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| **PHASE III RANDOMIZED STUDY OF CHIMERIC ANTIBODY 14.18 (ch14.18) IN HIGH RISK NEUROBLASTOMA FOLLOWING MYELOABLATIVE THERAPY AND AUTOLOGOUS STEM CELL RESCUE** |
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**Executive Summary**

The enclosed statistical analysis plan (SAP) provides details of the planned analyses for the randomized subjects in the ANBL0032 study, herein referred to as Study DIV-NB-301. This SAP details the study population, efficacy, safety and pharmacokinetics data analyses, summaries and listings for the randomized subjects in the ANBL0032 study.

At the time of the first submission of marketing applications for the ANBL0032 study, United Therapeutics Corporation (UTC) will present analyses of the study data from 30 June 2009 according to the specifications outlined in this SAP. Only those data from the randomized and Stratum 07 subjects enrolled during the randomization portion of the ANBL0032 study will be included in these summaries and analyses.

After 3 years of follow-up on the last randomized subject, the available study data from 30 June 2012 and the available AdEERS data from 30 September 2012 will be analyzed according to the specifications outlined in this SAP. These analyses will only include the subjects randomized or the Stratum 07 subjects enrolled into the randomized portion of the ANBL0032 study, but will include long-term follow-up data. As of the first submission of marketing applications, the data for HACA titer, soluble IL-2 receptor levels, ch14.18 plasma levels, and RT-PCR (TLDA) results will not be available from the 30 June 2012 data cut.

Upon completion of the ANBL0032 study, final analyses (including those lab analyses missing as of the 30 June 2012 data cut) will be conducted on the randomized subjects (and Stratum 07 subject enrolled during the randomized portion of the study) and a new revision of the final study report will be issued.

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ABBREVIATIONS AND DEFINITIONS

|  |  |
| --- | --- |
| ADCC | Antibody-dependent cellular cytotoxicity |
| ADE | Adverse drug experience |
| AdEERS | Adverse Event Expedited Report |
| ALT | Alanine Aminotransferase |
| APC | Absolute phagocyte count |
| ASCT | Autologous stem cell transplant |
| CI | Confidence interval |
| CNS | Central nervous system |
| COG | Children’s Oncology Group |
| CR | Complete Response |
| CRF | Case Report Form |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events (National Cancer Institute) |
| EFS | Event-free survival |
| GFR | Glomerular filtration rate |
| GM-CSF | Granulocyte-macrophage colony-stimulating factor |
| HACA | Human anti-chimeric antibody |
| HVA | Homovanillic Acid |
| IL-2 | Aldesleukin (Interleukin -2) |
| INSS | International neuroblastoma staging system |
| ITT | Intent-To-Treat |
| MIBG | Meta-iodobenylguanidine |
| MRD | Minimal residual disease |
| MRI | Magnetic resonance imaging |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFT | Pulmonary function test |
| PR | Partial Response |
| RA | 13-cis-retinoic acid (isotretinoin) |
| RDE | Remote data entry |
| RT-PCR | Reverse transcription polymerase chain reaction |
| TLDA | Taqman® Low Density Array |
| UTC | United Therapeutics Corporation |
| VGPR | Very Good Partial Response |
| VMA | Vanillyl mandelic acid |
| WBC | White Blood Cells |
| XRT | Radiotherapy |

# PREFACE

This plan provides further details of the planned analyses for the randomized subjects and the non-randomized Stratum 07 subjects enrolled during the randomized portion of the ANBL0032 study using data as of 30 June 2009 and separately using data as of 30 June 2012, as presented in the study protocol.

# STUDY OBJECTIVES AND ENDPOINTS

The study objectives noted here are reflective of the objectives stated in Amendment #8 of the protocol, dated 12 May 2008. This amendment was the last protocol amendment in place during the randomized portion of the study. Note, however, that the long term analysis was outlined in Amendment #9 after the cessation of randomization.

## Objectives

The primary objective of this study is to determine if monoclonal antibody chl4.18 + cytokines + isotretinoin (13-cis-retinoic acid, or RA) improves event-free survival (EFS) after myeloablative therapy and autologous stem cell transplant (ASCT) as compared to RA alone, in high risk neuroblastoma subjects who have achieved a pre-ASCT response of complete response (CR), very good partial response (VGPR), or partial response (PR).

The secondary objectives of this study are to:

* Determine if monoclonal antibody chl4.18 + cytokines + RA improves overall survival (OS) after myeloablative therapy and ASCT as compared to RA alone, in high risk neuroblastoma subjects who have achieved a pre-ASCT response of CR, VGPR, or PR
* Determine if immunotherapy + RA improves EFS and OS as compared to RA alone, in the subgroup of high risk International Neuroblastoma Staging System (INSS) Stage 4 neuroblastoma subjects who have achieved a pre-ASCT response of CR, VGPR, or PR
* In the subgroup of neuroblastoma subjects who have achieved a pre-ASCT response of CR, VGPR, or PR, determine if there is a difference between the two randomized regimens in reducing the minimal residual disease (MRD) burden as detected by the following parameters: meta-iodobenylguanidine (MIBG) scan, immunocytology (ICC) of blood and bone marrow samples, RT-PCR for tyrosine hydroxylase, PGP 9.5, and MAGE-1 in blood and bone marrow
* Determine if change from baseline of MRD as measured by above parameters is associated with EFS and OS
* Determine whether tumor biology at diagnosis correlates with EFS and OS, for either of the randomized regimens
* Determine the toxicities of the combination of monoclonal ch14.18 with cytokines
* Explore the relationship between antibody-dependent cellular cytotoxicity (ADCC) and EFS
* Determine a descriptive profile of human anti-chimeric antibody (HACA) during immunotherapy
* Compare outcome data of the subjects with persistent disease documented by biopsy to the historical data for the analogous subjects from CCG-3891
* To determine the variability of RA pharmacokinetics and relationship to pharmacogenomic parameters and determine if these levels and/or genetic variations correlate with EFS or systemic toxicity

## Endpoints

The efficacy endpoints are as follows:

* The primary study endpoint will be EFS. An event is defined as a relapse, progressive disease (PD), secondary malignancy, or death. The time‑to‑event is calculated from the time of study enrollment until the first occurrence of an event or until last contact with the subject if no event occurs.
* The secondary endpoint will be OS. The event is death. The time‑to-event is calculated from the time of study enrollment until death, or until last contact with the subject if the subject does not die.

# STUDY DESIGN

This study was a multi-center, randomized, active-controlled study in subjects who had completed frontline therapy as prescribed by A3973 or other frontline therapeutic regimens and had been evaluated for pre-ASCT responses. Subjects were enrolled and randomized into Regimen A or B on Day 50 post-ASCT, up to Day 85 post-ASCT; with a special exemption up to Day 100 for those subjects with significant post-transplant complications who were ineligible for registration on Day 85 due only to a delay caused by a specific complication. These exempt subjects were allowed to enroll on study between Day 85 and 100 with permission of the study chair once their complications had resolved.

Regimen A consisted of oral intake of RA starting on approximately Day 67 post-ASCT twice a day for 14 days every 28 days, for 6 courses. Regimen A will be referred to as “RA alone” for all data summarizations. For Regimen B, subjects received oral RA as in Regimen A, as well as 5 courses of ch14.18 + cytokines; with ch14.18 + Granulocyte-macrophage colony-stimulating factor (GM-CSF) administered in Courses 1, 3, and 5, and ch14.18 + aldesleukin (IL-2) given in Courses 2 and 4. The intervals between antibody administrations were 28 days for all courses. Regimen B will be referred to as “immunotherapy + RA” for all data summarizations.

Upon completion of the randomized therapy, subjects were to be followed every 3 months for one year, every 6 months from 1 to 5 years and annually after 5 years.

# RANDOMIZATION

Randomization to Regimens A or B was stratified by pre-ASCT CR versus VGPR versus PR and by purging vs. non-purging of the stem cells for ASCT. Randomization to a treatment group occurred in real-time within the Children’s Oncology Group (COG) based on the balance existing at that time within stratification “blocks”. This study was started in the COG’s Remote Data Entry (RDE1) system which included an algorithm to accomplish this randomization in real-time and then moved into their enhanced RDE system which made use of stratified permuted blocks to maintain balance with blocks. The one exception to randomization was for those subjects at the post ASCT/radiotherapy (XRT) evaluation who had persistent active disease documented by biopsy. These subjects (Stratum 07) were non-randomly assigned to Regimen B (immunotherapy + RA). Those who did not undergo biopsy were randomized, as all other subjects, to Regimens A or B.

Subjects randomized into the ANBL0032 study prior to the randomization halt will be analyzed in the treatment group to which they were randomized. Crossover subjects (those randomized to RA‑only who later crossed over into the non-randomized portion of the study and received immunotherapy only) will be analyzed as randomized and censored at the point of crossover for all efficacy analyses.

# STRATIFICATION

Randomization was stratified by pre-ASCT response status, CR vs. VGPR vs. PR and by pre-ANBL0032 treatment, as follows:

1. subject was randomized to receive purged stem cells in study A3973;
2. subject was randomized to receive unpurged stem cells in study A3973;
3. subject was not enrolled on but was treated per A3973 with purged stem cells;
4. subjects was not enrolled on but treated per A3973 with unpurged stem cells;
5. subject was treated per the POG 9341/9342 or CCG-3891 protocols;
6. subject was enrolled on or treated per ANBL02P1;
7. subject was enrolled on or treated per ANBL0532;
8. subject was treated per 9640;
9. subject was treated per ANBL00P1;
10. subject was treated per CHP594/DFCI34-DAT;
11. subject was treated per NANT 2001-02;
12. subject was enrolled on or treated per ANBL07P1 or,
13. other treatment.

In addition to the subjects randomized on ANBL0032, there was a small cohort of subjects who were not randomized. The subjects with persistent disease documented by biopsy post-ASCT/XRT (Stratum 07) were enrolled on the study and assigned to receive Regimen B. Based on results from CCG-3891, 11.6% of subjects were predicted to fall into Stratum 07, i.e., about 37 subjects. These subjects will be excluded from the analysis of the comparison of the two treatment arms.

Strata (pre-ASCT response; pre-ANBL0032 treatment group)

01 = CR; A3973 purged arm

02 = CR; A3973 not purged arm

03 = VGPR; A3973 purged arm

04 = VGPR; A3973 not purged arm

05 = PR; A3973 purged arm

06 = PR; A3973 not purged arm

07 = post-ASCT persistent disease documented by biopsy (assigned to Regimen B)

08 = CR; not enrolled on but treated per A3973, purged stem cells

09 = CR; not enrolled on but treated per A3973, unpurged stem cells

10 = VGPR; not enrolled on but treated per A3973, purged stem cells

11 = VGPR; not enrolled on but treated per A3973, unpurged stem cells

12 = PR; not enrolled on but treated per A3973, purged stem cells

13 = PR; not enrolled on but treated per A3973, unpurged stem cells

14 = CR; treated on or per POG 9341/9342 or CCG-3891

15 = VGPR; treated on or per POG 9341/9342 or CCG-3891

16 = PR; treated on or per POG 9341/9342 or CCG-3891

17 = CR; treated with SINGLE TRANSPLANT on or per ANBL02P1, NANT2001-02, ANBL0532 or ANBL07P1

18 = VGPR; treated with SINGLE TRANSPLANT on or per ANBL02P1, NANT2001-02, ANBL0532 or ANBL07P1

19 = PR; treated with SINGLE TRANSPLANT on or per ANBL02P1, NANT2001-02, ANBL0532 or ANBL07P1

20 = CR; other treatment

21 = VGPR; other treatment

22 = PR; other treatment

23 = CR; treated with TANDEM TRANSPLANT on or per ANBL0532, 9640, ANBL00P1, CHP594, or DFCI34-DAT

24 = VGPR; treated with TANDEM TRANSPLANT on or per ANBL0532, 9640, ANBL00P1, CHP594, or DFCI34-DAT

25 = PR; treated with TANDEM TRANSPLANT on or per ANBL0532, 9640, ANBL00P1, CHP594, or DFCI34-DAT

Note that all strata except Stratum 07 were randomized to treatment (Regimen A or B).

# SEQUENCE OF PLANNED ANALYSES

At the time of writing this analysis plan, an interim analysis had been completed by the COG (13 January 2009) on 251 subjects; 113 randomized to Regimen A, 113 randomized to Regimen B (immunotherapy) and 25 in Stratum 07 assigned to Regimen B. The results of this interim analysis lead to Amendment #9 and the cessation of randomization into the study due to reaching the interim monitoring boundary for large early benefit of immunotherapy. The study and its interim results which showed the benefits of immunotherapy were subsequently published in the New England Journal of Medicine in September 2010 (See Appendix 14.5). Upon initiation of Amendment #9, all subjects were either switched to, continued on, or enrolled into Regimen B (immunotherapy) and Regimen A was closed to accrual; thus the study is non-randomized moving forward.

Therefore, the ANBL0032 study will be summarized and analyzed in three distinct parts: the data from the randomized subjects in the study through 30 June 2009, the long-term follow-up data from the randomized subjects in the study through 30 June 2012 and the data from the non-randomized subjects (those enrolled into the study after the randomization was halted) in the study.

***Analysis of Randomized Subjects in the Study (Soft Lock)***

The randomized subjects in the study will be summarized and analyzed using the database as it existed as of 30 June 2009. This dataset contains 251 subjects; 113 randomized to Regimen A, 113 randomized to Regimen B and 25 additional subjects from Stratum 07 that were non‑randomized to Regimen B. All data from the case report form (CRF) as of 30 June 2009 will be included in the “soft lock database”. Once the COG statistician has reviewed the soft lock database and approved its release, the data cut will first be released to the COG statistician and subsequently the sponsor statistician for analysis and summary.

The randomized subjects will also be summarized and analyzed using the database as it existed as of 30 June 2012. Since this study will be ongoing at the time of the analysis, the data cut will be taken and all data collected to date will be included in this soft lock. Once the available data have been reviewed by the COG statistician, the database will first be released to the COG statistician and subsequently the sponsor statistician for analysis and summary. This dataset contains 255 subjects; 114 randomized to Regimen A, 114 randomized to Regimen B and 27 additional subjects from Stratum 07 that were non-randomized to Regimen B.

***Analysis of Non-Randomized Subjects in the Study (Soft Lock)***

The analyses of the non-randomized subjects in the study will be detailed in a separate statistical analysis plan.

# SAMPLE SIZE CONSIDERATIONS

For the randomized portion of the ANBL0032 study:

In consideration of the potential for study drug licensure, this study was powered at a level of 0.025 (i.e., a level of 0.05 in a two-sided test) to address the primary objective, involving the intent-to-treat cohort of all eligible randomized subjects. This required n=386, as shown in . However, a result of p<0.05 in a one-sided test was considered successful by COG members. At a level of 0.05 in a one-sided test, a sample size of 328 INSS Stage 4 subjects was to provide sufficient power for inferential testing within that cohort. Within each of the cohorts shown in , the following criteria were used to determine the required sample size:

Primary endpoint: Event-free survival (EFS)

Control 3-year EFS: 50% (Post ASCT)

Experimental 3-year EFS: 65% (Post ASCT)

Monitoring Method: Fleming-Harrington-O’Brien boundary calculated every 6 months, starting after 20% of the planned events have occurred. Note, after the first six interim analyses employed the Fleming-Harrington-O’Brien boundary calculation (Spring 2006 through Fall 2008), the DMC requested that the boundary be changed to a Lan-DeMets boundary. Therefore the Lan-DeMets boundary calculation was applied to all subsequent interim analyses starting with the Spring 2009 analysis.

Assumptions:

1. Proportional Hazards with average post- versus pre- 3-year hazard ratio of 25%;
2. Approximately 10% of subjects will be lost to follow-up; and,
3. ~ 85% of study subjects will be INSS Stage 4.

Follow-up: To event, or study end, whichever is first

Note that the ‘clock starts’ for duration of EFS time at the time of post-transplant randomization, i.e., study enrollment.

Table 7‑ Sample size required to detect a difference of 15% (50% vs. 65%) in a one‑sided log-rank test

|  |  |  |
| --- | --- | --- |
| **Cohort** | **Sample Size** | **Power** |
| 0.025 level test for All Eligible Subjects: |  |  |
| CR, VGPR, & PR | 386 | 80% |
| CR & VGPR | 281 | 62% |
|  |  |  |
| 0.05 level test for INSS Stage 4 |  |  |
| CR, VGPR, & PR | 328 | 85% |
| CR & VGPR | 238 | 74% |

In summary, to achieve 80% power at a level of 0.025 in the one-sided (i.e., 0.05 level two‑sided) EFS comparison of the two treatment arms, the sample size of randomized eligible subjects required was 386.

# ANALYSIS POPULATIONS

The *Randomized Intent-to-Treat* (or Randomized ITT) population is defined as all eligible subjects randomized into the study; which does not include Stratum 07 subjects. All subjects will be counted in the group to which they were randomized, regardless of the treatment they were actually given. All original stratification information used in the randomization procedure will be used, regardless of whether it was later found to be incorrect. All efficacy analyses will be performed on this Randomized ITT population, unless otherwise noted. Stratum 07 subjects will be analyzed separately for efficacy and this population will be noted as “Stratum 07 Population”.

The analyses of EFS and OS will be performed in two different Randomized ITT cohorts based on the subject’s INSS stage, although the primary analysis is based on cohort (a) below. The two cohorts of subjects are:

1. All Randomized ITT subjects with pre-ASCT response of CR, VGPR or PR
2. All INSS Stage 4 Randomized ITT subjects with pre-ASCT responses of CR, VGPR or PR

The *Randomized + Stratum 07 Safety* population is defined as all subjects in the study actually receiving study drug, which will include the Stratum 07 subjects enrolled during the randomized portion of the study. All subjects will be counted in the group corresponding to the treatment that they actually received. All safety analyses will be performed on the Safety population.

When outputs, such as subject accountability, are presented using the full population of enrolled subjects, the population will be noted as “Randomized + Stratum 07 Population”.

With respect to the Stratum 07 subjects, in order to differentiate those who enrolled during the randomized phase of the study from those who enrolled after randomization was halted, the population enrolled during the randomized phase will be labeled “Stratum 07 (enrolled up to 13JAN2009)”.

There were four crossover subjects in this study, defined as those subjects randomized to RA alone who later crossed over into the non-randomized portion of the study and received immunotherapy only. These four crossover subjects were part of the Randomized ITT population, as well as the Randomized + Stratum 07 Safety population. For efficacy analyses, these four subjects were analyzed as randomized and censored at the point of crossover. For safety analyses, these four subjects were analyzed in the RA alone arm until the point of crossover, at which time they were then analyzed in the immunotherapy + RA arm.

# GENERAL CONSIDERATIONS FOR DATA ANALYSES

All of the data collected in the CRF will be listed. In general, listings will be sorted by treatment group, subject number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), and study day. For data collected on a fixed schedule, the assessment identifier will also be included on the listing.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group and overall. For continuous variables, the summary statistics will include the mean, standard deviation, median, minimum, and maximum. Minimums and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal point. If a rounded value results in ‑0.0, the negative sign will be removed to avoid confusion. For discrete variables, summaries will include the frequency and percent in each category. Percentages will be rounded to one decimal point. In general, the denominator for percentages will be the population being summarized (i.e., safety population), except in the cases where summarization is at the course level or summarization is specific to an assessment. When a summary is produced within each course, the number of subjects exposed to study treatment within each course will be used as the denominator for percentage calculations. When a summary is produced specific to an assessment, the number of subjects who completed the assessment (i.e., provided data) will be used as the denominator for percentage calculations. For all inferential analyses and descriptive comparisons, p-values will be rounded to four decimal points. Values less than 0.0001 will be denoted as “<.0001”, and values greater than 0.9999 will be denoted as “> .9999”. Whenever practical, categories of discrete variables will be ordered and labeled as they appear in the CRF, and all categories represented on the CRF will be included in summaries, even when they do not apply to any subjects in the study.

## Covariates

No covariates will be used in the planned analyses, unless subgroup analyses determine otherwise.

## Examination of Subgroups

Event free survival and OS will be analyzed within the subgroup of INSS Stage 4 subjects (refer to Section 11.2.2 for details). Event free survival will be analyzed within the subgroup of Stratum 07 subjects (refer to Section 11.2.3 for details). Additionally, subject outcome may be compared within and between the following groups: (1) males; (2) females; (3) whites; (4) Hispanics; and (5) African-Americans, as the data permits. The result in any one of the subgroups will be considered at odds with the overall results only if the subgroup is found to be a significant predictor in a relative risk analysis (utilizing the regression method of Cox), even after taking account of possible differences by subgroup in terms of known prognostic variables.

## Premature Discontinuation and Missing Data

Subjects may not complete the full six courses of treatment for the following reasons: death, clinical deterioration, disease progression, adverse event unrelated to disease, loss to follow-up, protocol violation, or withdrawal of consent for other reasons. All available data from all subjects will be used as detailed in this analysis plan; no imputation method will be used for missing data.

## Multiple Comparisons and Multiplicity

For the randomized portion of the study, there was cause to stop the trial early if the ch14.18 + RA arm appeared to be insufficiently efficacious, significantly more efficacious, or if there were unacceptable toxicities. The need for curtailment for non-significance of the ch14.18 + RA arm was assessed first using Fleming-Harrington-O’Brien boundaries and then, as of the Spring 2009 analysis at the request of the DMC, Lan-DeMets boundaries for the hazard ratio (RA only: ch14.18+RA) at each interim analysis. The interim analyses of EFS took place every six months starting after 20% (29) of the planned events had occurred. The lower bound was calculated based on repeated testing of the alternative hypothesis that the relative risk is equal to 1.6 at a p-value of 0.005. This relative risk was calculated as control: experimental using the planning parameters for 3-year EFS. The upper bound uses an alpha\*t2 spending function for a cumulative alpha level of 0.025.

Using these planned interim analyses, the primary objective of the study was achieved when the Lan-DeMets interim monitoring boundary (Table 9‑1) for EFS was met (per data frozen 13 January 2009) and randomization was halted.

Table 9‑ Lan-DeMets interim monitoring boundary values for log-rank EFS comparison of treatment arms

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Monitoring Time point | Observed cumulative number of events | Observed proportion of total expected information | Observed upper boundary z-value | Upper boundary  z-value,  cum alpha = .025 |
| Spring 2009 | 83 | 0.606 | 2.528 | 2.55 |

In the planned analyses for the randomized portion of the study, no adjustments for multiplicity will be made in the primary and secondary analyses; nominal p-values will be presented only.

The EFS (primary) and OS (secondary) analyses will be performed in sequence. If the two‑sided log-rank test comparison of Randomized ITT treatment arms for EFS yields p< 0.05, then analysis of OS will proceed.

# STUDY POPULATION

All study population listings will be generated on the Randomized + Stratum 07 Population. All study population tables will be generated on the Randomized + Stratum 07 Safety Population and the Randomized ITT population unless otherwise specified below. Each of the listings and summary tables below will be created using both the 30 June 2009 and 30 June 2012 datasets, as applicable.

## Subject Accountability

1. Listing of Subjects that Discontinued Protocol Therapy
2. Listing of Subject Accountability
3. Summary of Subject Accountability

Each of the subject accountability outputs will be generated on the Randomized + Stratum 07 population. A listing of all subjects discontinued from the study will be included sorted by subject number and including treatment group, stratum, Safety Population status and Randomized ITT Population status.

The listing of subject accountability will include subject number, treatment group, stratum, date of enrollment/randomization, Safety Population status, Randomized ITT Population status, date subject completed or discontinued from study, completion status, date and reason for protocol therapy discontinuation, date and reason for study discontinuation (if premature) and off study comments. For observations that required stratification information to be corrected, both the original and corrected information will be listed. Also noted on the listing will be any modifications applicable to the subject for each population (e.g., randomized vs. actual treatment groups, etc.).

Number of subjects who were enrolled, randomized/non-randomized, completed, discontinued from study, in the Safety Population, in the Randomized ITT Population, in each stratum, and discontinued from protocol therapy by course will be summarized by treatment group and overall for the Randomized + Stratum 07 Population, as well as reasons for study discontinuation and protocol therapy discontinuation. Additionally, the duration of follow-up will be descriptively summarized by treatment group and overall for the Randomized + Stratum 07 Population. Duration of follow-up is calculated for each subject as the number of days since randomization/enrollment into the study, e.g. the total duration of study participation. Stratum 07 subjects will be included at each applicable summarization level (i.e. enrolled, non-randomized, completed, discontinued, Safety Population, etc.)

## Eligibility Criteria

1. Listing of Eligibility Criteria

The status of the eligibility criteria will be listed and will include all eligibility criteria noted in Appendix 14.1, as well as all eligibility comments.

## Other Descriptions of Study Population

### Demographics

1. Listing of Demographics
2. Summary of Demographics

All demographic data will be listed, including age at enrollment, sex, ethnicity, race, method of payment. Age at enrollment, sex, ethnicity, and race will be summarized by treatment group and overall.

### Diagnosis

1. Listing of Diagnosis Data

Diagnosis data will only be listed and will include diagnosis date, cancer stage, morphology and topography data. Note that cancer stage is not available for the June 2012 data cut.

### Baseline Disease Characteristics

1. Listing of Baseline Disease Characteristics
2. Summary of Baseline Disease Characteristics

Baseline disease characteristics data will be listed, including INSS stage, date of first induction chemotherapy after diagnosis, date of autologous stem cell transplantation, pre‑ASCT response, receipt of un/purged stem cells, number of days post-final ASCT procedure, absolute phagocyte count (APC), status of progressive disease, MYCN amplification, tumor ploidy and tumor histology. Pre-ASCT response, INSS stage, number of days post-final ASCT procedure, APC, MYCN amplification, tumor ploidy and tumor histology will be summarized descriptively or categorically, as appropriate, by treatment group and overall.

### Prior Therapy

1. Listing of Prior Therapy

All reported prior anti-cancer therapies for treatment of neuroblastoma will be listed. The listing will include the type of therapy, start and stop dates for each therapy, a description of each therapy and comments.

### Performance Status

1. Listing of Baseline Performance Status
2. Summary of Baseline Performance Status

Performance status scores measured at baseline will be listed. This listing will include the Karnofsky Performance Score or the Lansky Play Score for each subject. The Karnofsky Performance Score is measured on an ordinal scale ranging from 10-100, in increments of 10. The Lansky Play Score is measured on an ordinal scale ranging from 0-100, in increments of 10. The frequency and percent in each categorical score at each assessment and will be summarized by treatment group and overall. The denominator for percentage calculations will be the number of subjects who provided data for baseline performance status.

### Baseline Prognostic Factors

1. Summary of Baseline Prognostic Factors

Prognostics factors (dichotomized age, categorical age, INSS stage, MYCN amplification, tumor ploidy, histology, pre-ASCT response, and stem cell type) will be summarized by treatment group (frequency and percentage) for the Randomized ITT Population. All responses, including “unknown” and “missing” will be included in the summary. The distribution of prognostic factors between the two treatment groups will be tested with the use a chi-square test and the associated p-value will be presented.

The following responses (including unknown/missing, as appropriate) will be used for summarization of each prognostic factor:

* Dichotomized age: < 18 months, ≥ 18 months
* Age: pre-term newborn infants, term newborn infants (birth to 27 days),

infant/toddler (28 days to 23 months), child (2 to 11 years), adolescent (12 to 17 years) and adult (≥ 18 years)

* INSS Stage: 2, 3, 4S, 4
* MYCN amplification: not amplified, amplified
* Tumor ploidy: Diploid, Hyperdiploid
* Histology: favorable, unfavorable
* Pre-ASCT response: CR, VGPR, PR
* Stem Cell Type: purged, unpurged (derived from the stratification variable)

# EFFICACY ANALYSES

Except where otherwise noted, all efficacy analyses will only be performed on the Randomized ITT population (see Section 8). Each of the listings, summary tables and plots below will be created using both the 30 June 2009 and 30 June 2012 datasets, as applicable. Event-free survival and OS will be calculated at two years for the 30 June 2009 data cut and at three years for the 30 June 2012 data cut, except where otherwise noted.

A listing of subjects excluded from efficacy analyses (both 30 June 2009 and 30 June 2012) will be included at the beginning of the set of efficacy tables.

## Primary Efficacy Measure

1. Listing of Event-Free Survival
2. Listing of Event-Free Survival Differences
3. Summary of Event-Free Survival Analysis (primary analysis): Randomized ITT population
4. Summary of Time to Event-Free Survival
5. Plot of Event-Free Survival Analysis (primary analysis): Randomized ITT population

Two-year EFS data will be derived from the 30 June 2009 data cut, and separately three-year EFS will be derived from the 30 June 2012 data cut. All survival data will be listed. Additionally, a listing will be created documenting those subjects whose EFS time differs between the 13 January 2009 and 30 June 2009 data cuts. For all analyses of EFS, an event is defined as relapse, PD, secondary malignancy, or death. The time-to-event is calculated from the time of study enrollment until the first occurrence of an event or until last contact with the subject if no event occurs.

For the four subjects who were randomized into the study to Regimen A (RA alone), but later crossed over into the open-label non-randomized portion and were switched from Regimen A (RA alone) to Regimen B (immunotherapy + RA), they will be analyzed as randomized and censored at the time the crossover occurred.

For the primary analysis, a two-sided log-rank test with a significance level of 0.05 will be used to test for a difference between the EFS distributions of the immunotherapy + RA group versus the RA only group within the cohort of all randomized subjects (Randomized ITT).

The EFS analysis will be summarized for each treatment group and for the randomized subject population, including two-year survival rates for the 30 June 2009 data cut and three‑year survival rates for the 30 June 2012 data cut, the inferential statistics and p-value associated with the comparison of the two treatment groups. Time-to-EFS will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan‑Meier curves. A tabular summary of this analysis will include the sample size, number and percent of censored observations, estimated median duration, and a 95% confidence interval (CI) for the median duration for each treatment group. Incidence of EFS will be compared between treatment groups using Fisher’s exact test.

## Secondary Efficacy Measures

### Overall Survival: Randomized ITT Population

1. Listing of Overall Survival
2. Listing of Overall Survival Differences
3. Summary of Overall Survival Analysis: Randomized ITT Population
4. Summary of Time to Overall Survival
5. Plot of Overall Survival Analysis: Randomized ITT Population

Two-year OS data will be derived from the 30 June 2009 data cut and separately three-year OS data will be derived from the 30 June 2012 data cut. All OS data will be listed. Additionally, a listing will be created documenting those subjects whose OS time differs between the 13 January 2009 and 30 June 2009 data cuts.

All analyses of OS will only be performed on the 30 June 2009 and 30 June 2012 data cuts. For the OS analyses, the event is death. The time-to-event is calculated from the time of study enrollment until death, or until last contact with the subject if the subject does not die.

For the four subjects who were randomized into the study to Regimen A (RA alone), but later crossed over into the open-label non-randomized portion and were switched from Regimen A (RA alone) to Regimen B (immunotherapy + RA), they will be analyzed as randomized and censored at the time the crossover occurred.

For the analysis of OS, a two-sided log-rank test with a nominal significance level of 0.05 will be used to test for a difference between the OS rates of the immunotherapy + RA group versus the RA only group within the cohort of all randomized subjects.

The analysis of OS will be summarized, using two-year OS rates for the 30 June 2009 data cut and three-year OS rates for the 30 June 2012 data cut, by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan‑Meier curves. A tabular summary of this analysis will include the sample size, number and percent of censored observations, estimated median duration, and a 95% CI for the median duration for each treatment group. Incidence of death will be compared between treatment groups using Fisher’s exact test.

### Event-Free and Overall Survival: INSS Stage 4 Randomized ITT Population

1. Listing of Event-Free Survival: INSS Stage 4 Randomized ITT Population
2. Listing of Overall Survival: INSS Stage 4 Randomized ITT Population
3. Summary of Event-Free Survival Analysis: INSS Stage 4 Randomized ITT population
4. Summary of Time to Event-Free Survival: INSS Stage 4 Randomized ITT Population
5. Summary of Overall Survival Analysis: INSS Stage 4 Randomized ITT Population
6. Summary of Time to Overall Survival: INSS Stage 4 Randomized ITT Population
7. Plot of Event-Free Survival Analysis: INSS Stage 4 Randomized ITT population
8. Plot of Overall Survival Analysis: INSS Stage 4 Randomized ITT Population

For analyses of both EFS and OS, a two-year survival rate will be calculated from the 30 June 2009 data cut and a three-year survival rate will be calculated from the 30 June 2012 data cut. All analyses will use a two-sided log-rank test with a nominal significance level of 0.05 to test for a difference between the survival rates of the immunotherapy + RA group versus the RA only group. Three of the four crossover subjects were INSS Stage 4 and will be included in these EFS and OS analyses. They will be analyzed as randomized (RA alone) and censored at the time the crossover occurred.

The EFS and OS analyses will be summarized for each treatment group and for the randomized subject population, including two-year survival rates for the 30 June 2009 data cut and three-year survival rates for the 30 June 2012 data cut, the inferential statistics and p‑value associated with the comparison of the two treatment groups. Time-to-event (EFS or death) will be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan‑Meier curves. A tabular summary of this analysis will include the sample size, number and percent of censored observations, estimated median duration, and a 95% CI for the median duration (if data permit) for each treatment group. Incidence of event will be compared between treatment groups using Fisher’s exact test.

### Event-Free Survival for Stratum 07 vs. Historical Control

1. Listing of Event-Free Survival: Stratum 07
2. Summary of Event-Free Survival: Stratum 07
3. Plot of Event-Free Survival: Stratum 07

Event-free survival rates will be calculated at two years for the 30 June 2009 data cut and at three years for the 30 June 2012 data cut. The 30 June 2009 summary and plot will be purely descriptive and will not include the historical control. For the 30 June 2012 analysis, a historical comparison will be made. Due to the small sample sizes, this comparison will be a descriptive one only. The historical control is the n=37 subjects on CCG‑3891with documented residual disease who were treated with RA and who had a 3-year EFS rate of 12% ± 6%. This rate will be compared to the 3-year EFS rate for Stratum 07, calculated only from the 30 June 2012 data cut. For the CCG‑3891cohort, the ‘clock started’ for survival time when the RA treatment started, and for the Stratum 07 subjects, the clock will start at the time of ANBL0032 enrollment. Randomized treatment on ANBL0032 should begin within a few days after enrollment, so the few days’ difference between the two studies should be negligible.

The CCG-3891 historical control rate will be denoted by a point on the plot of EFS: Stratum 07 for the 30 June 2012 data cut.

### Event-Free and Overall Survival with Prognostic Factors

1. Summary of Event-Free Survival within Prognostic Factors
2. Summary of Overall Survival within Prognostic Factors
3. Summary of Event-Free Survival Interaction with Prognostic Factors
4. Summary of Overall Survival Interaction with Prognostic Factors

In order to replicate the prognostic factor analyses presented in the Yu et al. *NEJM* article, a two-sided log-rank test with a significance level of 0.05 will be used to test the difference between the EFS/OS distributions within each prognostic factor for the Randomized ITT population. The programming code for these analyses is comparable to the primary analysis using product‑limit estimates calculated by the Kaplan-Meier method, with the comparison being done within factors rather than treatment groups and will follow this example:

proc lifetest data=random;

time efstime\*efs(0);

 strata factor;

run;

where factor represents the dichotomized prognostic factor values (eliminating from the analysis any subjects with unknown or missing responses to the prognostic factor being tested and any factor groups that have no respondents), as detailed below:

* Age (< 18 months vs. ≥ 18 months)
* Age (infant/toddler [28 days to 23 months]and child [2 to 11 years] vs. adolescent [12 to 17 years])
* INSS Stage (2, 3, and 4S vs. 4)
* MYCN amplication (Not amplified vs. Amplified)
* DNA ploidy (Diploid vs. Hyperdiploid)
* Histology (Favorable vs. Unfavorable)
* Pre-ASCT Response (CR and VGPR vs. PR)
* Stem cell type (purged vs. unpurged using the stratification variable)

Event-free and overall survival rates (two-year rates for the 30 June 2009 datacut and three‑year rates for the 30 June 2012 datacut) plus 95% CIs and the log-rank test p-value will be summarized. The summaries will look like:

|  |  |  |  |
| --- | --- | --- | --- |
|  | No. of Patients  (N = ) | 2-Yr  Event-free Survival | P Value |
| *n (%)* | *%* |  |
|  |  |  |  |
| Age |  |  | 0.xxxx |
| <18 Mo | n(%) | xx (xx, xx) |  |
| ≥18 Mo | n(%) | xx (xx, xx) |  |
|  |  |  |  |
| INSS stage |  |  | 0.xxxx |
| 2,3,4S | n(%) | xx (xx, xx) |  |
| 4 | n(%) | xx (xx, xx) |  |
| Etc. |  |  |  |

Additionally, the interaction of each prognostic factor with treatment in the EFS/OS survival analysis will be analyzed using a Cox proportional hazards model, as follows:

proc phreg data=random ;

  class treat\_no factor ;

  model efstime\*efs(0) = treat\_no factor treat\_no\* factor;

  run ;

where factor represents the dichotomized prognostic factor values (eliminating from the analysis any subjects with unknown or missing responses to the prognostic factor being tested and any factor groups that have no respondents), as detailed below:

* Age (< 18 months vs. ≥ 18 months)
* Age (infant/toddler [28 days to 23 months]and child [2 to 11 years] vs. adolescent [12 to 17 years])
* INSS Stage (2, 3, and 4S vs. 4)
* MYCN amplication (Not amplified vs. Amplified)
* DNA ploidy (Diploid vs. Hyperdiploid)
* Histology (Favorable vs. Unfavorable)
* Pre-ASCT Response (CR and VGPR vs. PR)
* Stem cell type (purged vs. unpurged using the stratification variable)

The interaction p-values calculated from the Cox proportional hazard model will be summarized, along with the event-free and overall survival rates (two-year rates for the 30 June 2009 datacut and three‑year rates for the 30 June 2012 datacut) plus 95% CIs. The EFS and OS rates plus 95% CI’s will be estimated (and footnoted as) using product‑limit estimates calculated by the Kaplan-Meier method (similar to the primary analysis), but accounting for the prognostic factor in the model, as follows:

proc lifetest data=random;

time efstime\*efs(0);

 strata treat\_no factor;

run;

The summaries will look like:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Immunotherapy + RA (n=) | | RA Alone (n= ) | | Cox PH model Interaction p-value^ |
|  | No. of Patients  (N = ) | 2-Yr Event-free Survival | No. of Patients  (N = ) | 2-Yr Event-free Survival |  |
| *n (%)* | *% (95% CI)* | *n (%)* | *% (95% CI)* |  |
|  |  |  |  |  |  |
| Age |  |  |  |  | 0.xxxx |
| <18 Mo | n(%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
| ≥18 Mo | n(%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
|  |  |  |  |  |  |
| INSS stage |  |  |  |  | 0.xxxx |
| 2,3,4S | n(%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
| 4 | n(%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
| Etc. |  |  |  |  |  |

^ the interaction p-value is derived from a Cox proportional hazards model with treatment, factor and treatment\*factor interaction.

### Event-Free and Overall Survival within HACA Positive Subjects

1. Summary of Event-Free Survival Interaction with HACA Positive Findings
2. Summary of Overall Survival Interaction with HACA Positive Findings

HACA data is available for the 30 June 2009 data cut only. HACA positive subjects will be identified as having a HACA value > 0.300 OD. Based on the data from 30 June 2009, the following subjects were determined to be HACA positive: 714387, 719992, 722400, 725497, 734425, 748828, 756911, 774698, 776291, 741017, and 743324. An indicator variable will be created in the database to denote these subjects. The interaction of HACA with treatment in the survival analysis will be analyzed using a Cox proportional hazards model as follows:

proc phreg data=random;

  class treat\_no haca ;

  model efstime\*efs(0) = treat\_no haca treat\_no\* haca;

  run ;

The interaction p-value calculated from the Cox proportional hazard model will be summarized, along with the event-free and overall survival rates (two-year rates for the 30 June 2009 datacut and three‑year rates for the 30 June 2012 datacut) plus 95% CIs. The EFS and OS rates plus 95% CI’s will be estimated (and footnoted as) using product‑limit estimates calculated by the Kaplan-Meier method (similar to the primary analysis), but accounting for the prognostic factor in the model, as follows:

proc lifetest data=random;

time efstime\*efs(0);

 strata treat\_no haca;

run;

The summaries will look like:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Immunotherapy + RA (n=) | | RA Alone (n= ) | | Cox PH model Interaction  p-value^ |
|  | No. of Patients  (N = ) | 2-Yr Event-free Survival | No. of Patients  (N = ) | 2-Yr Event-free Survival |  |
| *n (%)* | *% (95% CI)* | *n (%)* | *% (95% CI)* |  |
|  |  |  |  |  |  |
| Haca Positive |  |  |  |  | 0.xxxx |
| Yes | n (%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
| No | n(%) | xx (xx, xx) | n(%) | xx (xx, xx) |  |
|  |  |  |  |  |  |

^ the interaction p-value is derived from a Cox proportional hazards model with treatment, factor and treatment\*factor interaction.

### Disease Status

1. Listing of Disease Status
2. Summary of Disease Status

Disease status data were collected as ordinal variables. Disease status will be listed by course/cycle, as well as summarized by number (percent) within course/cycle and treatment group and overall, using the ordinal categories: (1) remission/stable disease, (2) relapse, (3) progressive disease, (4) secondary malignancy, (5) death, and (6) unknown. The denominator for percentage calculations will be the number of subjects who provided data for disease status within each course.

### Minimal Residual Disease (MRD)

1. Listing of MRD Assessments by MIBG
2. Listing of MRD Assessments by RT-PCR (TLDA)
3. Summary of MIBG Results

MIBG data were collected on the CRF. RT-PCR (Taqman® Low Density Array [TLDA]) data were analyzed by Dr. Seeger’s laboratory. Immunocytology data have not yet been analyzed and are therefore not included in these planned analyses.

MRD assessments based on MIBG scans of the primary tumor, bone marrow, and bone were collected as ordinal variables. These assessments will be listed, using the ordinal categories: (1) no evidence of disease, (2) improved, (3) no change, (4) progression/new lesions and (5) not done. Date of MIBG scan will also be listed. The summary of MIBG results will include the number and percentage of subjects in each ordinal category by course. The denominator used for each percentage will be the number of subjects reporting MIBG results within each course.

MRD assessments based on RT-PCR data analyzed at Dr. Seeger’s laboratory will also be listed. This listing will include bone marrow type, bone marrow collection date, geometric mean detection genes, and geometric mean housekeeping genes.

In order to have adequate power for the analyses of MRD and thus meaningful results, the following analyses will be conducted upon completion of the study and receipt of final study data:

For immunocytology and RT-PCR assessments, the MRD measurements collected are the number of neuroblastoma cells per 105 blood or marrow cells. A descriptive analysis of the change from baseline of MRD will be performed for ch14.18 + RA versus RA only for the ITT subjects with pre-ASCT response of CR, VGPR, or PR (excluding Stratum 07 subjects), who have at least one specimen time point after baseline at which they have not progressed/died. Also, a Wilcoxon rank-sum test will be performed to compare the median change from baseline of MRD between the two treatment arms. MRD will be measured at two time points: 1) up to 4 weeks before starting therapy on ANBL0032 and, 2) after completion of RA. To assess the change in MRD due to immunotherapy, the change from time point 1) to time point 2) will be used. This statistical testing will be performed using MRD measurements made with immunocytology and then repeated using MRD measurements made with RT‑PCR.

For MIBG assessments, the comparison between the two treatment arms will be performed using an ordinal logistic regression model for the ITT subjects with pre-ASCT response of CR, VGPR, or PR (excluding Stratum 07 subjects), who have at least one specimen time point after baseline at which they have not progressed/died. MRD will be measured at two time points: 1) up to 4 weeks before starting therapy on ANBL0032 and, 2) after completion of RA. To assess the change in MRD (based on MIBG) due to immunotherapy, the assessment at time point 2) will be used as the dependent variable, the assessment at time point 1) (“baseline”) will be included as a predictor in the model, and the term for treatment will be tested as an additional term in the model.

The MRD treatment arm comparisons will be performed independently for immunocytology, RT-PCR, and MIBG. No adjustment for multiple comparisons will be made.

Upon completion of the study and receipt of final study data, in order to determine if changes from baseline in MRD, as measured by MIBG and RT-PCR, are associated with EFS and OS, a multivariate Cox Proportional hazards regression model will be used. Significant biologic prognostic factors will also be included in the model. All Randomized ITT subjects and Stratum 07 subjects will be included in these analyses.

### Antibody-Dependent Cellular Cytotoxicity (ADCC)

ADCC data have not yet been analyzed and are therefore not included in these planned analyses.

### Human Anti-chimeric Antibody (HACA)

1. Listing of HACA Results
2. Summary of HACA Results
3. Summary of HACA Frequency Across Treatment Groups

HACA data were analyzed by Dr. Sondel’s lab (30 June 2009 data cut only) and will be listed by subject for those subjects in the Safety Population only. Descriptive statistics of HACA and HACA titer results at each collection time point during immunotherapy will be calculated and summarized by treatment group. Additionally, the number and percentage of subjects with HACA positive results will be summarized by treatment group. HACA positive is considered a HACA value > 0.300 OD. The distribution of HACA positive subjects across the treatment groups will be tested with a chi-square test and the p-value presented next to the frequencies. Upon completion of the study, a multivariate Cox proportional hazards regression model will determine if changes from baseline in HACA titer results are associated with EFS and OS, as the data permit.

### Soluble IL-2 Receptor Levels

1. Listing of Soluble IL-2 Receptor Levels
2. Summary of Soluble IL-2 Receptor Levels

Soluble IL-2 receptor levels data were analyzed in Dr. Sondel’s lab (30 June 2009 data cut only) and will be listed by subject for those subjects in the Safety Population only. Descriptive statistics of soluble IL-2 receptor levels at each collection time point during immunotherapy will be calculated and summarized by treatment group.

# SAFETY ANALYSES

All safety analyses will be performed only on the *Safety* population (see Section 8); unless otherwise noted. Each of the listings and summary tables below will be created in duplicate using both the 30 June 2009 and 30 June 2012 datasets, as applicable, respectively. Note that the four crossover subjects will be represented in both treatment groups, as data driven, due ot the fact that they were randomized and received RA alone and were then crossed over to the immunotherapy group upon the cessation of randomization into the study.

## Extent of Exposure

1. Listing of Study Drug Dosing
2. Summary of Study Drug Dosing and Exposure

All study drug dosing will be listed. The listing will include course/cycle of treatment, start and stop date of each course/cycle of treatment, subject’s weight and height, steroid use (including start/stop dates of use), protocol therapy status (including date off therapy and reason, if therapy ended) and dose reductions ≥ 25% with associated comments. The number of courses/cycles completed for each subject (both continuous summary with descriptive statistics and categorical summary with frequencies and percentages), and number of subjects reporting steroid use by course will be summarized within each treatment group and overall. The denominator for “by course” summaries will be the number of subjects reporting data for each of the assessments.

## Relapse/ Progression

1. Listing of Relapse/ Progression Reports
2. Summary of Relapse and Progression Reports

Relapse/ progression dates and sites (primary site, bone, bone marrow, liver, lymph nodes, lung and other), including other site free text will be listed. The number (percent) of relapse and progression reports overall and for each site will be summarized by treatment group and overall. The denominator used for calculation of percentage for the number of relapse/progression reports will be the number of subjects exposed to protocol therapy, but the denominator used for each site will be the number of subjects reporting a relapse/progression overall.

## Targeted and Non-Targeted Toxicities

1. Listing of All Toxicities
2. Overall Summary of Toxicities
3. Overall Summary of Targeted Toxicities
4. Overall Summary of Non-targeted Toxicities
5. Summary of All Toxicities by System Organ Class
6. Summary of All Toxicities by Preferred Term
7. Summary of Targeted Toxicities by Preferred Term
8. Summary of Non-Targeted Toxicities by Preferred Term
9. Summary of All Toxicities by Course, Grade and Preferred Term
10. Summary of Targeted Toxicities by Course, Grade and Preferred Term
11. Summary of Non-targeted Toxicities by Course, Grade and Preferred Term
12. Summary of Pain-Related Toxicities by Course, Grade and Preferred Term
13. Summary of All Attributable Toxicities by Preferred Term
14. Summary of Attributable Targeted Toxicities by Preferred Term
15. Summary of Attributable Non-Targeted Toxicities by Preferred Term
16. Summary of Attributable Grade 3 or Higher Toxicities by Preferred Term

Toxicities meeting the reporting requirements outlined in Section 10 of the protocol will be listed. All of these toxicities were reported after study treatment was initiated; thus all toxicities are treatment emergent toxicities. The listing will include adverse event, preferred term, non/targeted status, grade, start date, course, relationship to study drug, adverse drug experience (ADE) status, dose limiting toxicity status and comments.

An overall summary of toxicities by treatment group and overall and by overall, targeted and non-targeted toxicities will be included. This summary will include the total number of subjects reporting and total number of events for:

* any toxicity
* each grade of toxicity
* any attributable toxicities
* any ADE toxicity, and
* any Grade 3 or higher toxicities

Toxicities (overall, targeted and non-targeted) will be further summarized for each treatment group and overall by SOC and PT (overall only) and by PT only. The overall summary by PT (Summary of All Toxicities by Preferred Term) will include one-sided p-values (favoring the RA alone group) from Fisher’s Exact Test comparing the incidence rates between the treatment groups. Values greater than 0.25 will be denoted as “>.2500”. Those considered attributable to study drug (overall, targeted and non-targeted) will be summarized by preferred term. Attributable toxicities are defined as those toxicities with attribution to investigation drug documented on the CRF as: definite, probable or possible. Any toxicities documented on the CRF as unrelated or unlikely related are not considered to be attributable toxicities for summarization purposes. Summaries will include incidence of each preferred term, sorted by overall frequency within each preferred term.

All toxicities (overall, targeted and non-targeted) will be summarized by course, grade and preferred term within each treatment group, where the denominator for percentage calculations within each course will be the number of subjects exposed to treatment during each course. Likewise, pain-related toxicities will be summarized within each treatment group by course and grade, using preferred terms; the denominator will be subjects exposed to treatment within each course. Pain-related adverse events will be selected based on the preferred term including the word “pain” or any “algia” (myalgia, arthralgia, etc).

All toxicities that are of Grade 3 or higher and attributable to study drug will be summarized by preferred term for each treatment group and overall.

Due to the Common Terminology Criteria for Adverse Events (CTCAE) coding version (V3) being updated during the conduct of this study in October 2011, all AEs existing in the June 2009 data cut were converted to the new CTCAE version (V4) before the June 2012 data cut. Thus the June 2012 AE data has slightly different coding than that presented in the June 2009 data and therefore comparisons between the summary tables should be viewed with caution.

## AdEERS (Serious Adverse Events)

1. Listing of Data in the AdEERS Database
2. Summary of Adverse Events in the AdEERS Database by CTCAE Code
3. Summary of Adverse Events in the AdEERS Database by Course at Onset

In this study, adverse events meeting the protocol requirements for reporting of commercial and non-commercial products were reported through the Adverse Event Expedited Reporting System (AdEERS). These adverse events are considered to represent the serious adverse events for this study, albeit only those that met the protocol specified criteria for reporting. These data will be listed, including course number, subject number, AdEERS number, adverse event term, start date of primary adverse event, and attribution to each study drug.

These data will also be summarized by CTCAE code within each course and overall. The summary should include the number and percent of subjects reporting each event, as well as the number of events, both within treatment group and overall. The denominator used for each percentage will be the number of subjects exposed within each course and overall.

## Deaths

1. Listing of Deaths
2. Summary of Deaths

Information for all subjects who died during the study period, including the date of death, cause of death and whether an autopsy was completed will be listed. The number and percent of subjects who died and the causes of death will be summarized by treatment group and overall.

## Physical Exam

Physical exams in this study included measures of weight, height, vital signs, performance status, CBC and differential with APC, chemistry survey and urinary vanillyl mandelic acid (VMA) and homovanillic acid (HVA). The only data that was databased from the physical exams were weight and height, which are summarized with Extent of Exposure (see Section 12.1). The other assessments were not databased, but clinically significant lab values were noted as toxicities according to Section 10 of the protocol.

## Clinical Laboratory Evaluations

Blood samples were taken before each cycle and sent to a local laboratory for the evaluation of hematology and clinical chemistry. Urine samples were also collected before each cycle and sent to a local laboratory for urinalysis. These blood and urine sample results were not databased, but clinically significant values were noted as toxicities according to Section 10 of the protocol. Urine catecholamine and clinical course laboratory data were collected within each course/cycle and databased.

### Urinalysis

1. Listing of Urine Catecholamine

Urine catecholamine results (categorical) will be listed, using the categorical formats: (1) no evidence of disease, (2) improved, (3) no change, (4) progression/new lesions and (5) not done.

### Course Labs

1. Listing of Course/Cycle Labs
2. Summary of Segmented and Bands by Course/Cycle
3. Summary of Lymphocytes by Course/Cycle
4. Summary of Monocytes by Course/Cycle

Course/cycle labs will be listed by course/cycle. This listing will include course/cycle number, white blood cells (WBC) (µL), segmented and band (%), lymphocytes (%), and monocytes (%). Each parameter, except for WBC (due to errors in recording with the correct unit), will be summarized by course/cycle and treatment group.

## Other Safety Measures

### Hospitalizations and Infections

1. Listing of Hospitalizations and Infections
2. Summary of Hospitalizations and Hospitalization Caused by Infection

Hospitalization and any infections requiring hospitalization will be listed by course/cycle. This listing will include course/cycle number, number of days hospitalized, details on the infections requiring hospitalization (organism type [bacterial, fungal viraql, protozoan, organism unknown], organism name, and location [blood, pulmonary, upper GI, lower GI, skin & subcutaneous, central nervous system (CNS), urinary tract, liver, upper respiratory, other], and other specify field). The number of days hospitalized, incidence of hospitalization caused by infection, incidence of infections by location, and incidence of infections by organismwill be summarized by course/cycle and treatment group and overall. The denominator used for incidence of hospitalizations within each course will be the number of subjects exposed to study treatment within each course. The denominator used for incidence of infections by location and by organism class will be the number of infections resulting in hospitalization within each course.

# PHARMACOKINETICS

Pharmacokinetic samples collected for the determination of plasma concentrations of 13-cis-RA, ATRA and the metabolite 4-oxo-13-cis-RA, will be determined by HPLC analysis by Dr. Min Kang at Texas Tech University Health Sciences Center School of Medicine. DNA obtained from these sample will be genotyped for metabolizing enzymes thought to be involved in the metabolism of 13-cis-RA, such as CYP2C8 and CYP3A7, using PCR methodology. These analyses are not included as part of this analysis plan.

## ch14.18 Plasma Levels

1. Listing of ch14.18 Plasma Levels
2. Summary of ch14.18 Plasma Levels

ch14.18 plasma level data were analyzed in Dr. Sondel’s lab and will be listed for all Randomized ITT subjects from the 30 June 2009 data cut only. Descriptive statistics of ch14.18 plasma levels at each collection time point during immunotherapy will be calculated and summarized. In order to have adequate power for the analyses of ch14.18 plasma levels and the association with EFS and OS, and thus meaningful results, these analyses will be conducted upon completion of the study and receipt of final study data. A multivariate Cox proportional hazards regression model will test to see if the ch14.18 plasma level is associated with EFS and OS. Significant biologic prognostic factors will also be included in the model, as data permit.

# APPENDICES

## Inclusion and Exclusion Criteria

**As per Amendment #8 (12-MAY-2008):**

**Important note**: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). 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.**

Enrollment on A3973, ANBL0532 or ANBL00B1 is not an eligibility requirement for ANBL0032.

1. All patients must be diagnosed with neuroblastoma, and categorized as high risk at the time of diagnosis and must be ≤ 30.99 years of age at diagnosis.

2 All patients must have completed therapy including intensive induction followed by ASCT and radiotherapy, AND have achieved CR, VGPR or PR at pre-ASCT evaluation to be eligible for ANBL0032. Examples of such therapies include:

Following treatment per A3973 protocol

Following treatment per POG 9341/9342 protocol

Following treatment per CCG3891

Following treatment on NANT 2001-02

Enrollment on or following treatment per ANBL02P1

Enrollment on or following treatment per ANBL07P1

Tandem transplant patients are eligible:

1) Following treatment on or per ANBL0532;

2) Following treatment per POG 9640;

3) Following treatment per COG ANBL00P1; or,

4) Following treatment per CHP 594/DFCI 34-DAT

3 No more than 9 months from the date of starting the first induction chemotherapy after diagnosis to the date of ASCT. For tandem ASCT patients, this will be the date of the FIRST stem cell infusion. **PATIENTS WHO UNDERWENT ASCT WITH CD34 + CELL SELECTION METHOD ARE INELIGIBLE.**

4 Prior to starting therapy on ANBL0032, a determination of residual disease must be performed (Tumor imaging studies including computed tomography (CT) or magnetic resonance imagin (MRI), bone scan, MIBG scan, bone marrow aspiration & biopsy, and blood and bone marrow samples). This disease assessment is required for eligibility. For those with residual disease before radiotherapy, re-evaluation of irradiated residual tumors should be performed at the earliest 5 days after completing radiotherapy. All patients who have biopsy proven residual disease after ASCT are eligible for ANBL0032 and will be non-randomly assigned to immunotherapy on Stratum 07.

5 Patients must be enrolled and randomized between Day 50 and Day 85 post final-ASCT procedure (second ASCT for tandem ASCT patients), when the total absolute phagocyte count (APC = neutrophils + monocytes) is at least 1000/μL (cytokine support allowed), and at least 7 days after completing radiotherapy, and patient has undergone tumor assessment. Informed consent should be obtained within 3 weeks pre-ACST up to the time of registration.

6 Patients must not have progressive disease.

7 Patients must have a Lansky or Karnofsky Performance Scale score of ≥ 50% and patients must have a life expectancy of ≥ 2 months.

8 Patients must have adequate organ functions at the time of registration:

Adequate Renal Function Defined As:

* Creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥ 70 mL/min/1.73 m2 or
* A serum creatinine based on age/gender as follows:

|  |  |  |
| --- | --- | --- |
| Age | Maximum Serum  Creatinine (mg/dL) | |
| Male | Female |
| 1 month to < 6 months | 0.4 | 0.4 |
| 6 months to < 1 year | 0.5 | 0.5 |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the Center for Disease Control.

Hepatic- total bilirubin ≤ 1.5 x normal, and SGPT (ALT) ≤5 x normal. Veno-occlusive disease, if present, should be stable or improving.

Cardiac- shortening fraction of ≥ 30% by echocardiogram, or if shortening fraction abnormal, ejection fraction of ≥ 55% by gated radio­nuclide study.

Pulmonary- FEV1 and FVC > 60% of predicted by pulmonary function test (PFT). For children who are unable to do PFTs, no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% on room air.

Central nervous system (CNS)- Patients with seizure disorder may be enrolled if on anticonvulsants and well-controlled. CNS toxicity < Grade 2.

9 Written informed consent in accordance with institutional and US Food and Drug Administration guidelines must be obtained from parent or legal guardian.

10 Females of childbearing potential must have a negative pregnancy test. Patients of childbearing potential must agree to use an effective birth control method. Female patients who are lactating must agree to stop breast-feeding.

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