis.

Processing: gDNA extracted from frozen BM pellets will be utilized in the high-throughput sequencing analysis.

The results of an MRD determination is a continuously distributed variable down to the LOD of the assay, the LOD being a function of the number of cells that are analyzed in a given reaction.

Assay sensitivity (Limit of Detection (LOD)) is defined as the lowest number of lymphocyte input templates that the bioanalytical method can detect. The lower limit of quantitation (LLOQ) is the lowest number of input lymphocyte template that can be reliably quantitated across multiple dilution curves. Data for LOD and LLOQ can also be expressed as a percentage of the total T cell templates or total cells present in a sample.

To determine the LOD and LLOQ, we designed an experiment consisting of a dilution series of seven samples containing a monoclonal sample (100% of a single TCRG or IgH clone from a T-cell Acute Lymphoblastic Leukemia (T-ALL) or a B-cell precursor Acute Lymphoblastic Leukemia (B-ALL) cell line (Coriell Institute)). Each initial dilution sample contained 10% of the reference T-ALL or B-ALL clonal DNA, 10% of a diverse, non-reference PBMCs, and 80% fibroblast (non-amplifiable) DNA. The combined mixture of lymphoid and fibroblast DNA is representative of clinical test samples that contain a combination of amplifiable (lymphocytes) and non-amplifiable DNA (non-lymphocyte) targets.

In a representative experiment the sensitivity data shows that we reliably detected the reference clone at input templates levels from 50,654 to 5.59 templates (i.e., cells) from where the reference clone was observed at the levels in the top five dilutions (50%, 5%, 0.5%, 0.05%, 0.005% cell input) across all three experiments. At lower dilutions (0.0005% and 0.00005%) the reference clone was able to be detected in only one or two reactions and showed the expected dropouts due to low input sampling effects while maintaining linearity with other data points.

Limit of Detection (LOD): Based on the dilution series the sensitivity of this assay was determined to 0.302 reference cell input templates (0.00005% cell input dilution sample). This was equivalent to 1 cell per 1,635,107 detection sensitivity in the total input cell DNA (data not shown), and corresponds to the clinical measurement of minimal residual disease (MRD).

Lower Limit of Quantitation (LLOQ): Based on the dilution series, the LLOQ of this assay was determined to be 5.15 reference cell input templates (0.005% cell input dilution sample), using the average detection levels across the three experiments. This was measured to be 5.0×10^{-3} % (1 cell per 20,089) LLOQ of the total input cell DNA and equivalent to 1 cell per 100,445 LLOQ in the total input cell DNA, and corresponds to the clinical measurement of minimal residual disease (MRD).

Analysis Plan:

In order to measure the strength of association between the BM and PB MRD as determined by the highly sensitive DNA-based MRD detection method of HTS of IgH loci in NCI SR B-ALL patients at EOI, we will use the Kendall's Tau-b rank correlation coefficient³⁰ accounting for the left censoring inherent to sensitivity of the method³⁰. A high positive value would be strong evidence that the PB retains the relative information contained in the BM readings. An estimate and 95% Confidence interval will be calculated using banked SR-Average and SR-High samples at EOI. Available samples will be chosen sequentially until n=1,000 successfully measured pairs are attained. This would allow a 95% confidence interval of width 0.069 at r=0.4, width 0.053 at r=0.6, and width 0.03 at r=0.8¹⁸⁹.

In order to measure the strength of association between flow cytometry-determined MRD and HTS of IgH loci determined-MRD from the BM at EOC in NCI SR B-ALL patients who are MRD positive by flow cytometry at EOI, we will use the Kendall's Tau-b rank correlation coefficient accounting for the left censoring inherent to sensitivity of the methods³⁰. A high positive value would be strong evidence that HTS of IgH loci determined-MRD from the BM at EOC retains the relative information contained in the flow-cytometry-determined readings. An estimate and 95% Confidence interval will be calculated using pairs of banked samples at EOC. All available samples will be used. Since about 70% of SR-High subjects will be MRD positive by flow cytometry at EOI, and expecting 5% of subjects will not have available or determinate readings for the HTS MRD at EOC, we expect n=92 subjects/year to be evaluable for this objective, or n=460 over the 5 years of enrollment. This would allow a 95% confidence interval of width 0.102 at r=0.4, width 0.078 at r=0.6, and width 0.044 at r=0.8¹⁸⁹. Further, exploratory analysis will seek to determine the prognostic significance of a positive EOC test by BM HTS MRD at EOC on DFS and OS outcomes.

APPENDIX XIII: FLOW CYTOMETRIC TESTING FOR MINIMAL MARROW AND MINIMAL RESIDUAL DISEASE IN B-LLY PATIENTS

Hypothesis: Minimal marrow disease (MMD) at diagnosis and minimal residual disease at the end of Induction can be correlated with outcome and be used in risk stratification.

Procedure:

1. A copy of the pathology report of the original biopsy establishing the diagnosis has to be included with the bone marrow sample at diagnosis.
2. Bone marrow samples of B-Lly patients who consent to the optional studies will be collected at diagnosis and end of induction and shipped to the laboratory of Dr. Rodney Miles at the University of Utah Laboratories.
3. Samples will be analyzed by flow cytometry using the COG-approved procedure for evaluation of MRD in B-ALL. In brief, samples will be tested against a template known to outline normal pathways of B-cell differentiation. Generally, alterations in the intensity of expression of CD9, CD10, CD13, CD19, CD20, CD33, CD34, CD38, CD45 or CD58; or changes in light scatter properties relative to expression of any of these markers have been most useful for discriminating normal and abnormal populations. In order to have adequate cell numbers to achieve sensitivity, a sufficient number of cells will be labeled to allow a minimum of 750,000 cells to be acquired through the flow cytometer. Clusters of events that are distinct from positions occupied by normal cells will be sought on dual-parameter displays of antigenic intensity, using the diagnostic displays as a guide. Clusters of events will allow the recognition of abnormal populations at a level of sensitivity of 1/10,000; in practice, well defined clusters can be recognized when they constitute as few as 15-20 cells, so that in many cases sensitivity is better than 1/10,000.
4. Reporting: MMD and MRD testing is performed on a research basis. Results do not affect any treatment decisions on this protocol and will NOT be communicated to the local institution, but will be stored in an electronic database.

APPENDIX XIV: CONTACTS FOR TREATMENT PLAN INQUIRIES BY GEOGRAPHICAL DISTRIBUTION**Institutions in the Eastern Division: Eastern US, and Eastern Canada (Ontario, Quebec, Nova Scotia, and Newfoundland)**

- Address questions regarding treatment plans to the following:
 - Study Co-Chair:
Dr. Sumit Gupta
The Hospital for Sick Children
 - Study Vice Chair:
Dr. Anne Angiolillo
Children's National Medical Center

Institutions in the Western Division: Western US, Australia, New Zealand, and Western Canada (British Columbia, Alberta, Saskatchewan and Manitoba)

- Address questions regarding treatment plans to the following:
 - Study Co-Chair:
Dr. Rachel Rau
Baylor College of Medicine
 - Study Vice Chair:
Dr. Karen Rabin
Baylor College of Medicine

APPENDIX XV: PATIENT CLINICAL TRIAL WALLET CARD

THE WALLET CARD IS FOR PATIENTS TO SHARE IMPORTANT CLINICAL TRIAL INFORMATION WITH THEIR OTHER HEALTHCARE PROVIDERS. THE PATIENT CLINICAL TRIAL WALLET CARD MUST BE PROVIDED TO THE PATIENT AT THE TIME OF ENROLLMENT. IT'S A CONVENIENT WALLET-SIZED INFORMATION CARD FOR THE PATIENT TO CUT OUT AND RETAIN AT ALL TIMES. THE SITES MUST COMPLETE THE FILLABLE FIELDS BEFORE GIVING THE CARD TO PATIENT.



NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

Version JAN/2019

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

REFERENCES

1. Nguyen K, Devidas M, Cheng SC, et al: Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia 22:2142-50, 2008
2. Mattano LA DM, Friedmann AM, et al: Outstanding Outcome for Children with Standard Risk-Low (SR-Low) Acute Lymphoblastic Leukemia (ALL) and No Benefit to Intensified Peg-Asparaginase (PEG-ASNase) Therapy: Results of Children's Oncology Group (COG) Study AALL0331. Blood 111:5477-5485, 2014
3. Larsen RA SW, Devidas M, et al: Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Oncology Group Study AALL0232. J Clin Oncol 29:Abstract 3, 2011
4. Sun W, Malvar J, Spoto R, et al: Re-Induction Outcome for Pediatric Patients with Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia: A Retrospective Cohort Study of the Therapeutic Advances in Childhood Leukemia Consortium. Blood 126:3760-3760, 2015
5. Roberts KG, Li Y, Payne-Turner D, et al: Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 371:1005-15, 2014
6. Mattano LA, Devidas M, Friedmann AM, et al: Outstanding Outcome for Children with Standard Risk-Low (SR-Low) Acute Lymphoblastic Leukemia (ALL) and No Benefit to Intensified Peg-Asparaginase (PEG-ASNase) Therapy: Results of Children's Oncology Group (COG) Study AALL0331. Blood 124:793-793, 2014
7. O'Connor D, Enshaei A, Bartram J, et al: Genotype-Specific Minimal Residual Disease Interpretation Improves Stratification in Pediatric Acute Lymphoblastic Leukemia. J Clin Oncol 36:34-43, 2018
8. Borowitz MJ, Pullen DJ, Shuster JJ, et al: Minimal residual disease detection in childhood precursor-B-cell acute lymphoblastic leukemia: relation to other risk factors. A Children's Oncology Group study. Leukemia 17:1566-72, 2003
9. Winick NJ, Devidas M, Maloney KW, et al: The impact of initial cerebrospinal fluid (CSF) findings on outcome among patients with NCI standard (SR) and high-risk (HR) B-lymphoblastic leukemia (ALL): A report from the Children's Oncology Group (COG) Studies AALL0331 and AALL0232. Journal of Clinical Oncology 32:10016-10016, 2014
10. Anne Angiolillo M, Reuben Schore, MD1, Meenakshi Devidas, Xiaomin Lu, PhD, Karen R. Rabin, MD, PhD, Patrick A. Zweidler-McKay, MD, PhD, Michael Borowitz, MD, PhD, Brent Wood, MD PhD, Andrew J. Carroll III, PhD, Nyla A. Heerema, PhD, Cindy Wang, MS, Kelly Maloney, MD, Naomi Winick, MD, William L. Carroll, MD, Elizabeth A. Raetz, MD, Mignon L. Loh, MD and Stephen P. Hunger, MD: Intensification of Oral Methotrexate Is Not Superior to Standard Methotrexate Dosing during Maintenance in Children with National Cancer Institute (NCI) Standard-Risk B Acute Lymphoblastic Leukemia (SR B-ALL): A Report from Children's Oncology Group (COG) Study AALL0932. ASH, 2017
11. Gaynon PS, Steinherz PG, Bleyer WA, et al: Intensive therapy for children with acute lymphoblastic leukaemia and unfavourable presenting features. Early conclusions of study CCG-106 by the Childrens Cancer Study Group. Lancet 2:921-4, 1988
12. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. Lancet 347:1783-8, 1996
13. Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol 30:1663-9, 2012

14. Moricke A, Zimmermann M, Reiter A, et al: Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. *Leukemia* 24:265-84, 2010
15. Pui CH, Boyett JM, Relling MV, et al: Sex differences in prognosis for children with acute lymphoblastic leukemia. *J Clin Oncol* 17:818-24, 1999
16. Silverman LB, Stevenson KE, O'Brien JE, et al: Long-term results of Dana-Farber Cancer Institute ALL Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1985-2000). *Leukemia* 24:320-34, 2010
17. Conklin HM, Krull KR, Reddick WE, et al: Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia. *J Natl Cancer Inst* 104:1386-95, 2012
18. Duffner PK, Armstrong FD, Chen L, et al: Neurocognitive and neuroradiologic central nervous system late effects in children treated on Pediatric Oncology Group (POG) P9605 (standard risk) and P9201 (lesser risk) acute lymphoblastic leukemia protocols (ACCL0131): a methotrexate consequence? A report from the Children's Oncology Group. *J Pediatr Hematol Oncol* 36:8-15, 2014
19. Borowitz MJ, Devidas M, Hunger SP, et al: Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood* 111:5477-85, 2008
20. Termuhlen AM, Smith LM, Perkins SL, et al: Outcome of newly diagnosed children and adolescents with localized lymphoblastic lymphoma treated on Children's Oncology Group trial A5971: a report from the Children's Oncology Group. *Pediatr Blood Cancer* 59:1229-33, 2012
21. Termuhlen AM, Smith LM, Perkins SL, et al: Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *Br J Haematol* 162:792-801, 2013
22. Wu D, Emerson RO, Sherwood A, et al: Detection of minimal residual disease in B lymphoblastic leukemia by high-throughput sequencing of IGH. *Clin Cancer Res* 20:4540-8, 2014
23. Kotrova M, Muzikova K, Mejstrikova E, et al: The predictive strength of next-generation sequencing MRD detection for relapse compared with current methods in childhood ALL. *Blood* 126:1045-7, 2015
24. Wood B, Wu D, Crossley B, et al: Measurable residual disease detection by high throughput sequencing improves risk stratification for pediatric B-ALL. *Blood*, 2017
25. Topp MS, Gokbuget N, Stein AS, et al: Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 16:57-66, 2015
26. Kantarjian H, Stein A, Gokbuget N, et al: Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med* 376:836-847, 2017
27. Gokbuget N, Zugmaier G, Klinger M, et al: Long-term relapse-free survival in a phase 2 study of blinatumomab for the treatment of patients with minimal residual disease in B-lineage acute lymphoblastic leukemia. *Haematologica* 102:e132-e135, 2017
28. Gokbuget N, Dombret H: Blinatumomab for minimal residual disease in adults with B-precursor acute lymphoblastic leukemia. 2018
29. Goekbuget N, Dombret H, Bonifacio M, et al: BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE[®]) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL). *Blood* 124:379-379, 2014
30. von Stackelberg A, Locatelli F, Zugmaier G, et al: Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia. *J Clin Oncol* 34:4381-4389, 2016

31. Maude SL, Teachey DT, Porter DL, et al: CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood* 125:4017-23, 2015
32. Buitenkamp TD, Izraeli S, Zimmermann M, et al: Acute lymphoblastic leukemia in children with Down syndrome: a retrospective analysis from the Ponte di Legno study group. *Blood* 123:70-7, 2014
33. Meyr F, Escherich G, Mann G, et al: Outcomes of treatment for relapsed acute lymphoblastic leukaemia in children with Down syndrome. *Br J Haematol* 162:98-106, 2013
34. Hitzler JK, He W, Doyle J, et al: Outcome of transplantation for acute lymphoblastic leukemia in children with Down syndrome. *Pediatr Blood Cancer* 61:1126-8, 2014
35. Rabin KR, Hitzler J, Rodriguez V, et al: Treatment-Related Mortality (TRM) in Children with Down Syndrome (DS) and B-Lymphoblastic Leukemia (B-ALL): An Interim Report from the Children's Oncology Group Trials AALL0932 and AALL1131. *Blood* 126:2502-2502, 2015
36. Wadhwa A, Kutny MA, Xavier AC: Blinatumomab activity in a patient with Down syndrome B-precursor acute lymphoblastic leukemia. *Pediatr Blood Cancer* 65, 2018
37. Conter V, Bartram CR, Valsecchi MG, et al: Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. *Blood* 115:3206-14, 2010
38. Borowitz MJ, Wood BL, Devidas M, et al: Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 126:964-71, 2015
39. Borowitz MJ, Devidas M, Hunger SP, et al: Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood* 111:5477-85, 2008
40. Pui CH, Pei D, Coustan-Smith E, et al: Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: a prospective study. *Lancet Oncol* 16:465-74, 2015
41. Coustan-Smith E, Sancho J, Hancock ML, et al: Use of peripheral blood instead of bone marrow to monitor residual disease in children with acute lymphoblastic leukemia. *Blood* 100:2399-402, 2002
42. Logan AC, Vashi N, Faham M, et al: Immunoglobulin and T cell receptor gene high-throughput sequencing quantifies minimal residual disease in acute lymphoblastic leukemia and predicts post-transplantation relapse and survival. *Biol Blood Marrow Transplant* 20:1307-13, 2014
43. Wu J, Jia S, Wang C, et al: Minimal Residual Disease Detection and Evolved IGH Clones Analysis in Acute B Lymphoblastic Leukemia Using IGH Deep Sequencing. *Front Immunol* 7:403, 2016
44. O'Connor D, Bate J, Wade R, et al: Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. *Blood* 124:1056-61, 2014
45. Lund B, Wesolowska-Andersen A, Lausen B, et al: Host genome variations and risk of infections during induction treatment for childhood acute lymphoblastic leukaemia. *Eur J Haematol* 92:321-30, 2014
46. Zapata-Tarres M, Arredondo-Garcia JL, Rivera-Luna R, et al: Interleukin-1 receptor antagonist gene polymorphism increases susceptibility to septic shock in children with acute lymphoblastic leukemia. *Pediatr Infect Dis J* 32:136-9, 2013
47. Roncadin C, Hitzler J, Downie A, et al: Neuropsychological late effects of treatment for acute leukemia in children with Down syndrome. *Pediatr Blood Cancer* 62:854-8, 2015
48. Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, et al: Behavioral and educational limitations after chemotherapy for childhood acute lymphoblastic leukemia or Wilms tumor. *Cancer* 106:2067-75, 2006
49. Landier W, Hughes CB, Calvillo ER, et al: A grounded theory of the process of adherence to oral chemotherapy in Hispanic and caucasian children and adolescents with acute lymphoblastic leukemia. *J Pediatr Oncol Nurs* 28:203-23, 2011

50. Johnson SB, Riis JL, Noble KG: State of the Art Review: Poverty and the Developing Brain. *Pediatrics* 137, 2016
51. Kunin-Batson A, Kadan-Lottick N, Neglia JP: The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia. *Psychooncology* 23:692-9, 2014
52. Patel SK, Wong AL, Cuevas M, et al: Parenting stress and neurocognitive late effects in childhood cancer survivors. *Psychooncology* 22:1774-82, 2013
53. Meyers A, Cutts D, Frank DA, et al: Subsidized housing and children's nutritional status: data from a multisite surveillance study. *Arch Pediatr Adolesc Med* 159:551-6, 2005
54. Cook JT, Frank DA, Berkowitz C, et al: Food insecurity is associated with adverse health outcomes among human infants and toddlers. *J Nutr* 134:1432-8, 2004
55. Frank DA, Neault NB, Skalicky A, et al: Heat or eat: the Low Income Home Energy Assistance Program and nutritional and health risks among children less than 3 years of age. *Pediatrics* 118:e1293-302, 2006
56. Black MM, Cutts DB, Frank DA, et al: Special Supplemental Nutrition Program for Women, Infants, and Children participation and infants' growth and health: a multisite surveillance study. *Pediatrics* 114:169-76, 2004
57. Bona K, London WB, Guo D, et al: Trajectory of Material Hardship and Income Poverty in Families of Children Undergoing Chemotherapy: A Prospective Cohort Study. *Pediatr Blood Cancer* 63:105-11, 2016
58. Topp MS, Zimmerman Z, Cannell P, et al: Health-Related Quality of Life (HRQoL) of Blinatumomab Versus Standard of Care (SOC) Chemotherapy in Patients with Relapsed or Refractory Philadelphia Negative B-Cell Precursor Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER). *Blood* 128:222, 2016
59. Johnston D, Gerbing R, Alonzo T, et al: Patient-Reported Outcome Coordinator Did Not Improve Quality of Life Assessment Response Rates: A Report from the Children's Oncology Group. *PLoS One* 10:e0125290, 2015
60. Coustan-Smith E, Sandlund JT, Perkins SL, et al: Minimal disseminated disease in childhood T-cell lymphoblastic lymphoma: a report from the children's oncology group. *J Clin Oncol* 27:3533-9, 2009
61. Mussolin L, Buldini B, Lovisa F, et al: Detection and role of minimal disseminated disease in children with lymphoblastic lymphoma: The AIEOP experience. *Pediatr Blood Cancer* 62:1906-13, 2015
62. Ariffin H, Omar KZ, Ang EL, et al: Severe vincristine neurotoxicity with concomitant use of itraconazole. *J Paediatr Child Health* 39:638-9, 2003
63. Bermudez M, Fuster JL, Llinares E, et al: Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. *J Pediatr Hematol Oncol* 27:389-92, 2005
64. Stock W, Douer D, DeAngelo DJ, et al: Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. *Leukemia & Lymphoma* 52:2237-2253, 2011
65. Langer T, Martus P, Ottensmeier H, et al: CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. *Med Pediatr Oncol* 38(5):320-8, 2002
66. Mulhern RK, Palmer SL: Neurocognitive late effects in pediatric cancer. *Curr Probl Cancer* 27(4):177-97, 2003
67. Harila-Saari AH, Paakko EL, Vainionpaa LK, et al: A longitudinal magnetic resonance imaging study of the brain in survivors in childhood acute lymphoblastic leukemia. *Cancer* 83(12):2608-17, 1998
68. Winick NJ, Bowman WP, Kamen BA, et al: Unexpected acute neurologic toxicity in the treatment of children with acute lymphoblastic leukemia. *J Natl Cancer Inst.* 84(4):252-6, 1992

69. Pui CH, Howard SC: Current management and challenges of malignant disease in the CNS in paediatric leukaemia. *Lancet Oncol* 9:257-68, 2008
70. Bucaneve G, Micozzi A, Menichetti F, et al: Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 353:977-87, 2005
71. Brackett J, Schafer ES, Leung DH, et al: Use of allopurinol in children with acute lymphoblastic leukemia to reduce skewed thiopurine metabolism. *Pediatr Blood Cancer* 61:1114-7, 2014
72. Schatz J, Kramer JH, Ablin A, et al: Processing speed, working memory, and IQ: a developmental model of cognitive deficits following cranial radiation therapy. *Neuropsychology* 14:189-200, 2000
73. Van den Berg HW, Desai ZR, Wilson R, et al: The pharmacokinetics of vincristine in man: reduced drug clearance associated with raised serum alkaline phosphatase and dose-limited elimination. *Cancer Chemother Pharmacol* 8:215-9, 1982
74. Group CAC: Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. *Lancet* 347:1783-8, 1996
75. Kantarjian HM, DeAngelo DJ, Stelljes M, et al: Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med* 375:740-53, 2016
76. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer* 35:1-39, 1977
77. Anderson JR, High R: Alternatives to the standard Fleming, Harrington, and O'Brien futility boundary. *Clin Trials* 8:270-6, 2011
78. Cruise MW: Immunohistochemistry in Acute Myeloid Leukemia. *Methods Mol Biol* 1633:33-49, 2017
79. Patrick K, Wade R, Goulden N, et al: Outcome of Down syndrome associated acute lymphoblastic leukaemia treated on a contemporary protocol. *Br J Haematol* 165:552-5, 2014
80. Maloney KW, Larsen E, Mattano LA, et al: Improvement in the Infection-Related Mortality for Children with Down Syndrome in Contemporary Children's Oncology Group Acute Lymphoblastic Leukemia Clinical Trials. ASPHO Annual Meeting, Plenary Session, 2008
81. Rabin KR, Hitzler J, Rodriguez V, et al: Treatment-related mortality in children with Down syndrome and B-lymphoblastic leukemia: An interim report from the Children's Oncology Group trials AALL0932 and AALL1131. *Blood* 126, 2015
82. Garrison MM, Jeffries H, Christakis DA: Risk of death for children with down syndrome and sepsis. *J Pediatr* 147:748-52, 2005
83. Barkin RM, Weston WL, Humbert JR, et al: Phagocytic function in Down syndrome--I. Chemotaxis. *J Ment Defic Res* 24 Pt 4:243-9, 1980
84. Kusters MA, Verstegen RH, Gemen EF, et al: Intrinsic defect of the immune system in children with Down syndrome: a review. *Clin Exp Immunol* 156:189-93, 2009
85. Bloemers BL, van Bleek GM, Kimpen JL, et al: Distinct abnormalities in the innate immune system of children with Down syndrome. *J Pediatr* 156:804-9, 809 e1-809 e5, 2010
86. Schoch J, Rohrer TR, Kaestner M, et al: Quantitative, Phenotypical, and Functional Characterization of Cellular Immunity in Children and Adolescents With Down Syndrome. *J Infect Dis* 215:1619-1628, 2017
87. de Hingh YC, van der Vossen PW, Gemen EF, et al: Intrinsic abnormalities of lymphocyte counts in children with down syndrome. *J Pediatr* 147:744-7, 2005
88. Ram G, Chinen J: Infections and immunodeficiency in Down syndrome. *Clin Exp Immunol* 164:9-16, 2011
89. Rabin KR, Smith J, Kozinetz CA: Myelosuppression and infectious complications in children with Down syndrome and acute lymphoblastic leukemia. *Pediatr Blood Cancer* 58:633-5, 2012
90. Damsker JM, Hansen AM, Caspi RR: Th1 and Th17 cells: adversaries and collaborators. *Ann N Y Acad Sci* 1183:211-21, 2010
91. Spitzer MH, Nolan GP: Mass Cytometry: Single Cells, Many Features. *Cell* 165:780-91, 2016

92. Wong MT, Ong DE, Lim FS, et al: A High-Dimensional Atlas of Human T Cell Diversity Reveals Tissue-Specific Trafficking and Cytokine Signatures. *Immunity* 45:442-56, 2016
93. Salazar EG, Li Y, Fisher BT, et al: Supportive care utilization and treatment toxicity in children with Down syndrome and acute lymphoid leukaemia at free-standing paediatric hospitals in the United States. *Br J Haematol* 174:591-9, 2016
94. Bi R, Liu P: Sample size calculation while controlling false discovery rate for differential expression analysis with RNA-sequencing experiments. *BMC Bioinformatics* 17:146, 2016
95. Valiathan R, Deeb K, Diamante M, et al: Reference ranges of lymphocyte subsets in healthy adults and adolescents with special mention of T cell maturation subsets in adults of South Florida. *Immunobiology* 219:487-96, 2014
96. Van Gassen S, Callebaut B, Van Helden MJ, et al: FlowSOM: Using self-organizing maps for visualization and interpretation of cytometry data. *Cytometry A* 87:636-45, 2015
97. Xu H, Robinson GW, Huang J, et al: Common variants in ACYP2 influence susceptibility to cisplatin-induced hearing loss. *Nat Genet* 47:263-6, 2015
98. Yang JJ, Cheng C, Devidas M, et al: Genome-wide association study identifies germline polymorphisms associated with relapse of childhood acute lymphoblastic leukemia. *Blood* 120:4197-204, 2012
99. Perova T, Grandal I, Nutter LM, et al: Therapeutic potential of spleen tyrosine kinase inhibition for treating high-risk precursor B cell acute lymphoblastic leukemia. *Sci Transl Med* 6:236ra62, 2014
100. Macartney S: Child Poverty in the United States 2009 and 2010: Selected Race Groups and Hispanic Origin
American Community Survey Briefs. US Census Bureau, 2011. Available at: <http://www.census.gov/prod/2011pubs/acsbr10-05.pdf>, (ed 2011)
101. Kunin-Batson A, Kadan-Lottick N, Zhu L, et al: Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 57:1197-203, 2011
102. Van Der Plas E, Erdman L, Nieman BJ, et al: Characterizing neurocognitive late effects in childhood leukemia survivors using a combination of neuropsychological and cognitive neuroscience measures. *Child Neuropsychol*:1-16, 2017
103. Hackman DA, Farah MJ: Socioeconomic status and the developing brain. *Trends Cogn Sci* 13:65-73, 2009
104. Ardila A, Rosselli M, Matute E, et al: The influence of the parents' educational level on the development of executive functions. *Dev Neuropsychol* 28:539-60, 2005
105. Brooks-Gunn J, Duncan GJ: The Effects of Poverty on Children. *The Future of Children* 7:55-71, 1997
106. Duncan GJ, Brooks-Gunn J, Klebanov PK: Economic deprivation and early childhood development. *Child Dev* 65:296-318, 1994
107. Chen E, Martin AD, Matthews KA: Trajectories of socioeconomic status across children's lifetime predict health. *Pediatrics* 120:e297-303, 2007
108. Hackman DA, Gallop R, Evans GW, et al: Socioeconomic status and executive function: developmental trajectories and mediation. *Dev Sci* 18:686-702, 2015
109. Pelletier W, Bona K: Assessment of Financial Burden as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer* 62 Suppl 5:S619-31, 2015
110. Lupien SJ, McEwen BS, Gunnar MR, et al: Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* 10:434-45, 2009
111. Blair C, Raver CC: Poverty, Stress, and Brain Development: New Directions for Prevention and Intervention. *Acad Pediatr* 16:S30-6, 2016
112. Adler NE, Newman K: Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood)* 21:60-76, 2002

113. Seeman M, Stein Merkin S, Karlamangla A, et al: Social status and biological dysregulation: the "status syndrome" and allostatic load. *Soc Sci Med* 118:143-51, 2014
114. Shonkoff JP, Garner AS, Committee on Psychosocial Aspects of C, et al: The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* 129:e232-46, 2012
115. Johnson SB, Riley AW, Granger DA, et al: The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics* 131:319-27, 2013
116. Braveman PA, Cubbin C, Egerter S, et al: Socioeconomic status in health research: one size does not fit all. *JAMA* 294:2879-88, 2005
117. Ward E, DeSantis C, Robbins A, et al: Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin* 64:83-103, 2014
118. Black MM, Cutts DB, Frank DA, et al: Special Supplemental Nutrition Program for Women, Infants, and Children participation and infants' growth and health: a multisite surveillance study. *Pediatrics* 114:169-76, 2004
119. Garg A, Toy S, Tripodis Y, et al: Addressing social determinants of health at well child care visits: a cluster RCT. *Pediatrics* 135:e296-304, 2015
120. Coleman-Jensen A NM, Andrews M and Carlson S: Household Food Security in the United States in 2013. US Department of Agriculture, Economic Research Service ERR 173, 2013
121. Cook JT, Frank DA, Casey PH, et al: A brief indicator of household energy security: associations with food security, child health, and child development in US infants and toddlers. *Pediatrics* 122:e867-75, 2008
122. Yoo JP, Slack KS, Holl JL: Material hardship and the physical health of school-aged children in low-income households. *Am J Public Health* 99:829-36, 2009
123. Zheng DJ, Shyr D, Ma C, et al: Feasibility of systematic poverty screening in a pediatric oncology referral center. *Pediatr Blood Cancer* 65:e27380, 2018
124. Hardy KK, Embry L, Kairalla JA, et al: Neurocognitive Functioning of Children Treated for High-Risk B-Acute Lymphoblastic Leukemia Randomly Assigned to Different Methotrexate and Corticosteroid Treatment Strategies: A Report From the Children's Oncology Group. *J Clin Oncol* 35:2700-2707, 2017
125. Bruner DW, Bryan CJ, Aaronson N, et al: Issues and challenges with integrating patient-reported outcomes in clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol* 25:5051-7, 2007
126. Clauer SB, Ganz PA, Lipscomb J, et al: Patient-reported outcomes assessment in cancer trials: evaluating and enhancing the payoff to decision making. *J Clin Oncol* 25:5049-50, 2007
127. Dobrozsi S, Yan K, Hoffmann R, et al: Patient-reported health status during pediatric cancer treatment. *Pediatr Blood Cancer* 64, 2017
128. Hinds PS, Brandon J, Allen C, et al: Patient-reported outcomes in end-of-life research in pediatric oncology. *J Pediatr Psychol* 32:1079-88, 2007
129. Klassen AF, Raina P, McIntosh C, et al: Parents of children with cancer: which factors explain differences in health-related quality of life. *Int J Cancer* 129:1190-8, 2011
130. Dupuis LL, Lu X, Mitchell HR, et al: Anxiety, pain, and nausea during the treatment of standard-risk childhood acute lymphoblastic leukemia: A prospective, longitudinal study from the Children's Oncology Group. *Cancer* 122:1116-25, 2016
131. Mitchell HR, Lu X, Myers RM, et al: Prospective, longitudinal assessment of quality of life in children from diagnosis to 3 months off treatment for standard risk acute lymphoblastic leukemia: Results of Children's Oncology Group study AALL0331. *Int J Cancer* 138:332-9, 2016
132. Zheng DJ, Lu X, Schore RJ, et al: Longitudinal analysis of quality-of-life outcomes in children during treatment for acute lymphoblastic leukemia: A report from the Children's Oncology Group AALL0932 trial. *Cancer* 124:571-579, 2018

133. Topp MS, Zimmerman Z, Cannell P, et al: Health-related quality of life in adults with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab. *Blood* 131:2906-2914, 2018
134. Garg A, Toy S, Tripodis Y, et al: Addressing Social Determinants of Health at Well Child Care Visits: A Cluster RCT. *Pediatrics*, 2015
135. Bona K, London WB, Guo D, et al: Prevalence and impact of financial hardship among New England pediatric stem cell transplantation families. *Biol Blood Marrow Transplant* 21:312-8, 2015
136. Hager ER, Quigg AM, Black MM, et al: Development and validity of a 2-item screen to identify families at risk for food insecurity. *Pediatrics* 126:e26-32, 2010
137. Frank DA, Casey PH, Black MM, et al: Cumulative hardship and wellness of low-income, young children: multisite surveillance study. *Pediatrics* 125:e1115-23, 2010
138. Gottlieb LM, Hessler D, Long D, et al: Effects of Social Needs Screening and In-Person Service Navigation on Child Health: A Randomized Clinical Trial. *JAMA Pediatr* 170:e162521, 2016
139. Chew LD, Griffin JM, Partin MR, et al: Validation of screening questions for limited health literacy in a large VA outpatient population. *J Gen Intern Med* 23:561-6, 2008
140. Services UHaH: U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES IMPLEMENTATION GUIDANCE ON DATA COLLECTION STANDARDS FOR RACE, ETHNICITY, SEX, PRIMARY LANGUAGE, AND DISABILITY STATUS, 2011
141. Moser A, Stuck AE, Silliman RA, et al: The eight-item modified Medical Outcomes Study Social Support Survey: psychometric evaluation showed excellent performance. *J Clin Epidemiol* 65:1107-16, 2012
142. Connor KM, Davidson JR: Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). *Depress Anxiety* 18:76-82, 2003
143. Dumas JE, Nissley J, Nordstrom A, et al: Home chaos: sociodemographic, parenting, interactional, and child correlates. *J Clin Child Adolesc Psychol* 34:93-104, 2005
144. Spitzer RL, Kroenke K, Williams JB, et al: A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 166:1092-7, 2006
145. Sternthal M, Slopen, N., & Williams, D. : RACIAL DISPARITIES IN HEALTH: How Much Does Stress Really Matter? *Du Bois Review: Social Science Research on Race* 8:95-113, 2011
146. Services UDHaH: Poverty Guidelines for the 48 Contiguous States and the District of Columbia. *Federal Register* 78:5182-5183, 2013
147. Services USDoHaH: Poverty Guidelines, 2017
148. al. JYe: Basic Facts about Low-Income Children, *Children under 18 Years, 2014*. Ney York, National Center for Children in Poverty, Mailmain Schoold of Public Health, Columbia University, 2016
149. Krieger N, Chen JT, Waterman PD, et al: Race/ethnicity, gender, and monitoring socioeconomic gradients in health: a comparison of area-based socioeconomic measures--the public health disparities geocoding project. *Am J Public Health* 93:1655-71, 2003
150. Wells DK, James K, Stewart JL, et al: The care of my child with cancer: a new instrument to measure caregiving demand in parents of children with cancer. *J Pediatr Nurs* 17:201-10, 2002
151. Klassen A, Klaassen RJ, Dix D, et al: Caregiving demands in parents of children with cancer: psychometric validation of the Care of My Child with Cancer questionnaire. *J Pediatr Nurs* 25:258-63, 2010
152. Lerner D, Parsons SK, Chang H, et al: The reliability and validity of the Caregiver Work Limitations Questionnaire. *J Occup Environ Med* 57:22-31, 2015
153. Portenoy RK, Thaler HT, Kornblith AB, et al: The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 30a:1326-36, 1994
154. Collins JJ, Byrnes ME, Dunkel IJ, et al: The measurement of symptoms in children with cancer. *J Pain Symptom Manage* 19:363-77, 2000

155. Collins JJ, Devine TD, Dick GS, et al: The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7-12. *J Pain Symptom Manage* 23:10-6, 2002
156. Pui CH, Evans WE: A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin Hematol* 50:185-96, 2013
157. Cheung YT, Krull KR: Neurocognitive outcomes in long-term survivors of childhood acute lymphoblastic leukemia treated on contemporary treatment protocols: A systematic review. *Neurosci Biobehav Rev* 53:108-20, 2015
158. Iyer NS, Balsamo LM, Bracken MB, et al: Chemotherapy-only treatment effects on long-term neurocognitive functioning in childhood ALL survivors: a review and meta-analysis. *Blood* 126:346-53, 2015
159. Jacola LM, Edelstein K, Liu W, et al: Cognitive, behavior and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukemia: A report from the Childhood Cancer Survivor Study. *The lancet. Psychiatry* 3:965-972, 2016
160. Jacola LM, Krull KR, Pui CH, et al: Longitudinal Assessment of Neurocognitive Outcomes in Survivors of Childhood Acute Lymphoblastic Leukemia Treated on a Contemporary Chemotherapy Protocol. *J Clin Oncol* 34:1239-47, 2016
161. Annett RD, Patel SK, Phipps S: Monitoring and Assessment of Neuropsychological Outcomes as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer* 62 Suppl 5:S460-513, 2015
162. Conklin HM, Ogg RJ, Ashford JM, et al: Computerized Cognitive Training for Amelioration of Cognitive Late Effects Among Childhood Cancer Survivors: A Randomized Controlled Trial. *J Clin Oncol* 33:3894-902, 2015
163. Buizer AI, de Sonneville LM, van den Heuvel-Eibrink MM, et al: Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukemia: effect of treatment intensity. *Pediatr Blood Cancer* 45:281-90, 2005
164. Buizer AI, de Sonneville LM, Veerman AJ: Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: a critical review of the literature. *Pediatr Blood Cancer* 52:447-54, 2009
165. Jacola LM, Edelstein K, Liu W, et al: Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study. *Lancet Psychiatry* 3:965-972, 2016
166. Jansen NC, Kingma A, Schuitema A, et al: Neuropsychological outcome in chemotherapy-only-treated children with acute lymphoblastic leukemia. *J Clin Oncol* 26:3025-30, 2008
167. Kadan-Lottick NS, Brouwers P, Breiger D, et al: A comparison of neurocognitive functioning in children previously randomized to dexamethasone or prednisone in the treatment of childhood acute lymphoblastic leukemia. *Blood* 114:1746-52, 2009
168. Kingma A, Van Dommelen RI, Mooyaart EL, et al: No major cognitive impairment in young children with acute lymphoblastic leukemia using chemotherapy only: a prospective longitudinal study. *J Pediatr Hematol Oncol* 24:106-14, 2002
169. Waber DP, Tarbell NJ, Kahn CM, et al: The relationship of sex and treatment modality to neuropsychologic outcome in childhood acute lymphoblastic leukemia. *J Clin Oncol* 10:810-7, 1992
170. Roncadin C, Hitzler J, Downie A, et al: Neuropsychological late effects of treatment for acute leukemia in children with down syndrome. *Pediatr Blood Cancer*, 2014
171. Konigs M, Heij HA, van der Sluijs JA, et al: Pediatric Traumatic Brain Injury and Attention Deficit. *Pediatrics* 136:534-41, 2015
172. Dennis M, Spiegler BJ, Simic N, et al: Functional plasticity in childhood brain disorders: when, what, how, and whom to assess. *Neuropsychol Rev* 24:389-408, 2014
173. Krull KR, Bhojwani D, Conklin HM, et al: Genetic mediators of neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia. *J Clin Oncol* 31:2182-8, 2013

174. Jacola LM, Hickey F, Howe SR, et al: Behavior and Adaptive Functioning in Adolescents With Down Syndrome: Specifying Targets for Intervention. *Journal of Mental Health Research in Intellectual Disabilities* 7:287-305, 2014
175. Esbensen AJ HE, Shaffer R, Chen E, Patel L, Jacola LM. : Reliability of parent report measures of executive functioning in children with Down syndrome. *Journal of the Association of Intellectual and Developmental Disabilities* in press 2018
176. Esbensen AJ HE, Shaffer R, Chen E, Patel L, Jacola LM.: Reliability of parent report measures of behavior in children with Down syndrome. *Journal of Intellectual Disability Research* in press 2018
177. Walsh KS, Noll RB, Annett RD, et al: Standard of Care for Neuropsychological Monitoring in Pediatric Neuro-Oncology: Lessons From the Children's Oncology Group (COG). *Pediatr Blood Cancer* 63:191-5, 2016
178. Gioia GA, Espy KA, Isquith PK: Behavior Rating Executive Function - Preschool Version (BRIEF-P). Lutz, FL, Psychological Assessment Resource, 2001
179. Gioia GA, Espy KA, Isquith PK: BRIEF-P: Behavior Rating Inventory of Executive Function--preschool Version: Professional Manual, Psychological Assessment Resources, 2003 pp. 48-49
180. Gioia GA, Isquith PK, Guy SC, et al: Behavior Rating of Executive Function, Second Edition (BRIEF-2). Lutz, FL, Psychological Assessment Resource, 2016
181. Roth R, Isquith PK, Gioia GA: Behavior Rating Inventory of Executive Function - Adult. Lutz, FL, Psychological Assessment Resource, 2001
182. RW RCK: Behavior Assessment System for Children, Third Edition (BASC-3), Pearson 2015
183. Harrison PL, Oakland T, Psychological C: ABAS, adaptive behavior assessment system : manual. San Antonio, Tex., Psychological Corporation, 2000
184. Varni JW, Seid M, Kurtin PS: PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 39:800-12, 2001
185. Oxelgren UW, Myrelid A, Anneren G, et al: Prevalence of autism and attention-deficit-hyperactivity disorder in Down syndrome: a population-based study. *Dev Med Child Neurol* 59:276-283, 2017
186. Xanthopoulos MS, Walega R, Xiao R, et al: Caregiver-Reported Quality of Life in Youth with Down Syndrome. *J Pediatr* 189:98-104.e1, 2017
187. Daunhauer LA, Fidler DJ, Hahn L, et al: Profiles of everyday executive functioning in young children with down syndrome. *Am J Intellect Dev Disabil* 119:303-18, 2014
188. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. *J Clin Oncol* 33:2106-11, 2015
189. Bonett D.G. and Wright T: 'Sample Size Requirements for Estimating Pearson, Kendall and Spearman Correlations.' *Psychometrika* 65:23-18, 2000