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**CHILDREN'S ONCOLOGY GROUP**

**ACNS0331**

**A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial**

**An Intergroup Study for Participation by COG and the Dutch Childhood Oncology Group – SKION (Stichting Kinderoncologie Nederland)**

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<u><b>AGENT NSC#</b></u>	
CCNU(Lomustine)	NSC#79037
Cisplatin (Platinol)	NSC#119875
Cyclophosphamide (Cytosan, CPM)	NSC#026271
Filgrastim (G-CSF)	NSC#614629
Mesna	NSC#113891
Vincristine (Oncovin, VCR)	NSC#067574

## STATEMENT OF CONFIDENTIALITY

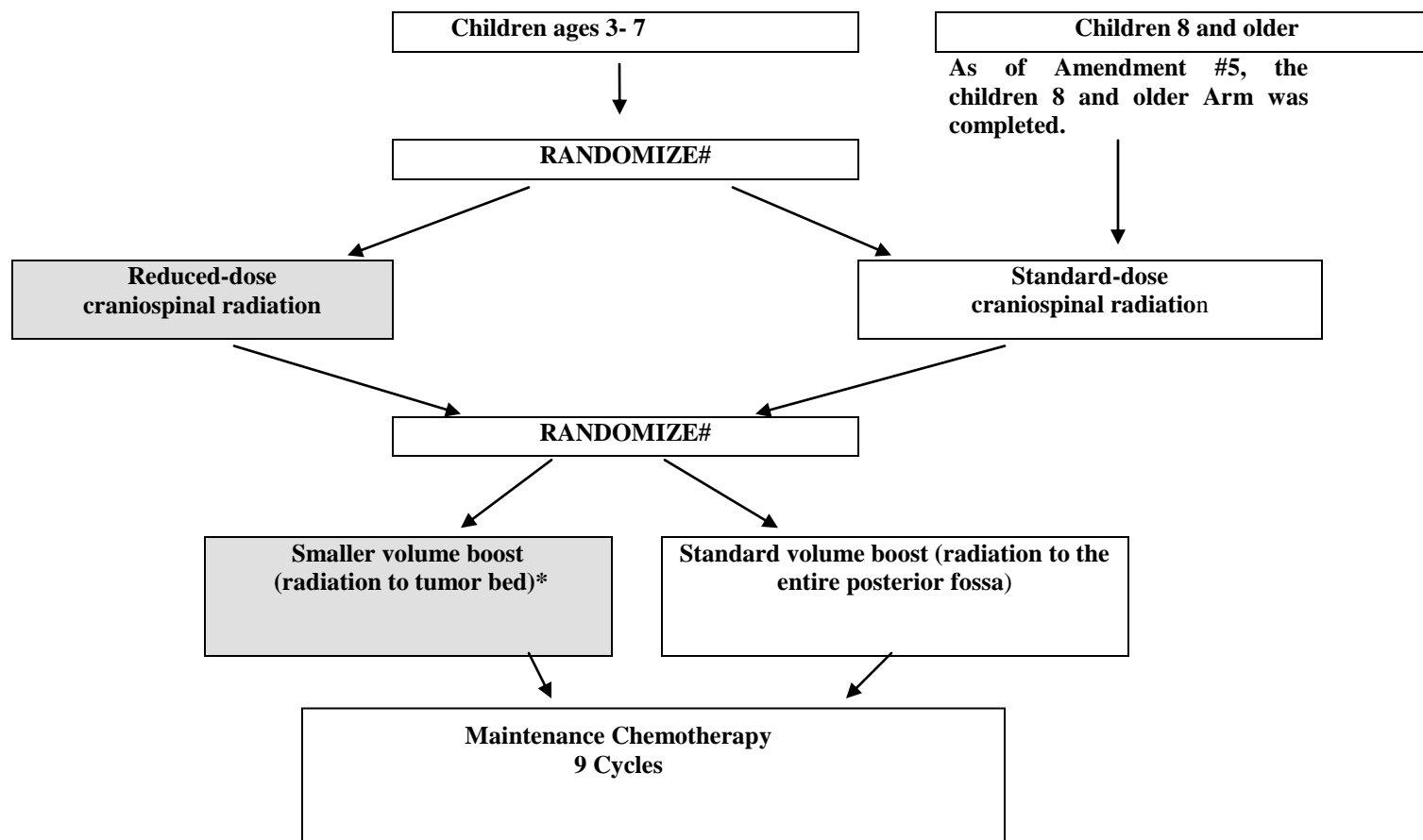
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## ABSTRACT

This trial is a Phase III randomized study designed to reduce the neuro-toxicity of treatment in children diagnosed with medulloblastoma. This approach incorporates two principal hypotheses: 1) It will be feasible to reduce the dose of craniospinal radiation by 25% in children age 3 to 7 years by moderate intensification of the adjuvant chemotherapy regimen using agents active against leptomeningeal disease; and 2) It will be feasible to safely reduce the volume of the boost dose of irradiation from the whole posterior fossa to the area of the tumor bed plus a circumscribed margin using three-dimensional treatment planning and conformal delivery techniques, which allow precise targeting of the area most prone to local failure. Outcome will be assessed in terms of event-free survival, exoprimary relapses (including posterior fossa relapses outside the tumor bed), toxicity of therapy, and quality of life indicators. If successful, this study would represent a landmark advance in the treatment of childhood favorable-risk medulloblastomas. We are coupling this therapeutic goal with a key biological goal, specifically the application in a groupwide context of molecular and biological markers that can potentially help to refine the therapeutic stratification of these tumors by identifying lesions with favorable clinical risk factors that in fact exhibit adverse biological features. This study will establish the feasibility of such an analysis as well as define standard analysis conditions needed to allow implementation of these novel stratification variables in future group studies.



## EXPERIMENTAL DESIGN SCHEMA



\* Patients ages 3 - 7 that are randomized to the reduced-dose (18Gy) craniospinal radiation will be given an additional dose of 5.4 Gy to the posterior fossa (18 Gy + 5.4 Gy = total 23.4 Gy) before the final boost dose. (Cumulative 54 Gy)

# Both Randomizations will occur at the time of Study Enrollment.

All patients get weekly vincristine (6 doses) during radiation phase of therapy.

## 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

### 1.1 Primary Objective

To determine whether reducing the craniospinal dose of radiation therapy to 18.00 Gy in children 3-7 years of age does not compromise event-free survival and overall survival as compared to treatment with 23.40 Gy of craniospinal radiation; and to determine if reducing the irradiated volume of the primary site tumor boost from the whole posterior fossa to the tumor bed only will not compromise event-free and overall survival.

### 1.2 Secondary Objectives

- 1) To evaluate patterns of failure in children treated with an irradiation boost volume smaller than conventional posterior fossa volumes.
- 2) To reduce the cognitive, auditory and endocrinologic effects of treatment of average-risk medulloblastoma by reducing the dose of craniospinal irradiation therapy.
- 3) To determine if the audiologic and endocrinologic toxicity will be reduced with the use of limited tumor boost volume irradiation compared to patients treated with conventional target volumes of radiation.
- 4) To develop an optimal gene expression medulloblastoma outcome predictor, validated prospectively in a multi-institution randomized clinical trial.
- 5) To improve compliance with long-term quality of life and functional status data submission by educating institutional nurses to administer and submit for analysis a battery of four instruments:
  - Behavior Assessment System for Children- 2<sup>nd</sup> Edition (BASC-2)
  - Adaptive Behavior Assessment System – 2<sup>nd</sup> Edition (ABAS-II)
  - Behavior Rating Inventory of Executive Function (BRIEF)
  - PedsQL™ 4.0.

## 2.0 BACKGROUND

### 2.1 Reduced Dose Radiotherapy

The rationale for examining radiotherapy dose reduction is that although recent studies for children with standard-risk medulloblastoma have achieved survival rates in the range of 70 to 80% with standard doses of craniospinal radiotherapy (i.e., 36.00 Gy), an unacceptable percentage of children suffer long-term cognitive sequelae from therapy.<sup>1-4</sup> The deleterious impact of craniospinal irradiation on the developing nervous system has been shown to increase with the dose administered and decrease with the age of the child at time of treatment.<sup>5</sup> To reduce these late treatment effects in survivors, several studies have reduced the dose of craniospinal radiation from 36.00 Gy to 23.40 Gy for children with standard risk disease.<sup>2,4</sup> Use of lower dose irradiation improved cognitive outcome. However, when radiation was used without adjuvant chemotherapy, children who received reduced doses had significantly higher relapse rates, particularly outside the primary site.<sup>4</sup> In contrast, when 23.40 Gy craniospinal irradiation was given with adjuvant chemotherapy (vincristine during radiation and CCNU, cisplatin and vincristine after radiation) the survival outcome was not reduced.<sup>2</sup> These results formed the basis for the CCG-9892 and A9961 studies, and together, these studies indicated that modest reductions in the dose of craniospinal irradiation to 23.40 Gy, if combined with adjuvant chemotherapy, were capable of preserving high rates of disease control (3, 4, 7-9) (Table 1) with potential improvements in functional outcome. However, it bears emphasis that CSRT doses in excess of 20.00 Gy still pose a significant risk for cognitive outcome, particularly in young children. Studies of Silber et. al.<sup>5</sup> demonstrate that the injurious impact of craniospinal irradiation is a particular problem in children younger than 8. Therefore, the rationale for targeting the study question regarding the feasibility of further dose reduction to patients between 3 and 8

years of age is the recognition that the neurotoxic effects of CSRT are most severely manifested in these patients and, therefore, this is the group most likely to have substantial benefits from CSRT dose reduction.

Between 1988 and 1990 investigators at the Children's Hospital of Philadelphia initiated a limited pilot study of reduced dose (18.00 Gy) craniospinal radiation therapy and adjuvant chemotherapy of children with standard risk medulloblastoma (CHP455: Treatment of newly diagnosed PNET of the posterior fossa (medulloblastoma) in children with radiation therapy and adjuvant chemotherapy with Cisplatin, CCNU and Vincristine).<sup>3</sup> The rationale for this treatment was based in part on results of large cooperative group studies showing a survival advantage for babies treated with chemotherapy and radiation compared to babies treated with radiation alone.<sup>6,7</sup> Ten patients were treated on this pilot study. As of September 2000, only three of the ten children have died due to tumor recurrence. For all three children, recurrence occurred within 2 years of diagnosis; one recurred in the posterior fossa and subarachnoid space, two outside the local bed (within the low dose craniospinal field). Overall, this is comparable to many other series of similar patients reported in the literature, all of which utilized higher radiation doses. While the number of patients in this series is small, the median follow-up is now over 10 years (12.26 years) and there has not been a relapse for 8.5 years. All these patients were under 5 years of age at time of diagnosis and radiation treatments. Neuro-cognitive data, available for six of seven surviving children shows that drop in full scale IQ at 1 and 2 years post radiation is less than that seen with 36.00Gy craniospinal radiation.<sup>3</sup>

This experience formed the foundation of an ongoing multicenter study piloted by Children's Hospital of Philadelphia in which children with standard risk medulloblastoma are treated with reduced dose craniospinal radiation (1800 cGy), full dose radiation to the tumor bed (5580 cGy) and chemotherapy including vincristine, cisplatin, CCNU, etoposide and cytoxan (CHP693). Participating centers included New York University Medical Center, Stanford and Children's National Hospital. In the 18 months since opening the study, nine children have been enrolled, three have completed therapy, two have suffered tumor relapse.

The current study will therefore build upon the therapeutic concept of craniospinal radiotherapy dose reduction in children with standard-risk medulloblastoma, initially validated in the CCG-9892 and A9961 studies, by evaluating in a randomized fashion the feasibility of further reducing the dose of craniospinal irradiation to 18.00 Gy in children between 3 and 7 years of age. Notwithstanding the reduction in craniospinal radiotherapy dose, we propose to maintain treatment efficacy in two ways. Local control will be maintained by employing a standard radiation dose to the tumor bed (54.00 Gy, using a 36.00 Gy conformal boost dose). To combat early and exo-primary relapse the intervals between surgery and radiation, and between radiation and post-radiation chemotherapy will be compressed and chemotherapy will include six cycles of CCNU, cisplatin and vincristine, as well as three additional cycles of cytoxan, an agent with known efficacy in treatment of PNET. All of these agents have been successfully administered at the proposed doses in CCG-9892 and A9961 studies.<sup>1-3,8-10</sup> In addition to monitoring survival and the rate of exo-primary relapse using serial neuro-imaging, we propose to monitor cognitive, endocrine and hearing function in these patients.

**Table 1: Treatment of Standard Risk Medulloblastoma**

AUTHOR	CSRT (Gy)	Rx	5yr EFS	EPR
Evans 1990	35.00	X -	65% 62%	NA
Packer 1994	36.00	+	85%	3/8
Thomas 2000	36.00 23.40	- -	67% 52%	8/21 14/25
Packer 1999	23.40	+	79%	3/14
Goldwein 1993	18.00	+	69%	2/3

CSRT – Craniospinal radiation therapy

Rx – Post-radiation chemotherapy

X – CCNU, VCR, prednisone

+ - Cisplatin, CCNU, VCR

EFS – Event free survival

EPR – Exo-primary relapse

NA – Not applicable

## 2.2 Limited Target Local Boost Radiotherapy by Reducing the Volume of Local Radiotherapy Delivered

This trial is also designed to reduce the neuro-toxicity of treatment in children diagnosed with medulloblastoma who have favorable risk factors by examining the feasibility of reducing the volume of radiotherapy to be given to the primary tumor site from the whole posterior fossa to the tumor bed plus a circumscribed margin. Such children have at least a 75% chance of five-year survival, but unfortunately suffer significant morbidity from treatment, even using reduced doses of neuraxis irradiation (i.e., 23.40 Gy as applied on the CCG-9892 and A9961 studies). Radiation to the posterior fossa continues to contribute a substantial dose to the parietal, occipital and temporal lobes. This cumulative dose to the cerebrum possibly has a contributing effect to the decline in neurocognitive function in children treated for medulloblastoma. A second strategy to be examined in this study is a reduction in the volume of the boost dose of irradiation from the entire posterior fossa to the tumor bed plus a circumscribed margin, using three dimensional conformal planning and delivery techniques. Preliminary data indicate that this should not be associated with an excessive increase in local failures and may provide a substantial improvement in functional outcome by reducing the incidence of hearing loss (by diminishing the cochlear radiation dose), endocrine dysfunction (by decreasing radiation to the hypothalamopituitary axis), and cognitive deterioration (by decreasing radiation to the temporal lobes).<sup>7,11-13</sup> Outcome will be assessed in terms of event-free survival, exoprimary relapses, toxicity of therapy, and quality of life indicators.

Another significant late effect that contributes to learning impairment is ototoxicity. Both radiation therapy and cisplatin based chemotherapy may affect the inner ear and result in a loss of high frequency hearing. Attempts to minimize the dose of radiation to the cochlea in children treated for medulloblastoma have been described.<sup>11,12</sup> With 3D conformal radiation therapy methods, the dose to the cochlea and the cerebrum may be reduced. Fukanaga-Johnson has shown that the dose to the cochlea can be reduced even further if the target volume is reduced to encompass not the posterior fossa, as traditionally has been done, but only the primary tumor bed with a margin for microscopic extension.<sup>11,12</sup> This reduction in cochlea radiation dose may lead to a lower rate of ototoxicity in these children.

The hypothalamic-pituitary axis (HPA) also is radiated with conventional posterior fossa irradiation. Generally, the anterior borders of traditional lateral posterior fossa fields are placed at the posterior clinoids. These fields encompass part of the hypothalamus and contribute scatter radiation dose to the pituitary gland. Ironically, conformal radiation plans to minimize cochlea dose while fully treating the posterior fossa may increase the radiation dose to the HPA.<sup>11,12</sup> The unique shape of the posterior fossa target volume necessitates beam arrangements that exit or enter through these uninvolved adjacent normal tissues. For this reason there is a rationale to study a reduction in the volume of the posterior fossa boost using conformal radiation therapy planning as a way of decreasing treatment-related sequelae.

### 2.3 Local Control as a Therapeutic Endpoint

Investigators at the University of Michigan and Children's Hospital of Pennsylvania have undertaken pattern of failure analysis of patients treated with standard radiation therapy.<sup>12</sup> In this series of 114 patients, 27 have failed. Failure was defined as local, if it was within the original tumor bed, and regional if it was outside of the tumor bed but still within the posterior fossa. Local failure within the posterior fossa was observed in only 3 recurrences, only one of which was outside the tumor bed. Similar results were obtained by an institutional report from the Memorial Sloan-Kettering Cancer Center.<sup>13</sup>

In a series of patients with 56 months median follow-up treated with a limited target volume boost with conformal therapy, Wolden reported posterior fossa control in 31 of 32 patients. The conformal boost plans delivered significantly lower doses to critical structures such as the cochlea and temporal lobes of the brain compared to a more traditional treatment approach. The overall and disease free survivals were comparable to other series, despite the reduction in posterior fossa treatment volume.<sup>14</sup>

Comparable observations have also been obtained in a series of cooperative group trials. The intergroup (POG 8631/CCG 923) study was conducted to determine if the dose of craniospinal irradiation could be safely reduced to 23.4 Gy in patients with standard-risk medulloblastoma.<sup>4</sup> Event free survival was 67% at 5 years and 8 years for patients receiving standard dose RT and 52% at 5 and 8 years for low dose RT patients. Of all 126 registered patients, there were 46 who experienced a recurrence, but the posterior fossa was the sole site of relapse in only nine cases.

The German Society of Pediatric Hematology and Oncology (GPOH) conducted a randomized, prospective, multicenter trial (HIT '91) in order to improve the survival of children with medulloblastoma by using postoperative neoadjuvant chemotherapy before radiation therapy as opposed to maintenance chemotherapy after immediate postoperative radiotherapy. Kortman reported the 3-year disease-free survival rate for 82 low-risk patients age 6 to 18 years with no residual disease was 72%. In 27 patients without prior residual disease who failed, only three had local failure only as the primary mode of progression.<sup>15</sup>

CCG-9892 was undertaken to determine the feasibility of treating children with nondisseminated medulloblastoma using reduced-dose craniospinal radiation therapy (23.40 Gy) and adjuvant chemotherapy, administered during and after radiation therapy, that consisted of CCNU, vincristine, and cisplatin.<sup>2</sup> This regimen was chosen after a prospective, nonrandomized study demonstrated a greater than 90% 5-year disease control rate using irradiation and identical chemotherapy in children with nondisseminated medulloblastoma, comparable to those obtained with standard dose of irradiation without chemotherapy.<sup>8</sup> PFS in these patients (n=65) was 86%  $\pm$  4% at 3 years and 79%  $\pm$  7% at 5 years. Of the 14 patients who developed progressive disease, only two had isolated posterior fossa recurrences (three had disseminated disease and nine had recurrences both at the primary site and within the leptomeninges).

These data suggest that with low-dose (23.40 Gy) craniospinal irradiation and adjuvant chemotherapy that the 3-year progression-free survival rate ranges from 72% to 85% with 5-year rates ranging from 70% to

79%. Of those patients that recur, the posterior fossa alone is involved in less than 20%, and isolated failures within the posterior fossa but outside the tumor bed are extremely uncommon.

These observations are consistent with a recent report of Miralbell et al.,<sup>16</sup> who analyzed radiation treatment technique and its impact on patterns of failure in 86 children treated for medulloblastoma in Switzerland. Although a significant correlation in patterns of failure could be demonstrated between quality of the whole brain fields, no correlation in local or posterior fossa failure could be found with the quality of the posterior fossa fields. Taken together, these observations suggest that targeting the boost dose of radiation therapy to a volume smaller than the posterior fossa may be adequate for these children. In support of this view, Merchant et al. reported on the treatment of 14 patients with medulloblastoma using conformal radiation therapy to the tumor bed. Among the 10 patients who received immediate post-operative radiation therapy that included craniospinal irradiation to doses of 23.40 Gy (n=5) and 36.00 Gy (n=5), no failures occurred with a median follow-up of 42 months (range 30-54 months).<sup>13</sup>

#### 2.4 Growth Hormone Deficiency as a Functional Endpoint

Sklar and Constine reviewed the published literature regarding neuroendocrine effects following radiation therapy. Growth hormone deficiency (GHD) is the most common and frequently the only anterior pituitary deficit to develop after cranial irradiation. It has been noted with conventional fractionated radiation with doses  $\geq 18.00$  Gy to the HPA. Data suggest that nearly all children treated with doses in excess of 35.00Gy will develop GHD, which generally occurs within the first 5 years after treatment. In children, a spectrum of Growth Hormone (GH) neurosecretory dysfunction exists that appears to be dose-dependent. When the HPA dose is  $> 30$  Gy, reduced GH following both pharmacologic and physiologic studies is noted. Following 20-24 Gy, spontaneous GH secretion remains low while the GH response to provocative agents is often normal.<sup>17</sup>

In a German study, Schiegelow identified ten patients that developed GHD 10–26 months after irradiation. Cox regression analysis identified the 90% dose-volume of the HPA as the strongest predictor of development of GHD ( $P=0.03$ ). The median dose to the 90% dose-volume of the HPA region was 37.5 Gy (range 2.3–55.3). The cumulated risk of GHD 2.5 years after radiotherapy for children receiving more than and less than 37.5 Gy to the HP region was 87% and 33%, respectively ( $P=0.036$ ).<sup>18</sup>

Stubberfield measured growth rates and GH levels in 48 patients after cranial irradiation for ALL. Growth rates in both groups did not differ for the first 5 years after diagnosis. After this time, however, a significant height decrease was observed in children who had received 24 Gy but not in children who had received 18 Gy (at 8 years the change from diagnosis was  $-0.32 \pm 0.14$  vs.  $-0.73 \pm 0.16$ , 18.00 Gy vs. 24.00 Gy,  $p < 0.05$ ). Overnight GH concentrations (12-h sampling every 20 min) were reduced in both groups compared with healthy age-matched control children but were even lower in the 24Gy group ( $12.7 \pm 0.7$  mU/L vs.  $7.9 \pm 0.6$  vs.  $6.1 \pm 0.5$ ; control vs. 18 Gy and 24 Gy,  $p < 0.001$ ; 18 Gy vs. 24 Gy,  $p < 0.025$ ).<sup>19</sup>

Taken together, these results indicate that sparing the hypothalamus and pituitary axis (HPA) in the posterior fossa boost should reduce the risk of hypopituitarism following radiation therapy. Because, in the proposed study, all patients will receive reduced-dose cranial irradiation, we seek to keep the dose to the HPA less than 35 Gy by delivering the posterior fossa boost in a conformal fashion, with a goal of lowering the incidence of GHD requiring therapeutic intervention.

#### 2.5 Ototoxicity As a Functional Endpoint

In the CCG 9892 study of low dose craniospinal RT (23.40 Gy) and cisplatin-based chemotherapy 32.3% of patients developed hearing loss. In these patients, hearing loss occurred as early as the third cycle of maintenance chemotherapy and as late as the seventh cycle (median, fifth cycle).<sup>2</sup>



In the German Trial, for patients on the radiotherapy and maintenance chemotherapy arm (similar to the proposed regimen), ototoxicity occurred in 34%, reaching Grade III/IV in 9% of patients.<sup>15</sup>

These data suggest that hearing loss is a significant problem following combined chemotherapy and radiation therapy for medulloblastoma. With standard radiation methods, the rate of severe hearing loss is at least one out of three. Reduction in the radiation dose to the cochlea as proposed in the current study may reduce the rate of severe hearing loss, assuming no higher cumulative dose of cisplatin is administered.

In support of this hypothesis, investigators at Baylor described a series of 15 patients treated with craniospinal RT and highly conformal boost to the tumor bed using Intensity Modulated Radiation Therapy, (IMRT) followed by cisplatin-based chemotherapy.<sup>20</sup> They compared ototoxicity in this group to a control group of 11 patients treated with conventional radiation and similar chemotherapy. In the conventional RT group, 64% had grade 3 or 4 ototoxicity (POG 9466 criteria) with a mean dose of 221 mg/m<sup>2</sup> of cisplatin. In the IMRT group with small boost volume treatment, only 13% of patients had grade 3 or 4 ototoxicity with a mean dose of 291 mg/m<sup>2</sup> of cisplatin.

## 2.6 Neuropsychologic Function

Patients between 3 and < 8 years of age, in this study, will be randomized to receive either 18.00 Gy or 23.40 Gy of cranial irradiation. Reduction in the radiation dose to the cerebral hemispheres will also likely be significant with the use of conformal radiation therapy. To assess the impact of reducing both the overall dose of cranial irradiation and the volume of radiotherapy, neuropsychological outcome will be assessed using the ALTE07C1 protocol. We propose collecting radiation dose and volume data (with assistance from QARC and other members of the Advanced Technology Consortium) to quantify the reduction in dose to the uninvolved brain. The RTOG has demonstrated that clinical outcomes can be correlated to dosimetry from 3D treatment plan data stored in treatment planning database at the Image-guided Therapy QA Center.<sup>21</sup>

## 2.7 Quality of Life and Functional Status

Despite treatment advances and improved long-term disease-free survival rates for children with some types of CNS tumors, treatment-related morbidity can be substantial. Two important areas of treatment-related morbidity include problems in behavioral adjustment and academic performance. Historical performance in the legacy research groups (CCG, POG) has been poor in the area of compliance with the administration of such instruments and the majority of studies have been unable to report evaluable results in this important area. We propose to employ a different approach in this study by instructing nurses at each involved institution to administer the QOL battery (BASC-2, BRIEF, PedsQL<sup>TM</sup> 4.0. and ABAS-II), to collate the instrument responses and to submit these important data for analysis.

## 2.8 Gender and Race Differences

There is no reported evidence to suggest that there are differences in outcome by gender or race when otherwise identical patients receive the same treatment.

### 3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

#### 3.1 Study Enrollment

##### 3.1.1 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located at on the CTSU web page (<https://www.ctsu.org>). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

##### 3.1.2 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system 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.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

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.

##### 3.1.2.1 Neurocognitive Testing

**Enrollment onto ALTE07C1 is strongly encouraged.**

##### 3.1.2.2 Quality-of-Life Assessments

Institutions participating in this study will be required to identify an individual (outpatient nurse, nurse practitioner, or research coordinator) who will be responsible for administration of the Quality of Life assessment battery to the child's parents, retrieval of completed assessment forms, and submission of these forms to the study nurse investigator for scoring, analysis, and entry into the COG eRDE. Institutional CRA's should contact the nurse investigator **at the time of study enrollment** to determine when the assessment forms, provided by the nurse investigator, should be mailed to the institution for this evaluation:



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### 3.1.3 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

### 3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 21 calendar days after enrollment. In the event that Day 21 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day. Patients must begin treatment within 31 days of definitive surgery (Day 0). In the event that Day 31 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day.

### 3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

### 3.1.6 Randomization

Randomization will take place at the time a patient is entered On Study via RDE. Eligible patients, between 3 and 7, years of age, inclusive, will undergo two randomizations. The first will assess the disease control rate of patients treated with 18.00 Gy of craniospinal radiotherapy as compared to those receiving 23.40 Gy of craniospinal radiotherapy. The second will assess the disease control rate of patients treated with posterior fossa boost radiotherapy as compared to those treated with tumor bed boost radiotherapy. Patients 8-21 years of age will undergo only the second randomization. **As of Amendment #5, the children 8 years of age and older Arm was completed.**

For those patients between 3 and 7 years of age who are randomized to receive 18.00 Gy of craniospinal irradiation, an additional 5.40 Gy of radiation will be given to the posterior fossa, so that all patients including those randomized to the limited target volume boost will receive a minimum of 23.40 Gy of radiation to the entire posterior fossa. Total dose to the boost target is 18Gy CSRT + 5.4 Gy PF + 30.6 Gy = 54 Gy.

## 3.2 Patient Criteria

**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.**

### 3.2.1 Age

Patients must be greater than or equal to 3 years and less than or equal to 7 years at the time of diagnosis. **As of Amendment #5, the children 8 years of age and older Arm was completed.**

### 3.2.2 Diagnosis

The presence of a posterior fossa medulloblastoma as determined by institutional pathologic evaluation. Preoperative and postoperative cranial MRI with and without contrast must be available.

**Patients with anaplastic medulloblastoma will not be eligible. See Section 15.1.3.1.** Patients with brain stem involvement are eligible.

Presence of minimal volume, non-disseminated disease, as defined by the following criteria:

- 1) There must be unequivocal evidence that the maximal cross-sectional area of residual tumor is 1.5 cm<sup>2</sup> or less on MRI, performed with contrast imaging (preferably within 48 hours, and at most 28 days following surgery) upon elimination of the tumor in all three phases.
- 2) No evidence of metastatic disease in the head, spine, or CSF.
  - Assessment must include a pre-operative (within 5 days prior to surgery) or postoperative enhanced MRI of the spine within 28 days after surgery
  - Cytological examination of CSF performed after surgery but before the time of enrollment. False positive cytology can occur within 10 days of surgery. Patients with positive CSF cytology obtained before 10 days after surgery may have cytology repeated to determine eligibility.

### 3.2.3 Performance Level (See Appendix I)

Patients must have a Karnofsky performance level of  $\geq 50$  for patients  $> 16$  years of age or a Lansky performance scale of  $\geq 30$  for patients  $\leq 16$  years of age.

### 3.2.4 Prior Therapy

Patients must have no previous radiotherapy or chemotherapy other than corticosteroids.

### 3.2.5 Organ Function Requirements:

#### 3.2.5.1 Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR  $\geq 70$ ml/min/1.73m<sup>2</sup> 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
$\geq 16$ 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 CDC.

#### 3.2.5.2 Adequate liver function defined as:

- Total bilirubin  $< 1.5 \times$  upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT)  $< 3 \times$  upper limit of normal (ULN) for age.

#### 3.2.5.3 Adequate Bone Marrow Function Defined as:

- Peripheral absolute neutrophil count (ANC) >1500/ $\mu$ L
- Platelet Count > 100,000/ $\mu$ L (transfusion independent)
- Hemoglobin greater than 10 gm/dL, (may receive RBC transfusions)

### 3.2.6 Pregnancy/Contraception

The Chemoradiotherapy and Maintenance regimens are cytotoxic and potentially mutagenic. They may potentially affect an unborn or nursing child. Therefore, patients who are pregnant or breast-feeding will not be eligible. Patients of childbearing potential must practice an effective method of birth control while participating on the study. Females who have achieved menarche must have a negative pregnancy test.

### 3.2.7 Regulatory

#### 3.2.7.1

All patients and/or their parents or legal guardians must sign a written informed consent.

#### 3.2.7.2

All institutional, FDA, and NCI requirements for human studies must be met.

## 4.0 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 per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Surgery			Chemoradiotherapy								Maintenance								
	31 Days		Radiation Therapy (XRT)							Rest									
		Cycle									1	2	3	4	5	6	7	8	9
		Week	1	2	3	4	5	6	7		11	17	23	27	33	39	43	49	55
		Day	1	8	15	22	29	36	43										
			Chemotherapy								Maintenance Chemotherapy								
			V	V	V	V	V	V	V		A	A	B	A	A	B	A	A	B

**As of Amendment #5, the children 8 years of age and older Arm was completed.**

### Chemoradiotherapy

XRT – Age 3 to 7

18.00 vs 23.40 Gy CSRT (*randomized*)

5.40 Gy Posterior fossa (if 18.00 Gy CSRT)

30.60 Gy Local vs Posterior fossa boost (*randomized*)

XRT – Age 8 to 21

23.40 Gy CSRT

30.60 Gy Local vs Posterior fossa boost (*randomized*)

V- VinCRISTine (1.5 mg/m<sup>2</sup>, maximum dose 2 mg) IV push or infusion weekly X6 during radiation

### Maintenance

Cycle A (42 Days)

CISplatin (75 mg/m<sup>2</sup>) IV over 6 hours on Day 1

Lomustine (CCNU) (75 mg/m<sup>2</sup>) orally on Day 1

VinCRISTine (1.5 mg/m<sup>2</sup>, maximum dose 2 mg) IV push or infusion Days 1, 8, and 15

Cycle B (28 Days)

Cyclophosphamide (1000 mg/m<sup>2</sup>) IV over 1 hour on Days 1 and 2

VinCRISTine (1.5 mg/m<sup>2</sup>, maximum dose 2 mg) IV push or infusion on Days 1 and 8

MESNA (360 mg/m<sup>2</sup>/dose) IV infusion over 15-30 minutes starting 15 minutes prior to or at the same time as cyclophosphamide and repeated at 4 and 8 hours.

### 4.1 Randomizations

Eligible patients, between 3 and 7 years of age, inclusive, will undergo two randomizations. The first will assess the disease control rate of patients treated with 18.00 Gy of craniospinal radiotherapy as compared to those receiving 23.40 Gy of craniospinal radiotherapy. The second will assess the disease control rate of patients treated with posterior fossa boost radiotherapy as compared to those treated with tumor bed boost radiotherapy. Patients 8 years of age and older will undergo only the second randomization. **As of Amendment #5, the children 8 years of age and older Arm was completed.**

## 4.2 Concomitant Medications Restrictions

### 4.2.1

Clinically significant drug interactions have been reported when using vincristine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors of cytochrome P450 3A4 include azole antifungals, such as fluconazole, voriconazole, itraconazole, ketoconazole, and strong inducers include drugs such as rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort. The use of these drugs should be avoided with vincristine.

### 4.2.2

The clinical outcome and significance of CYP450 interactions with cyclophosphamide are less clear. CYP450 3A4 stimulators or inhibitors should be avoided or used with great caution. Aprepitant also interacts with CYP3A4 and should be used with caution with etoposide or vincristine chemotherapy.

Additional inducers or inhibitors of CYP450 enzymes can be found at <http://medicine.iupui.edu/clinpharm/ddis/>.

### 4.2.3

CISplatin should be used with caution with nephrotoxic drug. Aminoglycoside should be avoided or used with caution during or shortly after cisplatin administration and concomitant use with amphotericin B should probably also be avoided. Patients receiving CISplatin and other potentially ototoxic drugs such as aminoglycoside or loop diuretics concomitantly should be closely monitored for signs of ototoxicity. In patients receiving cisplatin and phenytoin or fosphenytoin, serum concentrations of phenytoin may decrease. Carbamazepine concentration may also decrease with concomitant use. Plasma levels of anticonvulsant agents should be monitored and doses adjusted during therapy with CISplatin.

## 4.3 Administration Schedule for Chemoradiotherapy

All patients must begin therapy within 31 days of definitive surgery. Please see Section 18.0 for Radiation Therapy Guidelines.

**ALL PATIENTS WILL REQUIRE REVIEW OF RADIATION THERAPY TREATMENT PLAN. RADIATION TREATMENT PLAN MUST BE SUBMITTED TO QARC FOR QA REVIEW (SECTION 18.9)**

### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

1.5 mg/m<sup>2</sup>/day (maximum single dose 2 mg) once weekly Weeks 2-7 during radiation for a total of 6 doses. VinCRISTine should be started one week after initiation of radiation therapy and given weekly thereafter. The absolute dose of vinCRISTine should be rounded down to the nearest 0.1 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.

**ACNS0331: Chemoradiotherapy**

Six weeks of radiation therapy (Weeks 1-6) and 4 weeks of rest (Weeks 7-10) will constitute one reporting period.

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
DOB

Radiation Therapy (See Section 18.0) must begin within 31 days of diagnostic surgery. Week 7 to 10 is a rest period (4 Week Rest Period), then proceed to Maintenance. The Therapy Delivery Map is on **one** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m <sup>2</sup> (maximum dose 2 mg)	Administer once weekly Weeks 2-7 during radiation for a total of 6 doses	Begin one week after initiation of radiation therapy, then continue weekly for 6 doses. The doses of vinCRISTine should be rounded down to the nearest 0.1 mg.	a. Physical and Neurologic Exam, Weight b. CBC, Differential, Platelets c. Endocrine Evaluation (See Section 20.0)  <i>See Section 7.1 for a complete list of observations.</i>  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>

Date Due	Date Given	Week	Ht cm Day	VCR mg	Wt kg Studies	BSA m <sup>2</sup> Comments (Include any held doses, or dose modifications)
				<b>Enter calculated dose above and actual dose administered below</b>		
		1	1		a, b	
		2	8	mg#	a, b	
		3	15	mg#	a, b	
		4	22	mg#	a, b	
		5	29	mg#	a, b	
		6	36	mg#	a, b	
		7	43	mg#	a, b, c\$	
		11		To begin Maintenance, the ANC must be > 1000/μL, platelets ≥ 75,000/μL. If ANC ≤ 1000/μL or platelets < 75,000/μL then repeat CBC and differential at least twice a week until criteria are met.		

# - VinCRISTine can be administered any day during the week.

\$ - Obtain at the completion of XRT

**SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE**

#### 4.4 Administration Schedule for Maintenance Chemotherapy

Maintenance Chemotherapy begins 4 weeks after completion of chemoradiotherapy (Week 11). Each cycle of Maintenance will begin at full dose only when ANC > 1000/ $\mu$ l and platelets  $\geq$  75,000/ $\mu$ l. Myeloid growth factor will be used to maintain treatment schedule if there is a 2 week delay in initiation of chemotherapy due to low white count (See Section 8.3 for administration guidelines). If a cycle of Maintenance is due but the ANC or platelets are below the threshold values, therapy should be held or modified as per Section 5.2. If the patient is unable to start the next cycle of Maintenance within 6 weeks, notify the Study Chair or Vice-Chair and it is at the discretion of the treating physician whether to continue treatment. Nine (9) cycles of chemotherapy will be delivered in an AABAABAAB pattern. A venous access device is recommended prior to the start of Maintenance.

##### 4.4.1 Regimen A Cycles 1, 2, 4, 5, 7, 8 (6 weeks = 1 cycle)

#### **Lomustine (CCNU): PO**

75 mg/m<sup>2</sup> orally on Day 1. The availability of CCNU in 10, 40 and 100 mg capsules affects the ability to actually achieve the calculated dose of 75 mg/m<sup>2</sup> in many patients, especially those with the smallest surface area. A simple rule of rounding up or down to the nearest 10 mg does not produce consistent effects for all surface areas: variance from ideal dose may be as high as 20%. **[To achieve a more consistent approach to Lomustine administration, Appendix III provides a table outlining the dose to be given for specified surface areas.]** The actual doses given are those that result in the smallest absolute percent change from the calculated ideal dose.

In most instances, the actual dose is within  $\pm$  10% of the ideal dose; a change that is likely to be of minimal biologic significance. For patients whose surface area falls between those noted in the table, give a dose that results in the smallest absolute change from the ideal dose. A similar method should be used for calculating dose reductions, i.e., rounding off to the nearest 10 mg dose that results in the smallest absolute change.

Administer capsules whole on an empty stomach (at least 1 hour before or 2 hours after food) with plenty of fluids (at least 240 mL/8 oz for children > 3 years of age; at least 4 oz for children  $\leq$  3 years of age). Administer at bedtime, if possible, to reduce nausea and vomiting. Typically, the whole dose, even if comprised of several capsule sizes, is placed in one prescription bottle to be taken at one time.

#### **VinCRISTine: IV push over 1 minute or infusion via minibag as per institutional policy**

1.5 mg/m<sup>2</sup> (maximum single dose 2 mg) on Days 1, 8, and 15. The absolute doses of vinCRISTine to be delivered are a function of body surface area, rounded down to the nearest 0.1 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.

**CISplatin: IV over 6 hours**

75 mg/m<sup>2</sup> IV on Day 1.

Avoid use of aluminum containing needles or administration sets, since aluminum interacts with CISplatin causing black precipitate formation and loss of potency. The infusion solution should include at least 0.2% sodium chloride. CISplatin solutions should not be refrigerated to avoid precipitation. CISplatin is incompatible with sodium bicarbonate and alkaline solutions. Accidental extravasation with solutions that are > 0.5 mg/mL may result in significant tissue toxicity.

**Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).**

**Suggested hydration and supportive care:**

- 2 to 0 hrs      Prehydration 500mL/m<sup>2</sup> D5 1/2NS with Mannitol 10 GM/m<sup>2</sup> at 250mL/m<sup>2</sup>/hr
- 0-6 hrs          CISplatin 75 mg/m<sup>2</sup> with 10 gm/m<sup>2</sup> Mannitol in D5 1/2 NS 1000 mL/m<sup>2</sup> IV at 167mL/m<sup>2</sup>/hr for 6 hours.
- 6-24 hrs:      Continue hydration with D5 ½ NS with magnesium sulfate 0.5-1 mEq/kg in post hydration fluid to run at 125 mL/m<sup>2</sup>/hr IV. A Magnesium sulfate concentration of 8 mEq/L in the post hydration fluid will provide recommended supplementation of Magnesium. Give IV hydration for at least 6 hrs. For those patients who are not having problems with nausea or emesis the remainder of the hydration can be completed orally. Twenty-four hours after cisplatin continue magnesium supplementation IV At 0.5-1 mEq/kg/day or orally as recommended below.

Children will often require magnesium supplementations once CISplatin therapy is instituted. Close monitoring of magnesium levels is recommended and magnesium supplementation is recommended throughout therapy. Alternative oral forms of magnesium like magnesium gluconate and magnesium oxide are allowable according to investigator preference. The recommended oral dosing would be 10-20 mg/kg/dose of elemental magnesium three to four times daily. This would equal 0.8-1.7 mEq/kg/dose. See the conversion provided below:

Magnesium Oxide:              **400mg tab of MagOx = 242mg elemental Magnesium = 20 mEq Magnesium**

Magnesium Gluconate:        **500mg tab of Magnesium gluconate = 27mg elemental Magnesium = 2.4 mEq Magnesium**

Urine output, once CISplatin infusion is started, should be monitored hourly; if it falls below 3 mL/kg/hr for 2 hrs, a mannitol bolus of 0.5 g/kg and 10 mL/kg of D5W or NS are suggested. The use of furosemide is discouraged for clinical promotion of diuresis since furosemide may impair renal cisplatin clearance. However, if a mannitol bolus fails to increase urine output over the ensuing hour period, then furosemide 1 mg/kg could be given as an IV bolus.



<b>ACNS0331: Regimen A Cycles 1, 2, 4, 5, 7, 8</b> Six weeks will constitute one reporting period.	_____ Patient name or initials	_____ DOB
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Maintenance Chemotherapy begins on Week 11 after completion of chemoradiotherapy. Each cycle of Maintenance will begin at full dose only when ANC > 1000/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L. Myeloid growth factor will be used to maintain treatment schedule if there is a 2 week delay in initiation of chemotherapy due to low white count (See Section 8.3 for administration guidelines). Use one copy of the TDM for each cycle. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Lomustine (CCNU)	PO	75 mg/m <sup>2</sup>	Day 1	See Section 4.4.1 and Appendix III	a. History, Physical and Neurologic Exam, Height, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Audiogram e. GFR or Creatinine Clearance Based on Age/Gender (See Section 3.2.5.1) f. CBC, Differential, Platelets g. Liver function, BUN, Creatinine, Electrolytes, Ca, Magnesium,  *- If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M <sub>3</sub> ).  <i>See Section 7.0 for a complete list of observations.</i>  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m <sup>2</sup> (maximum single dose 2.0 mg)	Day 1, 8, 15	The absolute doses of vinCRISTine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg. See Section 4.4.1	
CISplatin (CDDP)	IV over 6 hours	75 mg/m <sup>2</sup>	Day 1	See Section 4.4.1 for suggested hydration and supportive care. Audiograms should be obtained prior to Cycles 1, 2, 4, 5, 7 and 8.	

		Cycle _____		Ht _____ cm		Wt _____ kg		BSA _____ m <sup>2</sup>	Comments (Include any held doses, or dose modifications)
Date Due	Date Given	Week	Day	CCNU _____mg	VCR _____mg	CDDP _____mg	G-CSF _____mcg	Studies	
				<b>Enter calculated dose above and actual dose administered below</b>					
		1	1	_____mg	_____mg	_____mg		a,b#,c#,d,e,f,g	
		2	8		_____mg		_____mcg\$	f	Indicate last day of G-CSF (if given) _____
		3	15		_____mg			f	
		7	42	Each cycle of Maintenance will begin at full dose only when counts are met.					

# - Obtain within 1 week prior to Cycles 1, 4, and 7.

\$ - Only administer if needed per section 8.3. Start myeloid growth factor (G-CSF 5 mcg/kg/day SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1500/ $\mu$ L after the expected nadir. May be continued without regard to VCR. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

**SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE**

#### 4.4.2 Regimen B Cycles 3, 6, 9 (4 weeks = 1 cycle)

**Cyclophosphamide:** IV over 1 hour

1000 mg/m<sup>2</sup> IV on Days 1 and 2.

May be administered as undiluted drug (only when reconstituted with 0.9% NaCl to a 20 mg/mL solution to avoid a hypotonic solution) or further diluted.

**Suggested Hydration:**

Prehydrate at 125mL/m<sup>2</sup>/hour before and Post hydrate for at least 6 hours IV at 125 mL/m<sup>2</sup>/hour.

**MESNA:** IV over 15 to 30 minutes or by continuous infusion

360 mg/m<sup>2</sup>/dose on Days 1 and 2. Administer at least 15 minutes prior to or at the same time as cyclophosphamide and repeat at 4 and 8 hours post-cyclophosphamide. The 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 8 hours after the end of the cyclophosphamide infusion, or by institutional protocol.

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

1.5 mg/m<sup>2</sup> (maximum single dose 2 mg) on Days 1 and 8. The absolute doses of vinCRISTine to be delivered are a function of body surface area, rounded down to the nearest 0.1 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.

**ACNS0331: Regimen B Cycles 3, 6, 9**

Four weeks of chemotherapy will constitute one reporting period.

\_\_\_\_\_  
Patient name or initials

\_\_\_\_\_  
DOB

Each cycle of Maintenance will begin at full dose only when ANC > 1000/ $\mu$ L and platelets  $\geq$  75,000/ $\mu$ L. Myeloid growth factor will be used to maintain treatment schedule if there is a 2 week delay in initiation of chemotherapy due to low white count (See Section 8.3 for administration guidelines). Use one copy of the TDM for each cycle. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Cyclophosphamide (CPM)	IV over 1 hour	1000 mg/m <sup>2</sup>	Days 1 and 2	<u>Suggested hydration:</u> Prehydrate at 125 mL/m <sup>2</sup> /hour before and post hydrate for at least 6 hours IV at 125 mL/m <sup>2</sup> /hour.	a. History, Physical and Neurologic Exam, Height, Weight b. MRI of Brain with and without Gadolinium c. Audiogram d. GFR or Creatinine Clearance Based on Age/Gender (See Section 3.2.5.1) e. CBC, Differential, Platelets f. Liver function, BUN, Creatinine, Electrolytes, Ca, Magnesium
MESNA	IV push	360mg/m <sup>2</sup> /dose	Days 1 and 2	Administer at least 15 minutes prior to or with cyclophosphamide and repeated at 4 and 8 hours post-cyclophosphamide.	* - If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M <sub>3</sub> ).  <i>See Section 7.0 for a complete list of observations.</i>  <b>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE</b>
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m <sup>2</sup> (maximum dose of 2.0 mg)	Days 1 and 8	The absolute doses of vinCRISTine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg.	

Date Due	Date Given	Cycle	Week	Day	Ht cm	CPM mg	MESNA mg	Wt kg	VCR mg	G-CSF mcg	BSA m <sup>2</sup>	Studies	Comments (Include any held doses, or dose modifications)
			1	1		mg	mg		mg			a, e, f,	
				2		mg	mg			mcg\$			Indicate last day of G-CSF (if given) _____
			2	8					mg			e	
			3	15								e	
			4	22									
				28								b#, c@, d@, e#	
													Each cycle of Maintenance will begin at full dose only when counts are met.

# - Obtain at the end of Maintenance Therapy

\$ - Only administer if needed per section 8.3. Start myeloid growth factor (G-CSF 5 mcg/kg/day SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1500/ $\mu$ L after the expected nadir. May be continued without regard to VCR. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

@ - Obtain within 6 weeks of completion of chemotherapy

**SEE PROTOCOL SECTION 5.0 FOR DOSE MODIFICATIONS. SEE SECTION 8.0 FOR SUPPORTIVE CARE**

## 5.0 DOSE MODIFICATIONS FOR TOXICITIES

### 5.1 Vincristine Toxicity

#### 5.1.1 Vincristine Neurotoxicity

For seizures, hold one (1) dose, then reinstitute at  $1 \text{ mg/m}^2$  (1.5 mg maximum) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

Neurotoxicity Grade 3/4, foot drop, severe paresis, disabling paresthesias or ileus: hold one dose, resume vincristine at  $1 \text{ mg/m}^2$  (1.5 mg maximum) and then escalate to full dosage when symptoms resolve.

#### 5.1.2 Jaw Pain

Treat with analgesics (not salicylates). Do not hold or reduce vincristine.

#### 5.1.3 Hepatotoxicity

If total bilirubin is greater than 1.9 mg/dL, hold vincristine dose. If direct bilirubin is 1.5 - 1.9 mg/dL, administer vincristine at  $1 \text{ mg/m}^2$ .

### 5.2 Hematological Toxicity

#### 5.2.1

If chemotherapy is due and the absolute neutrophil count remains below  $750/\mu\text{L}$  or the platelet count is less than  $75,000/\mu\text{L}$ , the next cycle of chemotherapy should be delayed. Repeat CBC and platelet count weekly.

If the next cycle of Maintenance is due and  $\text{ANC} < 750/\mu\text{L}$  hold chemotherapy until  $\text{ANC} \geq 750/\mu\text{L}$ .

- If the patient is due to receive Regimen A, the dose of Lomustine (CCNU) should be reduced to  $20 \text{ mg/m}^2$ .
- If the patient is due to receive Regimen B, the dose of Cyclophosphamide should be reduced by 50% on Days 1 and 2.

If the next cycle of Maintenance is due and ANC is above or equal to  $750/\mu\text{L}$  but below  $1,000/\mu\text{L}$  or the platelet count is  $< 75,000/\mu\text{L}$ :

- If the patient is due to receive Regimen A, the dose of Lomustine (CCNU) should be reduced by 50% ( $38 \text{ mg/m}^2$ )
- If the patient is due to receive Regimen B, the dose of Cyclophosphamide should be reduced by 25% ( $750 \text{ mg/m}^2/\text{day}$ ) on Days 1 and 2.

If the ANC is less than  $750/\mu\text{L}$  when the next cycle is due, despite the dose reduction in CCNU, hold chemotherapy until the ANC is greater than or equal to  $750/\mu\text{L}$ . For the next cycle of Regimen A, reduce Lomustine (CCNU) to  $20 \text{ mg/m}^2$ .

If a cycle of chemotherapy is delayed for over 2 weeks due to neutropenia, subsequent cycles of chemotherapy should include myeloid growth factor as detailed in Section 8.3.

#### 5.2.2

If the platelet count is less than  $75,000/\mu\text{L}$  for longer than four weeks, perform a bone marrow aspirate and biopsy to differentiate between tumor invasion, marrow hypoplasia, or other causes of thrombocytopenia.

### 5.2.3 Hemorrhagic Cystitis (Hematuria)

#### Microscopic Hematuria

For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), there is no modification of the cyclophosphamide or mesna.

For persistent microscopic hematuria (> 2 abnormal urinalyses during a cycle of therapy), increase hydration to 3500-4000 mL/m<sup>2</sup>/day.

#### Gross Hematuria

All episodes of gross hematuria should be evaluated in conjunction with a pediatric surgical consult. Further testing, such as cystoscopy, urine culture, excretory urogram, and voiding cystogram should be considered based on good clinical judgment.

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during or following a cycle of therapy, do not modify cyclophosphamide dose. Use continuous infusion mesna, at 100% of the cyclophosphamide dose. Start the mesna infusion 15-30 min prior to or at the same time as cyclophosphamide and continue for 24 hours after the completion of the cyclophosphamide infusion.

For persistent gross hematuria after completion of a cycle of therapy, hold subsequent cyclophosphamide until the urine clears to less than gross hematuria. Reinstitute cyclophosphamide at full dose, with the mesna changed to a continuous infusion.

For persistent gross hematuria occurring during a cycle of cyclophosphamide, interrupt the cyclophosphamide. Withhold further cyclophosphamide until the next cycle of therapy or until urine clears. For subsequent cycles give mesna by continuous infusion. For occurrence of a second episode of gross hematuria or persistence of microscopic hematuria on the continuous infusion regimen, continue the cyclophosphamide when the urine clears to less than gross hematuria.

For persistent gross hematuria on the mesna continuous infusion regimen, discontinue the cyclophosphamide.

## 5.3 **Nephrotoxicity**

### 5.3.1

If the creatinine clearance or GFR is less than 50% of baseline value, then the cisplatin should not be administered. It should be held until the creatinine clearance rises above 50% of baseline value.

### 5.3.2

If the creatinine clearance or GFR is less than 75% of baseline value, then the cisplatin dose should be reduced by 50% of the calculated dose.

### 5.3.3

If the creatinine clearance or GFR does not rise above 30 mL/min/1.73 m<sup>2</sup>, the cisplatin should be deleted from treatment.

### 5.3.4

Following transient renal dysfunction, as defined above, the cisplatin should be reinstituted at 50% dosage until the creatinine clearance or GFR has maintained above 50% of baseline value for two cycles of chemotherapy. After two cycles of therapy with acceptable creatinine clearance, cisplatin should be given at full doses.

#### 5.4 **Ototoxicity**

For a decrease in auditory acuity of  $\geq 30$  decibels at 4,000 – 8,000 Hz, a 50% reduction in cisplatin dosage should be made. For a  $\geq 20$  decibel loss at 500-3,000 Hz, a 50% reduction in cisplatin dosage should be made. For Grade 4 ototoxicity, cisplatin should be held and not restarted unless follow-up audiograms show an improvement in hearing function.

#### 5.5 **Hypomagnesemia**

As a consequence of renal tubular wastage of magnesium caused by cisplatin, hypomagnesemia can develop. It may become symptomatic manifested by paresthesias, muscle cramps, weakness and occasionally disorientation seizures. If this occurs, magnesium should be given orally or intravenously.

### 6.0 **DRUG INFORMATION**

See the consent document for toxicities. All other information is available on the COG website in the manual titled “Drug Information for Commercial Agents used by the Children’s Oncology Group” at: [https://members.childrensoncologygroup.org/prot/reference\\_materials.asp](https://members.childrensoncologygroup.org/prot/reference_materials.asp) under **Standard Sections for Protocols**.

### 7.0 **EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED**

All entry/eligibility studies must be performed within 2 weeks prior to entry onto the trial (unless otherwise specified).

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 per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

## 7.1 Required Clinical, Laboratory and Disease Evaluations

### 7.1.1 Required Evaluations Before and During Protocol Therapy

Test	At Diagnosis	During RT	Completion of RT	Prior to Each Maintenance Cycle	Completion of Treatment	At Relapse or Suspected Relapse
MRI Brain	Pre-op and Post-op <sup>2</sup>			X <sup>6</sup>	X	X
MRI Spine	Pre or post –op <sup>1</sup>			X <sup>6</sup>		X
CSF Evaluation	post –op <sup>4</sup>					X
Audiogram	X			X <sup>7</sup>	X <sup>9</sup>	
Height/Weight	X			X		X
GFR or Cl <sub>Cr</sub> or serum creatinine based on age/gender (See Section 3.2.5.1)	X			X <sup>7</sup>	X <sup>9</sup>	
Endocrine Evaluation <sup>3</sup>	X		X <sup>3</sup>		X <sup>10</sup>	
CBC, Diff. and Platelet Count	X	X Weekly		X <sup>8</sup>	X	
Liver function, BUN Creatinine, electrolytes (Ca, Mg)	X			X		
History & Physical with Neurologic Exam	X <sup>5</sup>	X Weekly		X		X
Pathology Central Review Requirements (See Section 15.4)	X					
Biology Studies (See Section 16.7)	X					

- 1 - Spinal MRI to include an enhanced complete (cervical, thoracic, lumbar and sacral) pre-op (within 5 days prior to surgery) or post-op within 28 days after surgery.
- 2 - Assessment must include pre-op and post-op MRI performed with and without contrast preferably within 48 hours and at most 28 days after surgery.
- 3 - See Section 20.0
- 4 - Recommended that CSF be obtained 10 days following surgery but before time of registration.
- 5 - History and physical to include assessment of head circumference and sexual maturation.
- 6 - Obtain within 1 week prior to Cycles 1, 4, and 7.
- 7 - Obtain prior to each cycle of Regimen A (Cycles 1, 2, 4, 5, 7, 8)
- 8 - Obtain prior to each cycle of chemotherapy and weekly the first 3 weeks of each cycle
- 9 - Obtain within 6 weeks of completion of chemotherapy
- 10 - Obtain within 3 months of completion of chemotherapy. See Section 20.0

7.1.2 Required Evaluations Following Completion of Protocol Therapy

Observation	3 Months	6 Months	9 Months	1 Year	1.5 Years	2 Years	2.5 Years	3 Years	Annually After 3 Years	At Relapse/ Disease Progression <sup>1</sup>
History & Physical with Neurologic Exam <sup>4</sup>	X	X	X	X	X	X	X	X	X	X
Height /Weight	X	X	X	X		X		X	X	X
MRI Brain	X	X	X	X	X	X	X	X	X	X
MRI Spine <sup>3</sup>	X	X	X	X	X	X	X	X	X	X
CSF Evaluation										X
Audiogram				X				X	X <sup>5</sup>	
CBC, Diff. And Platelet Count	X	X	X	X	X	X	X	X	X	
Liver function, BUN, Creatinine, Electrolytes (Ca, Mg)	X	X	X	X	X	X	X	X	X	
Endocrine Evaluation <sup>2</sup>		X		X		X		X	X	

1 If patient has had relapse or disease progression, the required follow-up studies will include an annual physical and neurologic exam. All other tests will not be required.

2 See Section 20.0

3 Spinal MRI to include complete spine (cervical, thoracic, lumbar and sacral).

4 History and physical to include assessment of head circumference and sexual maturation.

5 Obtain at 5 years only unless clinically indicated.



## 7.2 Optional Studies

### 7.2.1 Neuropsychologic Evaluations

Patients who consent to participate on ALTE07C1 will be assessed at three time points: at 9 months ( $\pm 3$  months) post cancer diagnosis; at 30 months ( $\pm 3$  months) post diagnosis, and again at 60 months ( $\pm 3$  months) post diagnosis. Age appropriate tests will be used and will include measures of broad cognitive functioning (IQ) and specific areas of neuropsychological functioning, emotional-behavioral functioning, and quality of life. Total testing time should be approximately 1 hour at each assessment point. See Section 19.1.

### 7.2.2 Quality of Life Evaluations

Patients who consent to participate on the optional quality of life evaluations will be assessed at three time points: at 9 months ( $\pm 3$  months) post cancer diagnosis; at 30 months ( $\pm 3$  months) post diagnosis, and again at 60 months ( $\pm 3$  months) post diagnosis. Age appropriate tests will be used. Total testing time should be approximately 20 minutes at each assessment point. See Section 19.2.

## 8.0 SUPPORTIVE CARE GUIDELINES

See Section 18.7 for Supportive Care Guidelines during Chemoradiotherapy.

### 8.1 Venous Access

Patients are required to have an indwelling central venous access catheter prior to Maintenance Chemotherapy to facilitate chemotherapy and the use of sedation/anesthesia in young children.

### 8.2 Antiemetics

The preferred antiemetic for cisplatin is ondansetron (0.15 mg/kg) given  $\frac{1}{2}$  hour prior to infusion and every 4 hours thereafter for a total of 3 doses. Corticosteroid use as an antiemetic should be avoided if possible.

### 8.3 Myeloid Growth Factor

Myeloid growth factor (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) will be used to maintain treatment schedule if there is a 2 week delay in initiation of chemotherapy due to low white count. May be continued without regard to vinCRISTine. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

### 8.4 Fever and Neutropenia

Patients who develop a fever greater than 38.5°C should be evaluated for neutropenia and infection. If the patient has an indwelling catheter or has an ANC < 500/ $\mu$ l blood cultures should be drawn and antibiotics should be administered per institutional policy. Aminoglycosides should be avoided if possible to decrease the chance of ototoxicity. Filgrastim can be administered according to institutional guidelines.

### 8.5 Prophylactic Antibiotics

Patients who receive chemotherapy should be started on trimethoprim (TMP)/sulfamethoxazole (SMZ) by mouth at 2.5 mg/kg/dose (160 mg max) twice daily on 3 sequential days per week or per primary care institution's protocol for *Pneumocystis carinii* prophylaxis. TMP/SMZ can be discontinued 3 months after chemotherapy has discontinued. Patients with TMP/SMZ allergy should be considered for treatment with dapsone or pentamidine.

## Recommendations

1. All patients without a contraindication should receive TMP/SMX 5mg/kg/day TMP divided bid for 3 sequential days per week.
2. Dapsone 2 mg/kg/day (100 mg max) given once daily should be used as second line prophylaxis for the following groups:
  - Patients with TMP/SMX allergy or intolerance
  - TMP/SMX failure
  - Patients in whom a transient drop in hemoglobin would place them at significant risk should receive Pentamidine.
3. Pentamidine can be given IV or aerosolized and is generally efficacious once monthly. Pentamidine should be considered prophylaxis for the following groups:
  - Patients without prescription plans who are unable to afford TMP/SMX or Dapsone,
  - Patients who are non-adherent with oral TMP/SMX or Dapsone,
  - Patients with TMP/SMX and Dapsone allergy or intolerance,
  - Patients for whom a mild hemolytic anemia would not be tolerated.

## 8.6 Blood Products

### 8.6.1 Platelets

Patients will be transfused as necessary with platelets. It is suggested that the platelet count be maintained > 30,000/ $\mu$ L. All blood products will be irradiated to prevent graft-versus-host disease. Filters to remove leukocytes should be used to prevent WBC sensitization. CMV seronegative patients should receive CMV negative blood products.

### 8.6.2 Red Blood Cells

Therapy-induced anemia and reticulocytopenia are expected with this protocol. Patients will be transfused as necessary with irradiated packed red blood cells to maintain a hematocrit > 20-25%. Blood products will be irradiated to prevent graft-versus-host disease. Filters should be used to prevent WBC sensitization.

## 8.7 Nutritional Support

Any patient with greater than 10% weight loss should begin nutritional support. Aggressive nutritional support will be provided either enterally or via a central venous catheter with parenteral hyperalimentation. All patients should have their magnesium checked prior to each cycle and be supported with magnesium supplementation if necessary in a minimum dose of 3 mEq/m<sup>2</sup>/day p.o. or IV in three divided doses to maintain serum levels in the normal range.

## **9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA**

### **9.1 Criteria for Removal From Protocol Therapy**

- a) Progressive disease or relapse.
- b) Refusal of further protocol therapy by patient/parent/guardian.
- c) Completion of planned therapy.
- d) Physician determines it is in patient's best interest.
- e) Second Malignant Neoplasm

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 consent for follow-up was withdrawn.

### **9.2 Off Study Criteria**

- a) Death.
- b) Lost to follow-up status (must be granted by SDC).
- c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., at recurrence)
- d) Withdrawal of consent for any further data submission.
- e) Tenth anniversary of the date the patient was enrolled on this study.

## **10.0 STATISTICAL CONSIDERATIONS**

This is a randomized trial in average risk medulloblastoma comparing involved field radiation therapy (IFRT) to whole posterior fossa irradiation (PFRT) in children 3 to 21 years of age. An additional, factorial randomization in children 3 to 7 years of age will compare 18.00 Gy to 23.40 Gy craniospinal irradiation (CSI). The primary objective of the statistical analysis is to determine whether either of the reductions in radiation therapy results in a decrease in the long-term event-free survival in these patients. Other objectives include estimating the rate of late cognitive and endocrinological effects, and estimating the relative occurrence of LPF, NLPF, and NPF failures. As of Amendment #5, enrollment data so far has revealed a lower than expected proportion aged 3 to 7 years

### **10.1 Patient Accrual**

Recent experience indicates that approximately 70 patients with average risk medulloblastoma are available from COG institutions each year. Data from study A9961 suggests that 50% of patients (specifically  $49.8\% \pm 2.5\%$ ) enrolled in this study will be aged 3 to 7 years old.

### **10.2 Study Duration**

The final analysis data set used to address the primary objectives of the study will exclude patients who revealed unequivocal evidence of dissemination or excess residual disease based on central review. We expect approximately 10% of the patients falling in this category based on the central review data available so far. The amendment to exclude patients with anaplasia from this standard risk study was approved in year 2008. There were approximately ten anaplastic patients enrolled on the trial prior to the activation of the amendment, and they will be excluded from the primary analysis data set as well. Hence, the target accrual for this study was approximately 510 patients (455+45+10) overall to ensure 455 eligible and evaluable patients, and 255 patients to ensure 227 eligible and evaluable patients aged 3 to 7 years, for the primary analysis. As of Amendment #5, enrollment of 514 patients has revealed a lower than expected proportion aged 3 to 7 years old (42.7%). Therefore, the target accrual is an additional 40 patients in the 3-7 year age group to ensure 35 eligible and evaluable patients (allowing for

the 12% ineligible, evidence of dissemination or excess residual disease observed to date) for sufficient power in the primary analysis comparing LDSCI vs. SDSCI. These additional patients will also ensure there are 455 eligible and evaluable patients for the IFRT vs. PFRT comparison. It is expected to take an additional 10-12 months to enroll these patients.

### 10.3 Analytic Endpoints

#### 10.3.1 Efficacy endpoints

##### Primary endpoint

Time to Event, where event is defined as time from study entry to disease progression, disease recurrence, death from any cause, or occurrence of a second malignant neoplasm. This is used to compute the event-free survival (EFS) percent.

##### Secondary endpoints

Time to Recurrence, Progression or Death due to Cancer. This is used to compute Progression-free survival (PFS) percent. Death from causes that are clearly not associated with tumor recurrence or progression will be censored in this analysis.

Time to death from any cause, which is used to compute survival (S) percent.

Local Posterior Fossa (LPF) Failure: defined as tumor recurrence or progression within the tumor bed; i.e., within CTV<sub>boost</sub> for patients randomized to tumor-bed-only (involved field) boost (or within a theoretical CTV<sub>boost</sub> for patients randomized to standard PF radiation therapy). Recurrent tumors that straddle the boundary of CTV<sub>boost</sub> will be classified as LPF if more than 50% of the tumor volume is within CTV<sub>boost</sub>.

Non-local Posterior Fossa (NLPF) Failure: defined as tumor recurrence outside CTV<sub>boost</sub>, but within CTV<sub>PF</sub>. Recurrent tumors that straddle the boundary of CTV<sub>boost</sub> will be classified as NLPF if more than 50% of the tumor volume is outside of CTV<sub>boost</sub>. Recurrent tumors that straddle the boundary of CTV<sub>PF</sub> will be classified as LPF if more than 50% of the tumor volume is within CTV<sub>PF</sub>.

Non-Posterior Fossa (NPF) Failure: defined as tumor recurrence within the neuroaxis but outside of CTV<sub>PF</sub>. Recurrent tumors that straddle the boundary of CTV<sub>PF</sub> will be classified as NPF if more than 50% of the tumor volume is outside of CTV<sub>PF</sub>.

#### 10.3.2 Toxicity and Morbidity Endpoints

- 1) Post-treatment neurocognitive function
- 2) Post-treatment hearing loss
- 3) Post-treatment endocrine function: growth, sexual maturation, need for hormone replacement
- 4) Adverse Events: Incidence of Grade 3 and Grade 4 toxicities in any body system

### 10.4 Statistical Analysis and Power

The primary statistical analysis for each radiation therapy question will be based on logrank test, with time-to-event as the primary endpoint. The analysis of CSI dose will be stratified on the PF volume, and *vice versa*.

Both study questions will be formulated as reduction in therapy (so called 'equivalence') questions. Data from CCG-A9961 study indicates that long-term EFS ('cure' rate) in average risk medulloblastoma patients will be 80%. (The current estimate of the long-term EFS, based on a non-mixture parametric

cure model with Weibull kernel,<sup>22</sup> is  $81\pm 2.5\%$ , with 72% of events occurring within 2 years, 91% within 3 years, and 99% within 4 years from study enrollment.)

All patients will be randomized to IFRT vs PFRT, with patients 3 to 7 randomized in addition to 18.00 Gy vs 23.40 Gy CSI. It should be noted that patients receiving 18.00 Gy CSI will nevertheless receive a minimum dose of 23.40 Gy to the PF, so that the difference in field size between IFRT and PFRT does not result in a different reduction in PF dose in patients receiving 18.00 vs 23.40 Gy CSI. In addition, while recurrences outside of the PF can theoretically arise either from undetected metastatic lesions that were established before the start of treatment, or from lesions established during or after treatment by tumor cells circulating in the CSF during treatment, the contribution of the latter is thought to be negligible. It is reasonable, therefore, to consider the two factors as acting independently, with the CSI dose factor affecting only non-PF failures, and the PF volume reduction affecting only PF failures.

#### Comparison of IFRT vs PFRT

The comparison of IFRT vs PFRT will be based on N=455 eligible patients in one of three main strata: age 3 to 7 years with low dose CSI (LDCSI), age 3 to 7 years with standard dose CSI (SDCSI), and age 8 to 21 years with standard dose CSI. The number of patients and the expected long-term EFS in each analytic stratum is shown in the table below. Data from patients treated with study A9961 therapy suggest that EFS in these two age groups will be similar in patients treated on the standard arm. Three-year EFS in this study was  $83.4\pm 2.7\%$  in 3 to 7 year olds, and  $82.7\pm 3.1\%$  in 8+ year olds.

Strata for analysis of local treatment field			
Stratum	Number of patients	Long-term EFS	Long-term EFS *
Age 3 to 7, LDCSI	114	80%	70%
Age 3 to 7, SDCSI	114	80%	80%
Age 8 to 21, SDCSI	227	80%	80%
Aggregate	455	80%	77.5%

\* Numbers in this column represent assumed outcome when there is ~ 1.6 fold increase in failure rate due to LDCSI compared to SDCSI.

Using a one-sided log-rank test with 0.20 Type I error, with long-term EFS as in the table above, 2.5% independent censoring per year, 455 patients accrued over 6.5 years, two year of follow-up on the last patient enrolled, and no reduced efficacy due to LDCSI compared to SDCSI, this study will have power of 0.94 to detect a 10% reduction in cure rate (to 70%), and power of 0.65 to detect a 5% reduction in cure rate, due to use of IFRT compared to PFRT.

#### Comparison of LDCSI vs SDCSI

The comparison of LDCSI vs SDCSI will be based on N=227 eligible patients in one of two main strata: 3 to 7 years with IFRT, and 3 to 7 years with PFRT. The number of patients and the expected long-term EFS is shown in the table below.

Strata for analysis of CSI dose			
Stratum	Number of patients	Long-term EFS	Long-term EFS*
Age 3 to 7, IFRT	114	80%	70%
Age 3 to 7, PFRT	113	80%	80%
Aggregate	227	80%	75%

\* Numbers in this column represent assumed outcome when there is ~ 1.6 fold increase in failure rate due to IFRT compared to PFRT.

Using a one-sided log-rank test<sup>23</sup> with 0.20 Type I error, with long-term EFS as in the table above, 2.5% independent censoring per year, 227 patients accrued over 6.5 years, two years of follow-up on the last patient enrolled, and no reduced efficacy due to IFRT compared to PFRT, this study will have power of 0.80 to detect a 10% reduction in cure rate (to 70%) due to use of LDCSI compared to SDCSI.

#### Decision rule and robustness to non-additivity

The table below shows the probability of selecting each of the four RT field and CSI dose combinations, based on the results of the two marginal hypothesis tests described above (i.e., if both marginal tests are rejected, standard PF field (PFRT) and standard cranio-spinal irradiation (SDCSI) would be the recommended treatment). Five different scenarios are presented.

- (1) Additivity on the  $\ln$  relative failure rate (RFR) scale, with RFR=1.6 for both factors
- (2) Additivity on the  $\ln$  RFR scale, with RFR=1.26
- (3) Perfect subadditivity – PFRT or SDCSI alone provide maximum efficacy, with the combination of PFRT+SDCSI provide no added benefit.
- (4) Perfect superadditivity – Neither PFRT nor SDCSI alone provide any increased efficacy, but the combination of PFRT+SDCSI provide maximum efficacy
- (5) Partial superadditivity – PFRT provides greater increase in efficacy if added to SDCSI than if added to LDCSI, and *vice versa*.

Probability of selecting different treatment combinations, for additivity and non-additive factor effects

Treatment	LT EFS (1)	Pr Select	LT EFS (2)	Pr Select	LT EFS (3)	Pr Select	LT EFS (4)	Pr Select	LT EFS (5)	Pr Select
PFRT/SDCSI	80%	0.88	80%	0.38	80%	0.26	80%	0.47	80%	0.42
PFRT/LDCSI	70%	0.10	75%	0.31	80%	0.20	70%	0.41	73%	0.36
IFRT/SDCSI	70%	0.02	75%	0.17	80%	0.31	70%	0.06	73%	0.12
IFRT/LDCSI	56%	0.00	70%	0.14	70%	0.24	70%	0.06	70%	0.10
<b>Average/Pr&lt;75%</b>	<b>79%</b>	<b>0.12</b>	<b>76%</b>	<b>0.14</b>	<b>78%</b>	<b>0.24</b>	<b>75%</b>	<b>0.53</b>	<b>76%</b>	<b>0.58</b>

*LT EFS – Long-term event-free survival; Pr Select – Probability of selection*

For scenarios (1) and (2), the probability of ultimately selecting a treatment with EFS less than 75% is at most 0.14. For scenario (3) the probability is 0.24. For scenarios (4) and (5) the probability is greater than 0.50.

While scenarios (1), (2) are plausible, scenarios (4) and (5) are biologically implausible. Scenario (3) is questionably plausible. Scenario (4), for example, would require that increasing the dose of CSI would have no added efficacy in curing occult spinal metastases unless the entire PF field were irradiation to the boost dose, even through the PF treatment field is irrelevant to a spinal metastasis. Hence, superadditive interaction effects like (4) and (5), for which this factorial design is the least robust, need not be considered serious possibilities.

#### 10.5 Analysis of Patients Who Had Dissemination and Residual Disease on Central Review

On CCG-A9961 study<sup>47</sup>, there were 313 eligible fully assessable patients, 66 patients who on central radiological review, had no evidence of excess residual or metastatic disease, but whose studies could not be fully evaluated because of poor quality or incompleteness of submission, 15 patients who on central review found to have unequivocal excess residual, and 15 patients found to have disseminated disease. Five-year EFS was 83%  $\pm$  2.2% versus 73%  $\pm$  5.8% versus 75%  $\pm$  13% versus 36%  $\pm$  15% in these four groups, respectively (logrank  $P < .005$ ). Patients who had disseminated disease had significantly worse outcome compared to the other three groups.



A secondary analysis consists of all eligible patients including the 10% patients who were found to have excess residual or metastatic disease will be performed. The outcome of these 10% patients will be compared to the remaining patients. Assume the long-term EFS (5-year) in average risk medulloblastoma patients will be 80%. Using a one-sided log-rank test with 0.05 Type I error, 2.5% independent censoring per year, 455+45 patients accrued, two year of follow-up on the last patient enrolled, this study will have power of 0.8 to detect a relative failure rate of 1.93. This relative failure rate represents a plateau of 65% in the 45 patients who were found to have disseminated disease or excess residual vs. 80% in the remaining 455 patients. Assume that there will be 27 patients with dissemination and 27 patients with excess residual, this study will have power of 0.8 to detect an approximately 20% difference in the long term EFS (60% in the 27 patient cohort vs. 80% in the 455 patient cohort).

#### 10.6 Analysis of Toxicity and Morbidity of Treatment

The analysis of toxicity and morbidity will compare the rates of adverse consequences of radiation therapy between treatment groups. The power of these comparisons can be demonstrated by reference to a two-sample test of means of normal random variables. Sample size will be at most 80% of the total sample size, to account for expected treatment failure rates. In addition, it is expected that 70% of patients who are event free will comply with neurocognitive, endocrine, and other tests. Hence approximately 50% of total patients will be available for these analyses, or 113 for the CSI dose effect, and 227 for the endpoints effect of PF treatment volume.

For the comparison in children 3 to 7 years of age, with 75 patients per CSI treatment group, and using a one-sided, two-sample t-test with 5% Type I error, this comparison will have 80% power to detect a 0.48 population standard deviation increase in a continuous measure of, for example, neurocognitive function. This is a clinical meaningful improvement in outcome, and this study will have sufficient power to detect it.

For the comparison in the whole cohort, with 113 patients per PF target volume group, and using a two-sided, two-sample t-test with 5% Type I error, this comparison will have 80% power to detect a 0.38 population standard deviation increase in a continuous measure of morbidity. This also is a clinical meaningful improvement in outcome, and this study will have sufficient power to detect it. A two-sided test is more appropriate in this case since conformal PF treatment could result in an increase in morbidity of some measures.

#### 10.7 Interim Monitoring

##### 10.7.1 Interim monitoring of event-free survival

Interim monitoring for each study question will be based on the Lan-Demets<sup>24</sup> criterion, with spending function  $\alpha$ . The time point for 100% information is defined as two years after the last patient has enrolled. Information expended will be computed based on the current available follow-up, using the parametric cure model for A9961 referred to above. Analysis year, percent information, and critical values for interim monitoring are listed in the table below.

Analysis Year	% Information	One-sided Z-value	Nominal one-sided p-Value
3.000	25%	1.645	.050
3.500	33%	1.718	.043
4.500	52%	1.471	.071
5.500	71%	1.322	.093
6.500	88%	1.212	.113
7.500	97%	1.192	.117
8.5	100%	1.216	.112

## 10.8 Laboratory Correlates

The statistical analysis of these data will comprise several distinct components. The first is to identify, in the training set, the “marker” genes that are most associated with three-year progression-free survival, and to use these to develop ‘optimal’ classification rules to predict which patients will or will not survive progression-free to three years. The second is to investigate in a subsequent, independent test set whether the resulting classification rules retain the correct-classification rates that were estimated in the initial development of the rules. The methods used by Golub and colleagues<sup>25</sup> and Pomeroy and colleagues,<sup>26</sup> as well as standard statistical techniques such as Cox regression analysis,<sup>23</sup> will be used in these analyses. Internal cross-validation procedures, such as the leave-one-out method,<sup>26</sup> will be utilized in the training set to provide less-biased estimates of correct classification rates. However, the test data set will provide the best estimate of the correct classification rates associated with these classification rules. It may be possible, in the analysis, also to include clinical measures of disease progression probability, such as metastasis stage and amount of post-surgical residual, to improve the classification rules developed from gene expression data.

### 10.8.1 Definition of Optimality

There is no universally applicable definition of optimality of a classification rule, since the relative importance of false-positive or false-negative errors will depend on the context in which the classification scheme is used. In this study, different predictors will be developed and investigated for a spectrum of optimality criteria based on weighted total cross-validation error, which is defined as

$$W \times (\# \text{ False Positive Errors}) + (1-W) \times (\# \text{ False Negative Errors}).$$

The weight  $W$  is between 0 and 1, and reflects the relative importance of classification errors that incorrectly identify progression-free survivors as failures (false positive) compared to errors that incorrectly identify failures as progression-free survivors (false negative). If classification rules based on different weighting criteria incorporate similar sets of marker genes and agree in their ability to identify patients that will or will not progress by three years, then a single, widely applicable classification rule can be developed. However, if the set of marker genes differs depending on the weighting scheme used, then a single, widely applicable classification rule probably may not exist.

### 10.8.2 Study Cohort

The patient cohort for this study will comprise patients treated on COG studies for average and poor risk medulloblastoma, in infants (age < 3 years) and older children (ages 3 to 21 years). Because this biological study will incorporate patients enrolled in several clinical studies, it is difficult to predict the precise composition of patients that will be represented in the biological cohort. Patients available to this study can be conservatively estimated from the performance of COG institutions in several past studies. We assume COG enroll ~70 average risk medulloblastoma patients per year. CCG-9921 enrolled 92 infants with medulloblastoma in 5 years, which would represent approximately 150 infants in 5 years in COG overall. CCG-9931 enrolled 85 patients with disseminated or unresected medulloblastoma in 3 years, which would correspond to 135 patients in COG overall. Hence, 145 patients per year (48% average risk age >3 years; 30% other > 3 years; 22% infant) are expected from these patient groups combined, with 3-years progression-free survival of 60 to 65% in aggregate. Very conservatively, if only 60% of patients enrolled on these studies have adequate tissue for this biological study, the minimum target accrual of 350 patients can be achieved in 4 years. This biological study will continue to accrue sample through the duration of these next-generation COG therapeutic studies, so that the sample size is expected to exceed 350 patients.



### 10.8.3 Precision

The elemental parameters that will best reflect the value of the classification rules will be the false positive fraction (FPF) and false negative fraction (FNF) of the resulting rules estimated from the test sample. Assume 275 patients will be available for this analysis (350 less the 75 patients used in the training set). 110 of these patients will be 3-year progressors, and are relevant to the estimation of FNF, and 165 will not have progressed, and are relevant to estimation of FPF. For observed FNF of 10%, the 95% confidence interval (CI) for this quantity will be approximately (4%, 16%). For observed FPF of 10% the 95% CI will be (5% to 15%). For FNF and FPF of approximately 50%, the 95% CIs will be (41%, 59%) and (42%, 58%), respectively.

### 10.9 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	26	37	63
Not Hispanic or Latino	202	289	491
<b>Ethnic Category: Total of all subjects</b>	228	326	554
Racial Category			
American Indian or Alaskan Native	1	3	4
Asian	9	12	21
Black or African American	15	21	36
Native Hawaiian or other Pacific Islander	1	1	2
White	202	289	491
<b>Racial Category: Total of all subjects</b>	228	326	554

## 11.0 EVALUATION CRITERIA

### 11.1 Response Criteria

#### Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

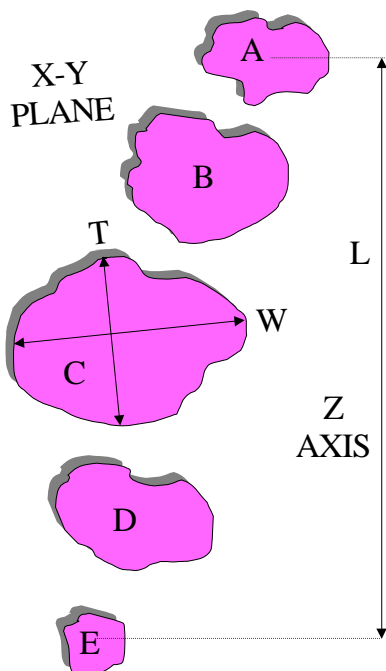
The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning January 1st, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0, and a copy can be downloaded from the CTEP web site (<http://ctep.cancer.gov>). Additionally, toxicities are to be reported on the appropriate data collection forms.

### 11.2 Methodology to Determine Tumor Measurement

In order to completely document the assessment of response, the three-dimensional tumor measurements for all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or

newly occurring lesions should also be enumerated in these reports, and changes in non-target lesions should be described.

Tumor response criteria are determined by changes in size using all 3 dimensional measurements: width (W), transverse (T), and length (L) measurements. Thus for all tumors these 3 measurements need to be recorded, using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). The following section describes the methodology. (See drawing below for illustration)



**COG GUIDELINE: TUMOR SIZE  
MEASUREMENT BASED ON  
CROSS-SECTIONAL IMAGING**

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) – tumor extent in the plane perpendicular to the selected plane)
4. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be “measurable”.  
Options:
  - if the cyst/necrosis is eccentric, the W, T and L of the solid portion should be measured, the cyst/necrosis excluded from measurement
  - if the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion
  - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured
5. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted, change in extent/thickness assessed on follow up studies.

## 6. Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	<b>CR</b>
CR	IR/SD	No	<b>PR</b>
PR	CR, IR/SD	No	<b>PR</b>
SD	CR, IR/SD	No	<b>SD</b>
PD	Any	Yes or No	<b>PD</b>
Any	PD	Yes or No	<b>PD</b>
Any	Any	Yes	<b>PD</b>

CR – Complete Response

PR – Partial Response

SD – Stable Disease

PD – Progressive Disease

IR – Incomplete Response

The sections that follow discuss the selection and evaluation of each of these types of lesions.

### 11.3 Selection of Target and Non-Target Lesions

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a “target” for measurement/follow up to assess for tumor progression/response.
2. If multiple measurable lesions are present, up to 5 should be selected as “target” lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions (including CSF positive for tumor cells).
3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).
4. Any change in size of non-target lesions should be noted, though does not need to be measured.

### 11.4 Response Criteria for Target Lesions

1. Response criteria are assessed in 3 dimensions – the product of LxWxT. An elliptical model volume ( $=0.5LxWxT$ ) is used.
2. To assess response/progression, the ratio is calculated:  

$$\frac{LxWxT \text{ (current scan)}}{LxWxT \text{ (reference scan)}}$$
3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g. when multiple lesions show opposite responses, the progressive disease takes precedence.
4. Response Criteria for target lesions:

**Complete Response (CR):** Disappearance of all target lesions.

**Partial response (PR):**  $\geq 65\%$  decrease in the sum of the products of the three perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

**Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

**Progressive Disease (PD):** 40% or more increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

In the rare circumstance that the length of a lesion cannot be determined, then comparison of 2 dimensional measurements, TxW (product of the longest diameter and its longest perpendicular diameter) can be used.

**Complete Response (CR):** Disappearance of all target lesions.

**Partial response (PR):**  $\geq 50\%$  decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements

**Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

**Progressive Disease (PD):** 25% or more increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

### 11.5 Response Criteria for Non-target Lesions

**Complete Response (CR):** Disappearance of all non-target lesions.

**Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.

**Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

## 12.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 12.1 Purpose

Adverse event 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.

### 12.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity), 2) the *relationship to the study therapy* (attribution), and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected*, for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- *The current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or*
- *the drug package insert*

### 12.3 Reporting of Adverse Events for Commercial Agents - AdEERS abbreviated pathway

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All appropriate treatment areas should have access to a copy of the CTCAE.

**Table B**

#### **AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days<sup>1</sup>**

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS
<sup>1</sup> This 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 which can be attributed (possibly, probably, or definitely) to the agent and is <u>not</u> due to cancer recurrence must be reported via AdEERS.			

**As of August 25, 2010 all secondary malignancies should be reported via AdEERS.**

### 12.4 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 AdEERS 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 Grade 3 and higher non-hematologic Adverse Events (any attribution).

### **13.0 RECORDS AND REPORTING**

#### **13.1 Categories of Research Records**

Research records for this study can be divided into three categories:

1. Non-computerized Information: Pathology Narrative Reports, Surgical Reports. These forms are submitted through the Document Imaging System in the eRDES.
2. Reference Labs, Biopathology Reviews, and QARC data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics and Data Center.
3. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes submission schedule.

#### **13.2 CDUS**

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

### **14.0 SURGICAL GUIDELINES**

Evaluation of disease stage and sites of tumor involvement should reflect a synthesis, by the primary treating physician, of neuroradiological, neurosurgical, neuropathological, and clinical opinions available after all required pre-treatment studies have been completed.

#### **14.1 Sites of Disease Involvement**

(Refer to Appendix II for Chang Staging System for Posterior Fossa Medulloblastoma)

Sites in the brain. Reporting of sites of initial disease involvement should include all brain structures found to be involved either by pre- and post-surgical imaging studies or by visual inspection at the time of surgery. Structures reported by the neurosurgeon to be involved but which are not considered unequivocally involved on imaging studies should generally be reported as involved. The primary site is defined as the likely site of origin of the tumor.

Spinal involvement. Spinal involvement is defined either as unequivocal or equivocal evidence of spinal involvement on spinal MRI, whether or not neurologic symptoms consistent with a spinal lesion are present. Only patients with unequivocally NO evidence of tumor in the spine on MRI are considered to not have spinal involvement.

CSF Involvement CSF involvement is defined as presence of any tumor cells in the lumbar cerebral-spinal fluid obtained between 3 days prior to surgery and study entry. Ventricular CSF may be used only in the rare instances that LP is medically contraindicated. Tumor cells in the cisternal CSF are not considered prognostic and may not be considered in the definition of CSF involvement.

#### 14.2 **Assessment of Residual Tumor**

The assessment of presence or absence of residual tumor will be based primarily on post-surgical MRI, with due consideration to the neurosurgeon's assessment of residual tumor from visual inspection of the tumor bed. Tumor unequivocally detectable on MRI or by surgical impression is considered residual tumor.

#### 14.3 **Size of Post-Surgical Residual Tumor**

The size of residual tumor present after surgery will be based on post-surgical MRI as delineated in section 11, with due consideration to the neurosurgeon's assessment of residual tumor based upon visual inspection of the tumor bed.

Measurements should include solid residual tumor or tumor cysts with enhancing walls only. Tumor cysts without enhancement in the wall should not be included in the measurements of residual.

#### 14.4 **Extent of Tumor Resection**

The extent of tumor resection will be based primarily on post-surgical MRI, with due consideration to the neurosurgeon's assessment of residual tumor from visual inspection of the tumor bed. Extent of tumor resection will be categorized as follows:

Biopsy: An open surgical removal or closed (e.g., needle) removal of tissue for the purpose of establishing a pathological diagnosis, with tumor removal less than 10% of the total tumor mass.

Partial: Removal of 10 - 49% of the tumor mass.

Subtotal Resection: Removal of 50 - 95% of the tumor mass.

Radical Subtotal Resection (Near Total): Removal of > 95% but less than 100% of the tumor mass.

Gross Total Resection: No visible tumor is left at the time of surgery and this is confirmed by postoperative CT or MRI.

#### 14.5 **Types of Surgery**

A suboccipital craniotomy is necessary to remove the bulk of the tumor, to re-establish CSF flow through the fourth ventricle, and to establish a tissue diagnosis. When feasible, an attempt will be made to perform a gross total tumor removal; if not feasible, an attempt will be made to remove as much tumor as possible without jeopardizing the patient. Eligible patients are strongly encouraged to undergo resection of residual tumor prior to radiation therapy. Biopsies alone, with no attempt at resection, may be associated with statistically worse survival and should not be done. No patient will be eligible for this study without a pathologic diagnosis.

#### 14.6 **Imaging Confirmation of Extent of Resection**

All patients will have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI scan, with and without contrast. This scan should be carried out within 21 days after surgery, preferably within 48 hours.

#### 14.7 **Peri-operative Corticosteroids**

Some patients with large tumors may require initiation of corticosteroid therapy preoperatively to reduce associated cerebral edema. If possible, this should not be started until after the initial MRI scan, since corticosteroids may affect tumor contrast enhancement.



#### 14.7.1

Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of Decadron, in divided doses, every 4-6 hours.

#### 14.7.2

Corticosteroids may be continued during the peri-operative period. Every attempt should be made to taper and discontinue corticosteroid therapy as soon as clinically feasible.

### 14.8 **Neurosurgical Procedure**

The goal of surgery is to re-establish CSF flow and to obtain a histologic diagnosis, to accurately state size, location, and extent of metastatic deposits, and to remove as much tumor as possible without causing further neurologic deficits.

#### 14.8.1 Operative Position

The surgical procedure may be carried out in any position in which the neurosurgeon feels comfortable; i.e. sitting, prone, or park bench.

#### 14.8.2 Opening the Dura

A wide dural opening should be made to allow for adequate exposure of the underlying brain. After opening the dura, the brain should be carefully inspected and the extent of tumor and any seeding noted and subsequently recorded.

#### 14.8.3 Leptomeningeal Examination

The neurosurgeon should examine the regional leptomeninges to determine whether metastatic nodules are present in the arachnoid or whether the entire leptomeningeal surface is infiltrated with tumor.

#### 14.8.4 Hemostatic Agents in the Intra-operative Field

Metallic clips should not be used for hemostasis, since these can cause MRI scan artifacts. Vanadium clips are preferable.

Placement of gelfoam or oxidized cotton, etc., for maintenance of hemostasis should be noted, since these agents can also appear radio-dense in the postoperative scan. An attempt should be made to remove all foreign bodies from the operative site prior to closure.

#### 14.8.5 Pathology Studies

As much tumor as possible should be sent for pathology and biology studies. Tissue should go directly to the institutional pathologist in saline prior to fixation by the pathologist in formalin for histologic diagnosis (see Neuropathology Guidelines, Section 15.0).

#### 14.8.6 Ancillary Neurosurgical Procedures

Surgical procedures not directly involving tumor removal also will be reported. These include ventricular shunt placement, removal of subdural or intracerebral hematoma, or cyst aspiration.

### 14.9 **Shunts**

#### 14.9.1

Children whose preoperative MRI scans indicate the possibility of a medulloblastoma/PNET may need precraniotomy external CSF shunts (EVDs), if they are primarily symptomatic because of tumor induced hydrocephalus.

#### 14.9.2

After removal of the tumor and the external shunt, approximately 30% of patients will require an internal shunt because of permanent hydrocephalus.

### 15.0 NEUROPATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

#### 15.1 Neuropathology Goals

##### 15.1.1

Precise histopathological diagnosis of tumors of primitive neuroepithelium.

##### 15.1.2

Assessment of prognostic value of histologic classification, clonogenicity, cell surface markers, oncogene expression.

##### 15.1.3

Tumors should be classified according to the Revision of the WHO Classification of Childhood Brain Tumors (see Cancer 56:1869-1886, 1985). Basically, embryonal central nervous system tumors previously diagnosed as medulloblastoma-desmoplastic medulloblastoma, ependymblastoma, pineoblastoma, and central (or cerebral) neuroblastoma have been placed under the general rubric 'primitive neuroectodermal tumor' (PNET). This does not include medulloepithelioma or the atypical teratoid/rhabdoid tumor, although these two histological subtypes of embryonal tumors may contain fields resembling primitive neuroectodermal tumors.

##### 15.1.3.1 Primitive Neuroectodermal Tumor

Tumors of this type arise most commonly in the midline region of the cerebellum and are best known as medulloblastoma. Tumors that are histologically identical may arise in other CNS sites, i.e. cerebrum, brainstem, spinal cord and pineal. It has been the practice to give them different names, e.g. pineoblastoma or cerebral neuroblastoma. It is illogical, however, to diagnose a tumor on the basis of location in the CNS; hence, the unifying term "primitive neuroectodermal tumor" is now used to diagnose all tumors with the histological features of medulloblastoma.

Basically, these tumors are composed of embryonal neuroepithelial cells which have the capacity to or actually do progress along various differentiation pathways. Whereas maturation along glial, neuronal, ependymal, muscular, retinal or melanotic lines may be clearly recognizable with a routine H&E stain, it is absolutely essential to apply a panel of monoclonal antibodies, utilizing immunoperoxidase techniques to identify differentiation at more primitive stages. For example, cells which look similar on H&E may exhibit a reaction to GFAP, NFP, desmin or retinal S agn when those specific antibodies are used. These often appear as clones. Use of synaptophysin, NSE and vimentin is not so helpful. Synaptophysin and other antibodies for neuropeptides are consistently positive, NSE is non-specific and a reaction to vimentin simply reflect acquisition of the most primitive intermediate filament by the embryonal cells.

The classical PNET is composed of a population of cells with small, deeply basophilic round nuclei with minimal surrounding perikaryon. These grow in patternless sheets interrupted by an inconspicuous vascular bed. Nuclei are rich in chromatin and may contain one or rarely two, nucleoli. The background has a granulo-fibrillar character but in some tumors the cells are so closely paced that the background is barely perceptible. The frequency of mitotic activity is variable; although field necrosis (including pseudo-palisading necrosis) is not common, individual cell necrosis, either karyorrhexis or apoptosis, is common. About 20 to 30% of these tumors exhibit Homer Wright rosettes.

Actually, there is considerable variation in the histological features of these tumors. Some are composed of cells which are larger and more pleomorphic than the routine small cell variety, and may have recognizable pink cytoplasm. Multinucleated giant cells may even be seen. Tumor architecture is sometimes characterized by nodules resembling germinal centers of lymph nodes in which cells are more loosely disbursed than in the more closely packed intervening regions. Sometimes there is a linear arrangement of small tumor cells that appear to rest on a delicate connective tissue strand. Special stains generally reveal reticulum encircling the nodules and in the strands. Tumors exhibiting these features are called desmoplastic medulloblastoma.

Another pattern resembling the desmoplastic medulloblastoma also has less well-defined nodules and many parallel rows of streaming cells that do not rest upon connective tissue strands but rather look like postmitotic neuroblasts migrating along radial glia. These tumors typically express neurofilament protein (as seen with the immunoperoxidase method), and some have called them "cerebellar neuroblastoma."

Less frequently, the nodules within a PNET-medulloblastoma (MB) are composed of neoplastic astrocytes. Rarely, mature but obvious ependymal canals/rosettes, neoplastic ganglion cells, smooth or striated muscle and/or melanocytes are found in nests or groups.

Anaplasia is defined as the presence of larger cells than in conventional medulloblastomas, with advanced cytological atypia, nuclear molding, cell-cell wrapping, frequent mitotic activity, and prominent apoptosis. A subset ("large cell medulloblastoma") is composed of cells with large round nuclei with prominent nucleoli. Although the majority of medulloblastomas will show some degree of anaplasia, for classification as "anaplastic", this must be severe, and represented in more than a small focus.<sup>45,46</sup>

Primitive neuroectodermal tumors are separated into sub-categories reflecting their pattern of expression of specific intermediate filaments or other differentiation antigens. Diagnosis should be based upon the histological features as seen with a routine H&E stain, as well as evaluation of antigen expression. A given tumor may express no differentiation markers, only one or more than one. The specific diagnostic categories to be used in classifying these tumors are as follows:

- 1) PNET, nos (tumor composed only of embryonal neuroepithelial cells)
- 2) PNET with astrocytic differentiation (GFAP expression by tumor cells)
- 3) PNET with neuronal differentiation (NFP expression by tumor cells)
- 4) PNET with ependymal cells (identification of ependymal canals/rosettes as seen on H&E)
- 5) PNET with melanocytes (identified on H&E and confirmed with Fontana or HMB45)
- 6) PNET with muscle (either identified as striated or smooth muscle on H&E or by desmin positivity with immunoperoxidase)
- 7) PNET with multidirectional differentiation

Finally, it is important to call attention to the ease with which the atypical teratoid/rhabdoid tumor (ATRT) may be confused with a PNET-MB. A large proportion of these embryonal tumors contain fields of typical PNET in addition to the rhabdoid cells, as well as malignant mesenchymal and/or epithelial component. They can be separated from ordinary PNETs by their expression of EMA, vimentin and smooth muscle actin

in the rhabdoid cells. These same cells may also express NFP and/or GFAP, however, primitive neuroepithelial cells comprising routine PNETs do not express EMA.

## 15.2 Requirements for Handling Biopsy or Surgical Resection Tissue

Standardized evaluation of each case requires that samples be handled according to the following guidelines.

### 15.2.1 Light Microscopy

A portion of tumor tissue should be fixed and processed in the usual manner. All tissue not used for other studies should be prepared for examination.

#### 15.2.1.1

If necropsy tissue becomes available it should be handled in the following manner.

##### 15.2.1.1.1

A complete autopsy protocol along with representative sections of residual tumor and/or metastases should be sent to the primary review pathologist.

## 15.3 Pathology Review Materials

The neuropathologist at each participating institution at the completion of review of each case originating at his/her institution, should submit the following to the COG Biopathology Center for confirmation of the diagnosis by central pathology review.

Required materials for continued inclusion in this study:

*Paraffin Blocks\**: Submit representative paraffin embedded tissue blocks. Please label blocks or slides with the institutional surgical pathology number, block number and the patient's COG Registration Number. If blocks are unavailable, send all of the following slides of tumor:

- Two (2) H&E stained slide of each representative lesion
- Six (6) unstained slides of tumor representative block

*Pathology Reports or Forms*: These forms must be submitted within 4 weeks of diagnostic surgery. Write the patient's COG Registration Number on all reports submitted to the BPC.

- Institutional pathology report
- Operative report
- Institutional pathology form (Institutional Neuropathology Worksheet), must be sent to the Biopathology Center within 4 weeks of diagnostic surgery.
- Electron Microscopy Report, if available.
- Photographs of representative gross lesions, if available
- Specimen transmittal form (with each shipment).

\*Paraffin blocks will be retained at the Biopathology Center at least until the Pathology Central Review Panel diagnosis is completed. For cases requiring urgent return of paraffin blocks to the primary institution, the referring institution should contact the Biopathology Center to request that initiation of the review process be expedited or blocks be returned immediately after completion of central review.

Send all materials for pathology review via U.S. mail or the institutional courier account to:  
COG Biopathology Center  
Nationwide Children's Hospital  
700 Children's Drive, WA1340\*  
Columbus, Ohio 43205

Phone: (614) 722-2894

Fax: (614) 722-2897

\*Be sure to include the room number. Packages received without a room number may be returned to sender.

## 16.0 SPECIAL STUDIES SPECIMEN REQUIREMENTS

In the past decade, several developmentally regulated genes have been identified as markers that are highly and independently associated with medulloblastoma outcome. Initially, expression of the neurotrophin-3 receptor, *TrkC*, was found to be associated with favorable clinical outcome.<sup>27-29</sup> Subsequently, increased expression levels of the neuregulin receptors *erbB2* and *erbB4* and of the immediate early gene *cMyc* were found to be highly correlated with poor outcome.<sup>27,30-32</sup> Pomeroy et al.<sup>26</sup> recently extended these findings by demonstrating that predictors based on microarray gene expression profiles can predict clinical outcome with high statistical significance. Using oligonucleotide microarray-based gene expression profiling to monitor the expression of over 6800 genes in the tumors of 60 children with medulloblastomas, 5 – 20 marker gene predictors were found to be the most accurate outcome predictors to date, performing significantly better than clinical staging.

### 16.1 Optimizing and Validating Outcome Predictors

The basic strategy of developing an outcome predictor requires a “training set” of tumor samples that is used to define the expression levels of marker genes that are characteristic of each outcome (alive versus dead). The training set will be collected in the initial phase of this study. A validation step on a “test set” of tumor samples is then needed to show that the predictor developed with the training set accurately assigns unknown samples to the correct outcome class.<sup>26</sup> Validation of the predictors will be performed using the test set of samples collected during the second phase. Note that although the training and validation samples will be collected and assayed, the development of the classification rule and the validation of the rule will be performed after sufficient follow-up is available to provide the necessary precision for these analyses. From a practical standpoint, the collection of samples and their biological analysis will be performed on an ongoing basis during the time period of this clinical study. The results from the first 75 to 100 samples (the training set) will be used to establish the outcome predictor model and subsequent samples (the test set) will be used to validate these observations. The process can be summarized as follows:

- a) Collect tumor samples suitable for gene expression analysis from a cohort of children with medulloblastoma;
- b) Identify “marker” genes that are associated with outcome class (tumor progression/recurrence-free at three years, or not), by measuring the expression levels of “marker” genes (ie. *TrkC*, *cMyc*, *erbB2/erbB4*) in all patients and comparing the range, mean/median, and variance of expression levels associated with each outcome. For microarray-based datasets, marker genes are selected using a class separation statistic such as the signal-to-noise ratio or<sup>25,26</sup> the logrank statistic.<sup>23</sup> Microarray based markers are tested by applying a permutation test to the top ranked genes to assess their class-correlation statistical significance;
- c) Build a classifier in cross-validation (leave-one-out) by removing one sample from the dataset and then use the remaining samples as a training set;
- d) Build several models using different numbers of marker genes in microarray datasets, or for single gene classifiers using different levels of expression, and choose a best model based on a minimum weighted total error in cross-validation (see Statistical Considerations);
- e) Validate optimal predictor selected from cross-validation analysis in the separate “test” cohort of patients.

## 16.2 Optimization and Validation of Gene Expression-based Outcome Predictors in the Children's Oncology Group (COG)

Over the next 3-5 years, approximately 500 children with medulloblastomas are anticipated to enroll on one of three treatment protocols (infant, standard risk, high risk). Combining gene-expression and outcome data from these diverse cohorts will enable us to identify expression markers that are associated with outcome in all of these cohorts, and to develop an 'optimal' predictor of three-year progression-free survival (PFS). The definition of 'optimal' is discussed in Statistical Considerations. Based on previous work, a training set of 75 to 100 samples will suffice for predictor development, carried out as an initial phase of the study, leaving the remaining samples as a predictor validation dataset to be completed during the remainder of the study.

RNA will be isolated by the Brain Tumor Resource Laboratory (BTRL) or by Dr. Pomeroy using standard techniques. The BPC will ensure that the frozen tissue samples are tumor tissue. Based on previous data, the total RNA yield typically is at least 20µg for 100 mg of snap frozen tumor sample. Three different groups within COG will develop outcome predictors based on published results:

### 16.3 Gene Expression Profiling (Pomeroy)

Sample requirements: 10 µg total RNA. RNA integrity will be assessed either by northern blotting or by gel electrophoresis. Reverse transcriptase generated biotinylated antisense RNAs will be hybridized overnight to Affymetrix (Santa Clara, CA) Human Genome U133 (HG-U133) microarrays.<sup>26</sup> Arrays will be scanned on Affymetrix scanners and the expression value for each gene calculated using Affymetrix GENECHIP software. Minor differences in microarray intensity will be corrected using a linear scaling method.<sup>26</sup> Scans will be rejected if the scaling factor exceeds 3, fewer than 1000 genes received 'Present' calls, or microarray artifacts are visible.

Genes correlated with particular class distinctions (survivors versus patients who died from treatment failure) will be identified by sorting all of the genes on the array according the signal-to-noise statistic  $(\mu_{\text{class0}} - \mu_{\text{class1}})/(\sigma_{\text{class0}} + \sigma_{\text{class1}})$  where  $\mu$  and  $\sigma$  represent the mean and standard deviation of expression, respectively, for each class. A permutation test will be used to calculate whether the top marker genes with respect to treatment outcome are statistically significant. To do this, the top signal-to-noise scores for top marker genes are computed and compared with the corresponding values for random permutation versions of the class labels. Typically 500 random permutations are used to build histograms for the top marker, the second best, etc. Based on this histogram the 50% (median), 5% and 1% significance levels will be determined.<sup>26</sup>

During the optimization phase of the study, decision boundaries between the alive versus dead classes will be determined using the *k-Nearest Neighbors* (k-NN) algorithm,<sup>33</sup> *Weighted Voting*,<sup>25,34</sup> *Support Vector Machines*,<sup>35,36</sup> and *SPLASH*.<sup>37</sup> The predictors will be optimized by calculating error rates on datasets of increasing size, observing as the error rates asymptotically approach a minimum.

### 16.4 TrkC/cMyc (Janss/Grotzer)

Sample requirements: 10µg total RNA and 10 formalin-fixed, paraffin embedded tissue sections. Expression of these genes will be measured by in situ hybridization<sup>38</sup> and by real time RT-PCR using the ABI Prism 7700 Sequence Detection System according to methods published<sup>39</sup> that have been used recently to quantitate TrkC and cMyc in 20 medulloblastomas. The primer concentrations that gave peak amplification were 250 nM/reaction and the maximum performances were achieved when samples were assayed in 25µl final volume in triplicate to ensure reproducibility. 18S rRNA showed an optimal performance as an endogenous control for normalizing TrkC and MYC mRNA expression levels. Positive controls will include TrkC transfected DAOY medulloblastoma cells and cMyc amplified D425 medulloblastoma cells. The TrkC and cMyc results obtained by real-time RT-PCR were consistent with the TrkC in situ results and the cMyc semiquantitative RT-PCR results previously published<sup>27,38</sup> therefore



validating this new method that is more rapid, more sensitive and more quantitative. Predictors using cMyc and TrkC will be constructed by finding the decision boundary half way between the classes:  $(\mu_{class0} + \mu_{class1})/2$ , and then predicting the unknown sample according to its location with respect to that boundary. The process will be repeated, moving the boundary until the total number of false positive and false negative errors is minimized.

#### 16.5 **ErbB2/ErbB4 (Gilbertson)**

Sample requirements: 50-100mg fresh frozen tumor tissue. Lysates (100mg total protein/sample) for western blotting will be fractionated with SDS/PAGE, transferred to nylon membranes and probed with anti-ERBB2 or ERBB4 antibodies. Positive controls and an expression baseline will be established with lysates from stable transfected ERBB2 or ERBB4 expressing cell lines. Following development, densitometric analysis is performed and each ERBB tumor signal is normalized to that of the stable expressing control. Blots are then re-probed for actin, each tumor actin signal is normalized to that of the cell line control and finally, these values are used to normalize the signals for ERBB expression. This technique was used recently to identify a significantly more favorable outcome for standard risk cases with ERBB2 negative tumors compared to those with ERBB2 signal on western blot. None of 8 ERBB2 negative cases have relapsed with all cases surviving disease free >30 months. In contrast, 4/11 ERBB2 immunopositive cases relapsed within the first 24 months (K-M,  $p < 0.05$ ). For the present work, decision boundaries will be established by the same method as for TrkC/cMyc.

#### 16.6 **Selecting an Outcome Predictor for Future Clinical Trials**

The optimal predictors determined by each of the three groups in cross-validation analysis of the training set will then be applied to the test dataset in the second phase of the study. Relative accuracy of each of the predictors will be compared, and the most accurate predictor will be selected. Moreover, during the final year of the study, it will be necessary for each of the groups to demonstrate on a cohort of at least 25 patients that their test can be completed within 2 weeks of receiving the sample. Proving the ability for "real time" analysis will be mandatory for selection of a lab to perform tumor stratification analysis in future clinical trials. Internal cross-validation procedures, such as the leave-one-out method,<sup>26</sup> will be utilized in the training set to provide less-biased estimates of correct classification rates. However, the test data set will provide the best estimate of the correct classification rates associated with these classification rules. It may be possible, in the analysis, also to include clinical measures of disease progression probability, such as metastasis stage and amount of post-surgical residual, to improve the classification rules developed from gene expression data.

#### 16.7 **Genome-wide Genetic Testing**

DNA will be isolated by the BTRL from the tumor tissue used for gene expression analysis, enabling correlative genome-wide genetic testing by comparative genomic hybridization (CGH). This technique involves labeling probes generated from tumor or normal DNA with different colored fluorescent labels. Tumor DNA deletions and amplifications are identified by cohybridizing the normal and tumor probes with DNA representative of the normal human genome. Standard format CGH, based on cohybridizing the probes with normal metaphase chromosomes, has limited resolution (~10-15 megabases). Therefore, Ching Lau and Pulivarthi Rao at Texas Children's Cancer Center have developed an array-based CGH format. Array CGH replaces normal metaphase spreads with a series of selected human genomic 100-200 kB DNA fragments packaged in bacterial artificial chromosomes (BACs) used for sequencing the human genome. These BACs are selected such that they are distributed every 1-2 megabases throughout the entire genome. Preliminary results by Lau and Scott Pomeroy demonstrate that chromosomal and array CGH have high concordance, and that CGH data can be directly compared to microarray-based genome-wide gene expression data. The combination of gene mutation and expression data will enhance classification of good versus poor prognosis medulloblastomas. Moreover, all genome-wide genetic data and gene expression profiles will be available to COG investigators through a web-based database accessible by the internet.



## 16.8 **Biology Specimens**

### 16.8.1 Recommended Materials for Submission:

If consent is obtained for participation in the optional biology component of the study, send the following materials to the Biopathology Center at the time of **diagnosis**:

*Snap Frozen Tissue:* Submit as many 100-mg pieces of tumor tissue as possible. Wrap each piece of tissue in sterile foil and snap freeze in vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen) within 10 minutes of removal. A minimum of  $> 0.5 \text{ cm}^2$  is preferred.

*Formalin Fixed Tissue:* Submit 10 sections from tissue fixed in 10% buffered formalin; two of which should be on positively charged slides for possible immunohistochemistry.

*Pathology Reports or Forms:* Write the patient's BPC Number on all reports submitted. Send the institutional pathology report and include a specimen transmittal form with each shipment.

Label specimens with the patient's BPC number, specimen type and collection date.

### 16.8.2 Shipment Of Specimens

The BPC will provide a specimen procurement kit upon request. Kits are ordered via the BPC Kit Management application. To access the application click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application.

For packing instructions please see **Shipping Specimens in a Dual Chambered Kit** at <https://members.childrensoncologygroup.org/prot/biology.asp>.

Institutions in the U. S. and Canada should ship the specimens to the COG Biopathology Center (BPC) using a Federal Express shipping label obtained through the BPC Kit Management application. Specimens must be shipped to the BPC Monday through Thursday for delivery Tuesday through Friday.

#### **Send the Specimens to:**

Biopathology Center  
Nationwide Children's Hospital  
700 Children's Drive, Room WA1340\*  
Columbus, OH 43205  
Phone: (614) 722-2865  
FAX: (614) 722-2897

\*The room number is required. Packages not listing the room number will be denied and returned to the sender.

## 17.0 NEURORADIOLOGY 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 per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

### 17.1 Whole Brain MRI With and Without Contrast

Preoperative cranial MRI is required with and without contrast to document the degree of residual tumor, postoperative MRI scan with and without contrast must be done prior to radiation. Preoperative cranial MRI is required with and without contrast.

Postoperative imaging should be done within 48 hours of surgery, prior to the onset of post-operative enhancement, which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time, then it should be done within 28 days following surgery. For a patient to be eligible for this protocol, the patient must have a localized tumor which cannot extend beyond the posterior fossa and postoperative imaging must demonstrate no more than 1.5 cm<sup>2</sup> of residual abnormal tissue thought to represent tumor. Disseminated disease within the posterior fossa, and/or at any intracranial site makes the patient ineligible for study.

(Note: all quoted slice thickness is maximal; thinner slices are encouraged, and necessary if the lesion imaged is very small)

#### Required sequences:

- Sagittal T1 localizer; 4-5 mm skip 1 mm
- Axial FSE T2; 4-5 mm, skip 0-1 mm,
- Axial FLAIR; 4-5 mm skip 0 (may also do post contrast)  
Can substitute 2 and 3 with axial spin echo proton density/T2, 5 mm skip 1 mm (if FSET2/FLAIR not available)
- Axial diffusion; 4-5 mm skip 0 (single shot, matrix 128 x 128 or 128 x 192, B=1000)
- Axial T1; 4 mm skip 1 mm

#### Contrast

- Axial T1; 4-5 mm skip 0-1 mm
- Coronal T1; 4-5 mm skip 0-1 mm

#### Optional sequences

##### Precontrast :

- Sagittal or coronal FSET2; 4-5 mm skip 0-1 mm, depending on tumor configuration/orientation

### 17.2 MR Spine With Contrast

MRI with gadolinium of the entire spine is required within 28 days of surgery and at relapse. If an MRI scan is performed within 5 days prior to surgery, then a postoperative scan does not need to be performed.

The MRI scan must be performed of the entire spine, with contrast. If there is significant motion artifact and/or hemorrhage, then the scan is not evaluable and must be repeated or the patient is not evaluable for study. Any evidence of possible metastases on the MRI scan makes the patient ineligible for study. A

spinal MRI will also be performed at 3, 6, 9 months then 1, 1.5, 2, 2.5, 3 years, then annually after completion of therapy and at relapse.

1. Whole spine sagittal T1; 3 mm skip 0 mm.

Technical notes:

- Acquire 2 separate acquisitions (one cervical and upper thoracic, the second lower thoracic and lumbosacral) to optimize placement of presaturation pulse.
- Phase direction AP, frequency direction SI
- Place anterior saturation pulse close to the anterior margin of the spinal column - to minimize motion artifacts from chest/abdomen.
- Pixel size 1 mm<sup>2</sup> or less (example: for 26 cm FOV, use 256 x 256 matrix)
- Keep TE to minimum (<15 msec)
- Fat saturation not necessary

2. Axial T1 images through the entire spine; 4-5 mm thick, skip 1-2mm.

Technical notes:

- Phase direction RL, frequency direction AP
- Keep TE to minimum (< 15 msec)
- DO NOT INTERLEAVE

### 17.3 Central Review

All patients will have central neuroradiological review. Submit the following studies with their corresponding reports to the address below.

- Pre-operative Cranial MRI with and without contrast
- Post-operative Cranial MRI with and without contrast
- Pre OR Post-operative Spinal MRI with contrast
- Cranial MRI at progression (relapse) with and without contrast
- Spinal MRI at progression (relapse) with contrast

Hard copies or digital data DICOM format (preferred) will be submitted for central review to:

Quality Assurance Review Center (QARC)  
640 George Washington Highway, Suite 201  
Lincoln, RI 02865-4207  
Phone: (401) 753-7600  
Fax: (401) 753-7601

Submission of Diagnostic Imaging data in digital format is preferred. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicom Communicator. Contact QARC at [Dicomcommunicator@QARC.org](mailto:Dicomcommunicator@QARC.org) for further information. Alternative electronic methods, e.g., sFTP are possible. Contact QARC for more information.

## 18.0 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 per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

**Radiation therapy for patients on COG protocols can only be delivered at approved COG RT facilities (see Administrative Policy 3.9). Contact QARC for questions or further information. Institutions using conventional 3D treatment planning must have a 3-dimensional Benchmark on file at QARC. If IMRT are to be used, then the benchmark specific to IMRT must be submitted. In addition, use of proton therapy requires prior credentialing by the Radiological Physics Center for the specific beam line that is to be used. Patients will be considered unevaluable if benchmarks are not approved.**

Submission of the radiation therapy treatment plan in digital format (either Dicom RT or RTOG format) is required. See the QARC website ([www.QARC.org](http://www.QARC.org)) for digital data submission information.

Three-dimensional image-based radiation therapy treatment planning and computer-controlled delivery systems (*conformal radiation therapy*) should improve disease control and functional outcome for children with brain tumors. The tools necessary to perform conformal radiation therapy have become widely available, thus sufficient experience has been gained to develop guidelines for use by investigators who treat these patients. At the present time there is limited evidence that the use of conformal radiation therapy is safe or able to reduce side effects in children with brain tumors. It is therefore not advisable to use these guidelines to treat children who are not enrolled on this study.

This clinical trial will test the safety of limited volume boost conformal radiation therapy as applied to children with medulloblastoma and will determine if these techniques maintain the expected rate of local control and reduce radiation-related side effects. For treatment planning and delivery all collaborating investigators should have (1) conformal radiation therapy capabilities as determined by the quality assurance committee, (2) general anesthesia and/or deep-sedation capabilities as needed, and (3) customized immobilization that provides for treatment that is both reproducible and safe.

This protocol proposes new dose, volume, and quality assurance guidelines for the use by eligible cooperative group institutions that treat children including: (1) conformal radiation therapy guidelines for childhood medulloblastoma, (2) gross and clinical target volumes based on pre- and post-operative neuroimaging, (3) acquisition of dose-volume data for normal tissue structures, and (4) prospective review of radiation therapy data.

### 18.1 Timing of Radiation Therapy

All patients shall receive irradiation to the craniospinal axis followed by a boost to the posterior fossa. All patients shall begin radiation treatments after registration on study and within 31 days of definitive surgery.

## 18.2 Equipment

### 18.2.1 Modality

X-rays with a nominal energy  $\geq 4$  MV. Craniospinal axis irradiation is best done with x-rays between 4-6 MV. The boost volume may be treated with a nominal energy  $\geq 4$  MV, as long as dosimetric constraints are accomplished. If IMRT is used, photon energy should be no greater than 10 MV. Electron beams of suitable energy to treat the spinal cord may be allowed if prior documentation has been reviewed and approved by QARC. Proton beams may be used in special circumstances and require prior approval by the study chair.

### 18.2.2 Calibration

The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center.

### 18.2.3 Equipment

Patients enrolled on this study must be treated using conformal radiation therapy treatment planning and delivery techniques. IMRT or Proton Therapy will be allowed if appropriate benchmarks have been submitted and approved by QARC. If IMRT is to be used, then the benchmark specific to IMRT must be submitted before the patient can be evaluated. The IMRT credentialing requirement can also be satisfied by irradiating the RPC's head and neck phantom. All patients must be treated on isocentric machines. All machines must have a minimum source-to-axis distance (SAD) of 80 cm. Treatments may be given with fixed SSD techniques. If proton beam or Tomotherapy is used, the study chair must be notified. For treatment to be conformal the following criteria must be met:

- Three-dimensional imaging data (CT or MR) are acquired with the patient in the treatment position. Three dimensional treatment planning software must be used in this trial. If IMRT is used, the IMRT Questionnaire and Benchmark must be completed as soon as possible. An approved benchmark must be on file at QARC before the case can be evaluated. Patients will be unevaluable if benchmarks are not approved. The benchmark material is available from the QARC website ([www.QARC.org](http://www.QARC.org)). See Section 18.8.1 for benchmark requirements.
- Image data are used to delineate and reconstruct a gross target volume, clinical target volume, planning target volume, and normal or critical structures in 3-dimensions.
- Radiation beams can be freely oriented in 3-dimensions for both the planning and delivery process, and structures traversed by the beam can be visualized with the eye of the beam.
- The distribution of dose relative to the target volume or any structure is computable on a point-by-point basis in 3-dimensional space.
- Institutions not equipped to perform conformal radiation therapy according to these guidelines should refer the patient to a participating COG institution with proven capabilities to comply with the outlined parameters.

## 18.3 3-D Target Volume and Organ At Risk Definitions

The definitions for the target volumes and treatment dosimetry will adhere as closely as possible to the recommendations of ICRU Reports 50, 62, and 78 whenever possible.

RT volumes for this study will be determined by the collective information that delineates the extent of disease at the time of diagnosis and prior to radiation therapy. These guidelines are meant to be comprehensive and include all anticipated treatment scenarios. If for any reason the following guidelines do not match the characteristics of a given patient, the treating physicians are asked to contact the radiotherapy coordinator(s).

### 18.3.1 Gross Tumor Volume (GTV)

The GTV includes all gross residual tumor and/or the walls of the resection cavity at the primary site based on the initial imaging examination that defines the tissues initially involved with disease anatomically and the post-operative and pre-irradiation neuroimaging examinations that identify residual disease and the tumor bed.

In accordance with ICRU-50, the Gross Tumor Volume (GTV) is defined as the contrast-enhanced tumor in the Brain and the Spine, unless the preoperative tumor is predominantly non-enhancing, in which case this represents the preoperative tumor extent as defined by the most informative MR imaging sequence.

### 18.3.2 Clinical and Planning Target Volumes (CTV and PTV)

The CTV includes the GTV with an added margin that is meant to treat subclinical microscopic disease and is anatomically confined (i.e., the CTV is limited to the confines of the bony calvarium and tentorium where applicable). For this study, multiple CTVs will be treated.

The Clinical Target Volume<sub>1</sub> (CTV<sub>1</sub>) is the entire craniospinal axis. The craniospinal axis Planning Target Volume (PTV<sub>1</sub>) is institution-defined according to immobilization techniques and their inherent setup uncertainties. The margin defining the PTV may range from 0.3 cm to 1.0 cm. For the Craniospinal volume, a larger PTV<sub>1</sub> margin should be considered due to inexactness of repositioning for the spinal fields.

Although conventional simulation will be allowed for the craniospinal axis PTV<sub>1</sub> treatments, it should be noted that CT based or 3D treatment planning for craniospinal axis irradiation may offer advantages over conventional simulation methods. (Reference Mah Int J Radiat Oncol Biol Phys 2000). A better appreciation of the cribriform plate and middle cranial fossa can be gained with a CT simulation. In most circumstances, the same CT simulation data used for planning the craniospinal axis RT can be used to plan the 3-D conformal boost.

If conventional simulation and treatment planning are used to treat the craniospinal axis, the cranial dosimetry from that part of the treatment course shall be included in the 3-D conformal plan for the target volume boost, including the DVHs.

Whole Brain (CTV<sub>1</sub>): The whole-brain field shall extend anteriorly to include the entire frontal lobe and cribriform plate region. The volume shall cover the superior orbital tissue (but not the posterior globe as in leukemia protocols). Inferiorly, the CTV<sub>1</sub> shall be at least 0.5 cm below the base of the skull at the foramen magnum. PTV<sub>1</sub> should be defined to account for setup error. The radiation fields to cover this target volume should follow established guidelines for cranial irradiation in medulloblastoma. There will be a junction with the spinal field.

For children age 3 to 7 years at diagnosis, the dose prescription for the brain and spine will be randomly assigned to 18.00 Gy in 10 fractions or 23.40 Gy in 13 daily fractions of 1.80 Gy. For children age 8 to 21 years, the dose prescription for the brain and spine will be 23.40 Gy in 13 daily fractions of 1.80 Gy.

Spine (CTV<sub>1</sub>): The spinal target volume will be the entire thecal sac. The field to cover this volume should extend laterally on both sides to cover the recesses of the entire vertebral bodies, with at least a 1 cm margin on either side. The superior border will be the junction with the whole brain field. The inferior border of the treatment volume will be placed after review of the spinal MRI. The border will be 2 cm below the termination of the subdural space. This will extend at least to the inferior border of the second sacral segment (S2-S3 interspace), but may be as low as the inferior border of S4. If this cannot be



accomplished in a single field, there will be a junction between the two spinal fields. PTV<sub>1</sub> should be defined to account for setup error.

For children age 3 to 7 years at diagnosis, the dose prescription for the brain and spine will be randomly assigned to 18.00 Gy in 10 fractions or 23.40 Gy in 13 daily fractions of 1.80 Gy. For children age 8 to 21 years, the dose prescription for the brain and spine will be 23.40 Gy in 13 daily fractions of 1.80 Gy.

Posterior Fossa Boost (CTV<sub>PF</sub>): 3D-based treatment planning is mandatory for these volumes. IMRT is allowed for the PTV<sub>PF</sub>. The CTV<sub>PF</sub> should encompass the entire posterior fossa. The posterior fossa must be defined on the planning CT scan. It is strongly recommended that a sagittal MRI be used to assist in identification of the position of the tentorium. The CTV<sub>PF</sub> extends inferiorly from C1 vertebral canal through the foramen magnum, laterally to the bony walls of the occiput and temporal bones and superiorly to the tentorium cerebelli. Generally, the sigmoid sinuses define the lateral-superior extent of the bony confines of the posterior fossa that attach contiguously to the tentorium above. The folia of the cerebellum and the anterior border of the brainstem and midbrain bound the CNS contents of the posterior fossa. The Planning Target Volume (PTV<sub>PF</sub>) is a 0.3cm to 0.5cm margin around the CTV to account for day-to-day setup variation. The PTV<sub>PF</sub> should not extend beyond the external bony confines of the skull except at the foramen magnum to C1-C2. The PTV<sub>PF</sub> should extend anteriorly to the posterior clinoids (the pituitary is not included) and inferiorly to the C1-C2 junction. In treatment planning, shielding of critical structures should be attempted. At least 95% of the prescription study dose of 54.0 Gy must encompass at least 95% of the PTV<sub>PF</sub> (the posterior fossa) as shown by DVH. No part of the PTV<sub>PF</sub> should receive less than 50 Gy. Treatment techniques for the PTV<sub>PF</sub> may include parallel opposed laterals or other 3D CRT methods to limit dose to the supratentorial brain, hypothalamus, pituitary or middle ear.

Additional Posterior Fossa Boost (PTV<sub>PF</sub>) For Children 3-7 Years Receiving 18.00 Gy: Children age 3 to 7 years randomized to 18.00 Gy CSRT will receive a posterior fossa dose of 5.40 Gy in 3 fractions prior to the boost to PTV<sub>boost</sub>. This PTV<sub>PF</sub> is defined in exactly the same manner as described above for patients randomized to receive whole posterior fossa boost. These three PF fractions ensure a posterior fossa dose of 23.4 Gy for all patients, including those receiving the limited target volume boost, and also ensure a cumulative dose of 54Gy for all patients.

Limited Target Volume Boost (CTV<sub>boost</sub>): 3D-based treatment planning is mandatory for this volume. IMRT is allowed for the PTV<sub>boost</sub>. The Gross Target Volume (GTV) is based upon the T1 signal changes with and without Gadolinium contrast. Identification of the GTV shall be based upon pre-operative extent and anatomic shifts or changes *after* surgery. The GTV should include any residual enhancing tumor mass and the wall of the resection cavity. The Clinical Target Volume (CTV<sub>boost</sub>) is defined as the GTV plus a 1.5-cm margin except at bone or tentorial interface (where it remains within the confines of the posterior fossa). The PTV<sub>boost</sub> margin should be an additional 0.3 to 0.5 cm around the CTV<sub>boost</sub>. In treatment planning, shielding of critical structures should be attempted, however, coverage of the PTV<sub>boost</sub> must not be less than 50 Gy. The cumulative dose to PTV<sub>boost</sub> will be 54.0 Gy. At least 95% of the prescribed study dose (54Gy) must encompass at least 95% of the PTV<sub>boost</sub> as shown by DVH. No part of the PTV<sub>boost</sub> should receive less than 50 Gy.

### 18.3.3 Organs at Risk (OAR)

The following organs must be defined for 3-D conformal radiation therapy or IMRT planning:

- Supratentorial brain (left and right)
- Cochlea (left and right)
- Hypothalamus/pituitary
- Eyes (left and right)



- Optic nerves (left and right)
- Optic chiasm
- Cervical spinal cord (foramen magnum to top of C2)
- Skin (non-specified tissues)

A Web based atlas with normal organ contours is available.

<http://www.qarc.org/cog/protocol%20resources/ACNS0331Atlas.pdf>

## 18.4 Dosimetry

### 18.4.1 Prescription Point

The prescription point for the neuroaxis (PTV<sub>1</sub>, whole brain and spine) is at or near the center of the targets. For the brain this may be a point other than the central axis. Consideration should be made to using a point midway of the biparietal diameter. The spinal axis dose should be prescribed to the anterior aspect of the spinal canal. In many cases, the depth of the anterior spinal canal will vary by vertebral level. An average depth may be used that keeps the dose uniformity within the constraints defined below. For the posterior fossa and limited target boost volumes, the doses shall be prescribed in order to have at least 95% of the 54 Gy isodose covers at least 95% of the respective planning target volumes. The minimum dose to the PTV<sub>PF</sub> or PTV<sub>boost</sub> shall not be < 50 Gy.

### 18.4.2 Dose Definition

Dose is to be specified in Gray (Gy)-to-muscle.

### 18.4.3 Prescribed Dose and Fractionation

Age 3 to 7

18.00 vs 23.40 Gy CSRT (*randomized*)

5.40 Gy Posterior fossa (if 18.00 Gy CSRT)

30.60 Gy Local vs Posterior fossa boost (*randomized*)

Age 8 to 21

23.40 Gy CSRT

30.60 Gy Local vs Posterior fossa boost (*randomized*)

### 18.4.4 Dose Fractionation

Patients will receive one fraction of 1.8 Gy per day, five days per week.

### 18.4.5 Dose Uniformity

The dose variations in each target volume shall be within +10%, -5% of the prescription-point dose. This applies to all photon modalities.

At least 95% of the PTV<sub>PF</sub> or PTV<sub>boost</sub> should be encompassed within 95% of the 54 Gy isodose surface and no more than 5% of the volume within this isodose surface should receive greater than 110% of the prescription dose as evaluated by DVH. These targets should not receive less than 50 Gy. Treatment should be planned to spare the spinal cord, brainstem, optic chiasm and optic nerves from the highest doses resulting from dose inhomogeneity. An effort to should be made to spare the cochlea and middle ear contents.

### 18.4.6 Treatment Interruptions

Treatment will not be interrupted for anemia, leukopenia, or thrombocytopenia unless life threatening.

Blood product support should be instituted according to institutional/protocol guidelines. For interruptions of more than 2 treatment days, please contact the radiation oncology study chair.

## 18.5 Treatment Technique

### 18.5.1 Craniospinal Axis Irradiation

#### 18.5.1.1 Patient Position

For cranio-spinal irradiation the patient may be treated prone or supine.<sup>40</sup> The neck should be extended sufficiently to keep the mandible out of the exit beam of the spinal field but not so much as to exceed the dose uniformity specifications of the spinal field. Reproducible setups are critical. Immobilization devices such as head holders or custom molds are highly recommended. Deep sedation or general anesthesia is strongly encouraged for young children. For the posterior fossa boost the patient may be in either the prone or supine position.

#### 18.5.1.2 Whole Brain Irradiation

Conformal treatment planning (or CT simulation) is encouraged but not required for this initial aspect of the protocol treatment. Regardless, dose from this component of the radiation therapy shall be included in the 3D CRT plan of the limited boost volume, including DVHs of the targets and adjacent organs at risk.

Parallel opposed fields may be used. Alternatively, the field center can be placed near the match line with the spinal field and an independent jaw or half-beam block technique utilized. This method decreases overlap at the match line. The collimation of the brain field should be rotated to match the divergence of the spinal field.

If symmetric collimator jaws are used:

$$\text{The angle} = \tan^{-1} \frac{\text{spine length}/2}{\text{SAD}}$$

If asymmetric collimator jaws are used:

$$\text{The angle} = \tan^{-1} \frac{\text{upperspine length}}{\text{SAD}}$$

The lateral fields may be angled posteriorly to spare the collateral lens, but, if this is done, great care must be taken to assure adequate coverage of the cribriform plate. Custom divergent blocking of at least 5 HVL should be used to shape the brain field at the base of the skull and around the eyes. The brain field should extend to at least 1 cm beyond the periphery of the scalp.

#### 18.5.1.3 Spine Irradiation

Preferably, the spinal volume should be treated with a single posterior field. An extended SSD is preferable to the use of adjacent ports. If adjacent ports are necessary, the 50% decrement should cross at the posterior margins of the vertebral body. It is preferable that the match line be placed inferior to the spinal cord (below L2) and should be moved every 9-12 Gy. Custom blocking may be required at the inferior border of the spine. Lateral field borders should cover 1-1.5 cm beyond the radiographic edge of the vertebral body.

#### 18.5.1.4 Abutting Fields

With the use of collimator rotation and an independent jaw technique, the cranial and spinal fields may be directly abutted (light fields). Many radiation oncologists, though, are more comfortable with a gap between the cranial and spinal light fields. A gap of 0.5 cm is allowed on this protocol. The match line

should be moved twice during treatment of the cranio-spinal axis. Also, a penumbra broadening “match line wedge” or a dynamic wedge may be used. The match line should never overlap the posterior fossa boost. Therefore, it is recommended that the first match line lie just above the shoulder, and the last 2 cm higher. Alternatively, the first match point could begin at the superior point and end at the inferior point.

#### 18.5.1.5 Conformal Boost Treatment

Conformal (three-dimensional) or IMRT planning is required for this study. Beam arrangements and treatment techniques should be used that minimize the dose to the auditory apparatus (cochlea), hypothalamic-pituitary unit and supratentorial brain providing that they do not compromise treatment of the intended PTV. Examples of 3-D conformal beam arrangements can be found at the QARC ([www.qarc.org](http://www.qarc.org)) or ITC ([itc.wustl.edu](http://itc.wustl.edu)) website.

#### 18.5.1.6 Field Shaping

Field-shaping is required. Shielding shall be at least 5 HVL thick. Multi-leaf collimation may be used.

#### 18.5.1.7 Example Cases

Example cases will be posted

<http://www.qarc.org/cog/protocol%20resources/ACNS0331Atlas.pdf>

#### 18.5.1.8 Imaging

CT (3 mm - 5 mm section thickness from the thoracic inlet to the most cephalad extent of the skull) should be performed for treatment planning. Preoperative and postoperative MR is used primarily (co-registered with CT planning data) or adjunctively in the treatment planning process. Surgical guidelines encourage postoperative imaging within 72 hours post-operatively.

### 18.6 Normal Tissue Sparing

#### 18.6.1 Spinal Cord

No more than 50 % of the cervical spinal cord between C-1 and C-2 should receive more than 54 Gy. A DVH for this volume shall be submitted, as indicated in section 18.3.3.

#### 18.6.2

Fields should be specifically designed to minimize dose to Organs At Risk such as the optic nerves, optic chiasm, cochlea, hypothalamic-pituitary unit and supratentorial brain. Maximum doses to these Organs At Risk should not exceed 54Gy.

### 18.7 Supportive Care During Irradiation

#### 18.7.1 Hematologic

CBC's should be obtained weekly. If  $ANC \leq 500/\mu l$ , either a break in treatment or the use of growth factors may be considered. The option of continuing therapy with the posterior fossa boost field may also be considered in patients who have lowered counts during the cranio-spinal therapy. Cranio-spinal radiation may be resumed when the ANC has risen over 10% on 2 consecutive tests, or is above  $750/\mu l$ . If ANC is less than  $1000/\mu l$  and the patient is febrile ( $\geq 38^\circ C$ ), a break may be instituted while the patient is being evaluated. During this time, the posterior fossa boost may be treated, but cranio-spinal irradiation should be avoided.

Platelets should be transfused as clinically indicated when counts are  $< 30,000/\mu l$ . Irradiated and Pall filtered blood products should be used. Cranio-spinal irradiation should be reinstituted when platelet counts exceeds  $50,000/\mu l$  or have risen  $> 10\%$  on 2 consecutive tests.

Hemoglobin: Transfusions are recommended when hemoglobin falls below 9 gm/dL. Radiated blood products should be used. Growth factors can also be utilized.

#### 18.7.2 Gastrointestinal

Patients should be weighed weekly. If there is greater than 10% weight loss, aggressive nutritional support, either enteral or parenteral, should be given. Prophylactic anti-emetic therapy, with e.g. a selective 5-HT<sub>3</sub> receptor antagonist, should be considered.

#### 18.7.3 Pneumocystis

Pneumocystis prophylaxis with trimethoprim/sulfamethoxazole (5 mg/kg/d of trimethoprim in two divided doses given 2 consecutive days per week) is recommended for all patients during radiotherapy and should be continued for 2 months after completion of radiotherapy.

#### 18.7.4 Varicella

If patients are seronegative for varicella, VZIG should be administered within 72 hours if history of exposure to chickenpox or zoster is elicited.

### 18.8 **Dose Calculations and Reporting**

#### 18.8.1

**Patients will be considered unevaluable if approved benchmarks are not on file at QARC.** Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark; those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center ([www.QARC.org](http://www.QARC.org)) Contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms.

#### 18.8.2 Prescribed Dose

Reporting Forms: A summary of the prescribed dose shall be submitted using the RT-1/IMRT Dosimetry Summary Form or Proton Reporting Form.

For IMRT techniques: The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

#### 18.8.3 Isodose Distributions

Digital submission of treatment plans is required. It is understood that some patients may be treated in 2 consecutive phases and have the CSA radiation therapy delivered in a position that is different from the boost radiation therapy. While it is sometimes not possible to accurately add radiation doses due to the change in patient shape and position, the institution must submit a plan that closely approximates the cumulative radiation dose that is delivered as part of both the cranial fields from the CSA and the boost treatments. This can generally be done by creating a cranial field in the boost plan that is dose-weighted and shaped similarly to that used in the CSA phase of therapy.

For conformal planning, the following isodose distributions are required by treatment site and for the composite and will include the gross tumor volume, clinical target volume and planning target volume and normal tissue structures listed in section 18.3.3. Axial, sagittal, and coronal isodose distributions through the treatment isocenter will be overlayed on reconstruction of the CT scan in the same plane. Isodose distributions corresponding to each CT image that shows protocol-specified normal tissue structures or tumor/target volume contours.

For cases in which the craniospinal axis is treated using 2D planning, at a minimum the following isodose distributions shall be submitted for that phase of treatment: an axial isodose distribution through the central axis for the brain field and a sagittal isodose distribution for the spine field. Composite isodose distributions that include both the CSA and boost components must also be submitted.

The following isodose curves should be shown to determine that the dose distributions conform to the protocol guidelines: dose-maximum, 110%, 105%, 100%, 95%, 90%, 70%, 50%, 30%, 10%.

#### 18.8.4 Dose Volume Histograms

Dose volume histograms will be calculated and submitted for organs at risk (section 18.3.3) including right and left optic nerves, optic chiasm, right and left cochlea, pituitary/hypothalamus, supratentorial brain, and spinal cord (foramen magnum to top of C2). Dose volume histograms will be calculated and submitted for the GTV, CTV and PTV of each volume treated.

#### 18.9 **Quality Assurance Documentation**

Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the QARC web site at [www.qarc.org](http://www.qarc.org) under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

All patients will undergo an on-treatment review of the CSI portion of their radiation therapy and a pre-treatment review of the boost, irrespective of institutional exempt status. All required imaging and RT data for the CSI must be submitted within three days of the start of radiotherapy. The required data for the boost volume must be submitted **before the start of the boost**. It is recommended that planning data for the boost volume be submitted at the time of the CSI on-treatment review.

#### Treatment Planning System Output:

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

#### Supportive Data:

- Copies of the operative reports for each surgical procedure.
- Preoperative MRI and postoperative cranial MRI with and without contrast
- Pre or postoperative spinal MRI with and without contrast; sagittal imaging should be included for both brain and spine
- Documentation of an independent check of the calculated dose when IMRT is used.

- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.
- Copies of verification (portal) films (or hard copy of real time portal images) for each field. For IMRT, orthogonal verification images of isocenter localization corresponding to setup DRR's are sufficient.

Forms:

- RT1/IMRT Dosimetry Summary Form (QARC)
- Proton Dosimetry Summary Form (QARC).

**18.9.1 Post Treatment Review**

Within one week of the completion of radiotherapy, the following data shall be submitted.

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

Electronic submission via sFTP for all data is preferred. Alternatively, the supportive data and forms may be sent to:

Quality Assurance Review Center  
640 George Washington Highway, Suite 201  
Lincoln, RI 02865-4207  
Phone: (401) 753-7600  
Fax: (401) 753-7601

Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist  
Quality Assurance Review Center  
640 George Washington Highway, Suite 201  
Lincoln, RI 02865-4207  
Phone: (401) 753-7600  
Fax: (401) 753-7601

**18.10 Definitions of Deviation in Protocol Performance**

**18.10.1 Prescription Dose**

Minor Deviation

Brain and spine fields: The dose to the prescription point differs from the protocol specified dose by more than 5% but less than 10%.

Boost field: Less than 95% of the study prescribed dose covers at least 95% of the PTV and/or < 50 Gy covers 100% of the PTV.

Major Deviation

Brain and spine fields: The dose to the prescription point differs from the protocol specified dose by more than 10%.

Boost field: Less than 90% of the study prescribed dose covers at least 95% of the PTV and/or < 48 Gy covers 100% of the PTV.

**18.10.2 Dose Uniformity**

Minor Deviation

The variation of dose in one of the target volumes exceeds + 10%, - 5%, but is within  $\pm 15\%$ .

Major Deviation

The variation of dose in one of the target volumes exceeds  $\pm 15\%$ .

18.10.3 Volume

Minor Deviation

Margins less than specified, or field(s) excessively large. Minor errors of Organs At Risk or Target volume definition.

Major Deviation

Transecting tumor or potentially tumor-bearing area(s). Major incorrect definition of Organs At Risk or target volumes.



## 19.0 NEUROCOGNITIVE ASSESSMENTS

### 19.1 Neurocognitive Assessments

Enrollment onto the neuropsychological function study ALTE07C1, *Neuropsychological, Social, Emotional, and Behavioral Outcomes in Children with Cancer*, is strongly encouraged. If the family agrees to participate in ALTE07C1, a separate informed consent for ALTE07C1 must be signed. Please refer to the ALTE07C1 protocol for eligibility requirements.

### 19.2 Quality of Life Assessments

The COG Statistical and Data Center will notify the study nurse investigators at the time a patient is enrolled on the study. The enrolling CRA should communicate directly with the nurse investigator **at the time of study enrollment** to determine the timeline for the quality-of-life assessments. If the patient agrees to participate, the quality-of-life assessment instruments (BASC-2, ABAS-II, BRIEF, and Peds QL Global Scale and Cancer Module) will be provided by the study nurse investigator at not cost to the institution. Information will also be provided regarding the proper methods of administration and instructions for returning the completed quality-of-life instruments to the nurse investigator. Once returned, this individual will also score the instruments, analyze the results, and enter these data into the COG eRDE system. Entry of completed neurocognitive testing results (not to include QOL assessments), performed at the institution, will be the responsibility of the institutional CRA. The QOL battery will be administered at 9 months, 30 months and 60 months ( $\pm$  3 months) after diagnosis.

**Please Note: The Quality of Life Assessments are also included on ALTE07C1 and can be completed either through ACNS0331 or ALTE07C1.**

To obtain quality-of-life assessment instruments or for additional information contact:

Patsy Cullen, PhD, CPNP  
Loretto Heights School of Nursing  
Regis University  
(303) 964-5132  
[pcullen@regis.edu](mailto:pcullen@regis.edu)

#### 19.2.1 Behavior Assessment System for Children – 2<sup>nd</sup> Edition (BASC-2)

The BASC-2 describes the behaviors, thoughts, and emotions of children and adolescents. The parent rating scale will be utilized for individuals who are at least 2 years and less than 18 years of age. Patients who are  $\geq$  18 years of age will complete a self-report form and no parent-report form will be used. The BASC-2 yields composite and scale scores in the domains of externalizing, internalizing, school, and other problems as well as adaptive skills and behavioral symptoms. Internal consistency reliability has been reported to be between 0.80 and 0.95, test-retest reliability between 0.72 to 0.92, and interrater reliability between 0.53 and 0.86. Content and construct validity have been established for this measure.

#### 19.2.2 Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P)

The 63-item preschool version of the BRIEF will be used to assess executive function in individuals who are at least 2 years and less than 6 years of age. This parent-report measure pertains to the following functional areas: inhibition, shifting of attention, emotional control, working memory, planning, and organization. Internal consistency of the BRIEF-P has been reported from 0.80 to 0.97 and test-retest reliability has been reported between 0.78 and 0.90. Construct, content, convergent, and discriminant validity have also been established.

#### 19.2.3 Behavior Rating Inventory of Executive Function (BRIEF)

The 86-item parent-report version of the BRIEF will be used to assess executive function in individuals between 6 years and 18 years of age. Patients who are  $\geq 18$  years of age will complete a self-report form (see BRIEF-A below). This parent-report measure pertains to the following functional areas: inhibition and shifting of attention, emotional control, initiation, working memory, planning, organization, and self-monitoring. Internal consistency of the BRIEF has been reported from 0.80 to 0.98 and test-retest reliability has been reported between 0.76 and 0.85. Construct, content, convergent, and discriminant validity have also been established for this measure.

#### 19.2.4 Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A)

The BRIEF-A is a 75-item self-report questionnaire that will be used to assess executive function in individuals who are  $\geq 18$  years of age. This self-report measure pertains to the following functional areas: inhibition, shifting of attention, emotional control, initiation, working memory, planning, organization, task monitoring, and self-monitoring. Internal consistency of the BRIEF-A has been reported from 0.73 to 0.96 and test-retest reliability has been reported between 0.82 and 0.93. Construct, content, convergent, and discriminant validity have also been established for this measure.

#### 19.2.5 Adaptive Behavior Assessment System – 2<sup>nd</sup> Edition (ABAS-II)

The parent-report form of the ABAS-II will be used for the assessment of adaptive skills in individuals from birth to 18 years of age (patients  $\geq 18$  years of age will complete a self-report form). Separate scale scores are available for 10 areas of functioning. Internal consistency has been reported to be 0.95 or greater for the composite adaptive behavior scale and between 0.85 and 0.95 for the sub-scales. Construct, convergent, and discriminant validity have also been established for this measure.

#### 19.2.6 Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0)

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 consists of 23 items, with separate parent-report forms for ages 2-4, 5-7, 8-12, and 13-18. Patients who are  $\geq 18$  years of age will complete a self-report form. 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. Reliability and validity have been established for this measure.

## 20.0 ENDOCRINE GUIDELINES

Obtain endocrine evaluations at diagnosis, completion of radiation therapy, completion of treatment, 6 months following the completion of treatment and then annually unless otherwise indicated.

Evaluation	Diagnosis	Completion of RT	Completion of treatment	6-months following the completion of treatment	Annually	2 years post start of treatment
Height, weight, BMI and percentiles <sup>1</sup>	X		X	X	X	
Growth Hormone stimulation test						X <sup>2</sup>
Free T4, TSH, and thyroid exam for nodules	X	X	X	X	X	
Perform ROS for failure to thrive, dehydration, hypoglycemia					X	
8 AM Cortisol			X	X	X	
Low Dose ACTH Stimulation test						X <sup>2</sup>
Tanner stage (See Appendix IV)	X		X	X	X	
LH, FSH, Estradiol or Testosterone					X	
If precocious puberty Bone age, LH, FSH, Estradiol or Testosterone, Bone age and pelvic ultrasound	X		X	X	X	
If delayed puberty obtain Bone age, LH, FSH, Estradiol, testosterone, and DEXA scan	X		X	X	X	
Serum sodium <sup>3</sup>	X					

<sup>1</sup> If abnormal patterns obtain Bone age annually

<sup>2</sup> Obtain 2 years off therapy and as clinically indicated

<sup>3</sup> If the patient is DDAVP check serum sodium at each visit

## APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

<b>Performance Status Criteria</b>					
Karnofsky and Lansky performance scores are intended to be multiples of 10					
<b>ECOG (Zubrod)</b>		<b>Karnofsky</b>		<b>Lansky*</b>	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

\*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

**APPENDIX II: M-STAGING SYSTEM FOR POSTERIOR FOSSA AND NON POSTERIOR FOSSA PNET**

STAGE	DEFINITION
	METASTASES
M <sub>0</sub>	No evidence of subarachnoid or hematogenous metastasis.
M <sub>1</sub>	Microscopic tumor cells found in CSF.
M <sub>2</sub>	Gross nodular seeding demonstrated in the intracranial subarachnoid space or ventricular system distant from the primary site.
M <sub>3a</sub>	Gross nodular seeding in the spinal subarachnoid space without evidence of intracranial seeding.
M <sub>3b</sub>	Gross nodular seeding in the spinal subarachnoid space as well as intracranial seeding.
M <sub>4</sub>	Extraneural metastasis

### APPENDIX III CCNU DOSING

Body Surface Area (m <sup>2</sup> )	Ideal Dose (mg)	Actual Dose to be given (mg)	Variance (%) from Ideal
2.0	150	150	0
1.9	143	140	-2
1.8	135	130	-4
1.7	128	130	+2
1.6	120	120	0
1.5	112	110	-2
1.4	105	100	-5
1.3	98	100	-2
1.2	90	90	0
1.1	82	80	-3
1.0	75	80	+7
0.95	71	70	-1
0.9	68	70	+4
0.85	64	60	-6
0.8	60	60	0
0.75	56	60	+7
0.70	53	50	-5
0.65	49	50	+2
0.6	45	40	-11
0.55	41	40	-2
0.5	38	40	+6
0.45	34	30	-12
0.4	30	30	0
0.35	26	30	+15
0.3	23	20	-11

Note: For patients whose body surface area falls between those noted in the table, give a dose that results in the smallest absolute change from the ideal dose. A similar method should be used for calculating dose reductions, i.e., rounding off the nearest 10 mg dose that results in the smallest absolute change.

## APPENDIX IV TANNER STAGING CRITERIA

Classification of Sex Maturity Stages in Girls (Adapted from: Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Diseases in Childhood 44:291, 1969)			
SMR Stage	Pubic Hair		Breasts (Females)
1	Preadolescent with vellus over the pubic area no more profuse than on the abdomen.	1	Preadolescent, with coloration of the papilla only.
2	Sparse growth of long, slightly pigmented downy hair which is straight or only slightly curled, and appearing usually at the base of the penis or along the labia.	2	Breast bud stage: breast and papilla are elevated above the chest in a small mound, without enlargement of the areolar diameter.
3	Pubic hair is darker, courser and more curly, and the hair is spreading sparsely over the pubic area.	3	Further elevation and enlargement of the breast and areola but no separation of the contours.
4	Further spread of the pubic hair, still considerably less than in the adult, and no extension of hair bilaterally up to the middle of the thigh.	4	The areola and papilla project from the breast to form a secondary mound.
5	Adult in amount and type of hair.	5	Adult state: projection of the papilla only, due to recession of the areola to the general contour of the breast.
Classification of Sex Maturity Stages in Boys (Adapted from: Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Diseases in Childhood 45:13, 1970)			
SMR Stage	Pubic Hair		Genitalia (Males)
1	Preadolescent with vellus over the pubic area no more profuse than on the abdomen.	1	Preadolescent: Testes, scrotum, and penis are of about the same size and proportion as in early childhood.
2	Sparse growth of long, slightly pigmented downy hair which is straight or only slightly curled, and appearing usually at the base of the penis or along the labia.	2	Beginning enlargement of the scrotum and testes; reddening of the scrotum, and changes in its texture.
3	Pubic hair is darker, courser and more curly, and the hair is spreading sparsely over the pubic area.	3	Penile enlargement (mm) with increase in length and further growth of the scrotum and testes (mm).
4	Further spread of the pubic hair, still considerably less than in the adult, and no extension of hair bilaterally up to the middle of the thigh.	4	Further increase in penile size; growth in breadth and development of the glans. Further enlargement of the testes and scrotum and continued darkening of the scrotal skin.
5	Adult in amount and type of hair.	5	Adult genitalia in size and shape.



## APPENDIX V: YOUTH INFORMATION SHEETS

### INFORMATION SHEET REGARDING RESEARCH STUDY ACNS0331 (for children from 8 - 12 years of age)

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#### **A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial**

*(A study of treatment for children with medulloblastoma using chemotherapy and comparing different doses of radiation therapy)*

1. My name is *(identify yourself to the child by name)*.
2. We have been talking with you about medulloblastoma. Medulloblastoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.
3. Children with medulloblastoma are normally treated with surgery and then by radiation therapy with or without chemotherapy. Radiation therapy is the use of high-energy x-rays to kill cancer cells. Chemotherapy is a type of medicine that destroys cancer cells.
4. Now we want to ask you to take part in a research study because you have a brain tumor called medulloblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat medulloblastoma. We will do this by comparing different doses of radiation therapy. We don't know which dose is better. That is why we are doing this study.
5. We have been talking with your parent(s) about this study. We want to include you as we talk more about it. Children who are part of this study will be treated with chemotherapy and radiation therapy. Being in this study may involve special risks which the doctor will discuss with you.
6. You may be enrolled on a separate study **ALTE07C1**, *Neuropsychological, Social, Emotional, and Behavioral Outcomes in Children with Cancer*, to measure the effects of radiation on your brain function, ability to learn and quality of life (general well-being).
7. Please talk this over with your parents. Together you can decide if you want to take part in the study. Please ask any questions that you can think of. If you have a question later, you can ask the next time you see me.

**INFORMATION SHEET REGARDING RESEARCH STUDY ACNS0331**  
**(for teens from 13 - 18 years of age)**

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**A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial**

*(A study of treatment for children with medulloblastoma to compare chemotherapy with standard doses of radiation therapy to chemotherapy with lower doses of radiation therapy)*

1. My name is *(identify yourself to the child by name)*.
2. We have been talking with you about medulloblastoma. Medulloblastoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.
3. Children with medulloblastoma are normally treated with surgery followed by radiation therapy with or without chemotherapy. Radiation therapy is the use of high-energy x-rays to kill cancer cells. Chemotherapy is a type of medicine that destroys cancer cells.
4. Now we want to ask you to take part in a research study because you have a brain tumor called medulloblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat medulloblastoma. We will do this by comparing different doses of radiation therapy. We don't know which dose is better. That is why we are doing this study.
5. We have been talking with your parent(s) about this study. We want to include you as we talk more about it. You have already had surgery to remove as much of the tumor as possible. Children and teens who are part of this study will be treated with chemotherapy and radiation therapy. Both of these types of therapy can cause side effects. For example, some types of chemotherapy cause changes in the blood cells. These changes can make a person feel tired or get an infection easier. Side effects from radiation therapy can include hearing loss and changes in brain and hormone function which could impact development.
6. You may be enrolled on a separate study **ALTE07C1**, *Neuropsychological, Social, Emotional, and Behavioral Outcomes in Children with Cancer*, to measure the effects of radiation on your brain function, ability to learn and quality of life (general well-being).
7. In this study, people who are treated with less radiation might have fewer side effects or less severe side effects than people treated with standard radiation. Treatment with less radiation might not work as well as the standard radiation therapy though. We don't know for sure, that is why we are doing the study. Being in this study may involve special risks which the doctor will discuss with you. The biggest risk is that if you are assigned to receive less radiation therapy than is standard then your treatment may not be as effective at destroying the cancer.
8. People who decide they don't want to take part in the study can still get treatment for their cancer. The treatment would be radiation therapy with or without chemotherapy.
9. Please talk this over with your parents. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don't want to be anymore, you can talk to your parents about withdrawing from this study. If you and your parents

agree to withdraw you from this study, you can do so and it won't affect your right to get other treatments and services. No one will be mad or upset with you.

10. Another part of this study is to see if there are ways to tell how the cancer will respond to treatment. We hope to find that out by doing tests on samples of tumor tissue. You have already had surgery. We would use a sample of the tumor that was removed during that surgery for tests. No extra procedures will be done to remove tissue for these tests. This part of the study is optional.

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## **SAMPLE INFORMED CONSENT/PARENTAL PERMISSION FOR PARTICIPATION IN RESEARCH**

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

### **ACNS0331: A Study Evaluating Limited Target Volume Boost Irradiation and Reduced Dose Craniospinal Radiotherapy (18.00 Gy) and Chemotherapy in Children with Newly Diagnosed Standard Risk Medulloblastoma: A Phase III Double Randomized Trial**

**If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say “you” in this consent form, we mean you or your child; “we” means the doctors and other staff.**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

This study is being carried out by the Children's Oncology Group (COG). COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, New Zealand, The Netherlands and Switzerland.

You are being asked to take part in this study because you have a cancer called medulloblastoma, which is a type of childhood brain tumor. This cancer is considered standard risk because you are over 3 years of age, the tumor is in the very back of the brain in an area called the posterior fossa, all or almost all of the tumor was removed by surgery, and the cancer has not spread to other parts of your body.

Standard therapy for medulloblastoma includes surgery followed by radiation therapy (use of high-energy x-rays to kill cancer cells) to the brain and spinal cord with or without chemotherapy (treatment with anti-cancer drugs).

Recent studies using a combination of chemotherapy and radiation therapy to treat children with standard risk medulloblastoma have been 70 and 80% effective in curing this disease. However, many children experience long-term side effects from radiation therapy to the brain and spine, including hearing loss, changes in hormone function (which can impact growth and sexual development), and learning difficulties (especially in younger children).

This study will look at what will happen if a smaller amount of radiation therapy is given to the brain and spinal cord of children with medulloblastoma. Some patients on this study will be given a standard dose of radiation and others will receive a reduced dose.

In addition this study will look at what will happen if the volume of radiation that is given during the “boost dose” of radiation is reduced. A “boost dose” is extra radiation delivered to the tumor area.



Some patients on this study will be given a standard-volume boost, which means that the radiation is targeted at the entire posterior fossa. Other patients will be given a smaller volume boost which means that they will be given radiation targeted more directly to the tumor bed.

All patients on this study will be treated with chemotherapy during and after radiation therapy.

### **WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to find out if the overall dose of radiation to the brain and spine can be reduced without decreasing rates of survival in children with medulloblastoma. The study will also look at whether the volume of radiation given during the boost can be reduced without decreasing survival rates in children with medulloblastoma.

Secondary goals of this study are:

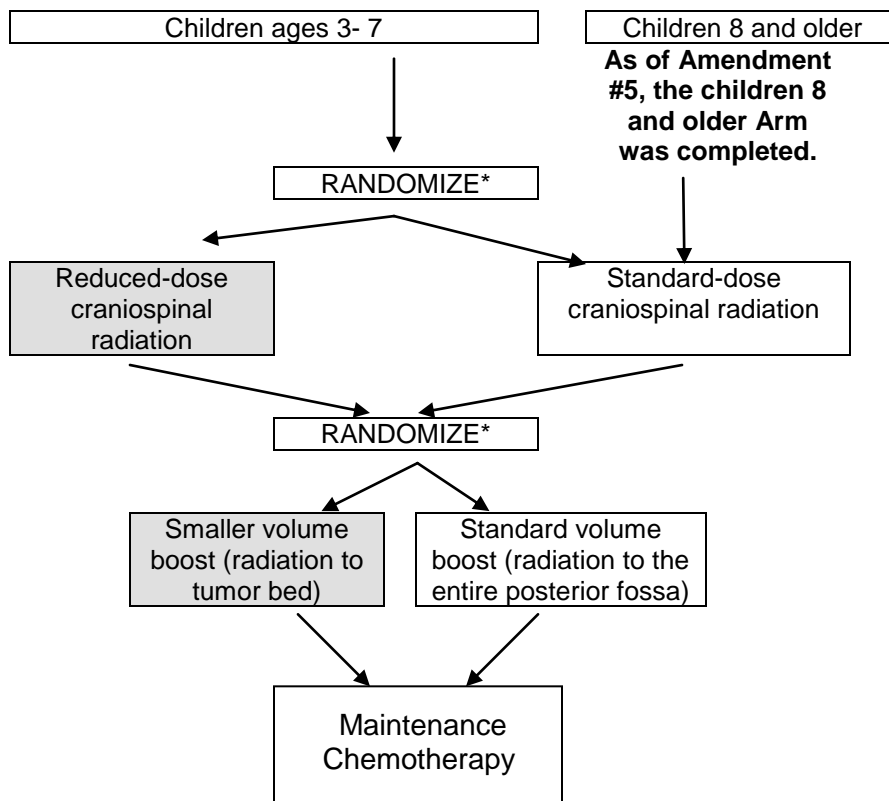
- To look at what characteristics are shared among children who are treated with a smaller volume boost dose of radiation and have a return of their cancer.
- To reduce the effects of radiation on children's hearing, ability to learn, and hormone function by reducing the dose of radiation delivered to the brain and spine.
- To look at whether children given a smaller volume boost dose of radiation have fewer effects to hearing and hormone function compared to children that receive the standard-volume boost dose.
- To develop a marker from the tumor's DNA that can predict how a child with medulloblastoma cancer may progress.

### **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 554 people will take part in this study.

### **WHAT IS INVOLVED IN THE STUDY?**

In order to compare the effects of different doses and volumes of radiation, children will be randomized to radiation treatment plans at the time of study entry. Children ages 3 to 7 will be randomized twice. They will be randomized between two doses of craniospinal radiation and between a standard volume boost and a smaller volume boost. All children 8 years and older will be given the standard dose of craniospinal radiation and will only be randomized for the boost volume of radiation. Randomization is a statistical method of making sure that each child has an equal chance of receiving any one of the treatments. Randomization means that you are put into a group by chance. It is like flipping a coin. The treatment plan assigned to you will be chosen by a computer. Neither you nor the study doctor will choose which treatment you will be given. You will have an equal chance of being assigned any of the treatment plans. There is an ongoing evaluation of results. If one treatment plan is found to be better, all children will be assigned to that treatment plan. An outline of the radiation treatment assignment possibilities is provided below.



\* Both Randomizations will occur at the time of Study Enrollment.

Therapy will begin about 4 weeks after surgery. Below is an outline of the planned therapy. More details are provided below the calendar.

Surgery		Chemoradiotherapy								Maintenance								
	31 Days	Radiation Therapy							4 wks									
	Cycle									1	2	3	4	5	6	7	8	9
	Week	1	2	3	4	5	6	7		11	17	23	27	33	39	43	49	55
	Day	1	8	15	22	29	36	43										
		Chemotherapy								Maintenance Chemotherapy								
		V	V		V	V	V	V		A	A	B	A	A	B	A	A	B

### Chemoradiotherapy

Chemoradiotherapy begins about 4 weeks after surgery.

#### Radiation Therapy

Radiation therapy to the brain and spine will be given 5 days each week for 6 weeks.

#### Chemotherapy

V = Vincristine will be given directly into the vein (IV) over one minute or using a minibag over several minutes by some institutions once a week for 6 weeks beginning at Week 2 (one week after the start of radiation).

### Maintenance Chemotherapy

Maintenance chemotherapy begins 4 weeks after the completion of chemoradiotherapy. There will be 9 cycles of maintenance. There are two different kinds of cycles given. They are referred

to as A and B. Cycle A lasts for 6 weeks and Cycle B lasts for 4 weeks. As shown on the calendar above, B cycles are given after the completion of 2 A cycles. Below are the details of the drugs and schedules for A and B cycles.

Cycle A (This cycle lasts 42 days)

CCNU is given by mouth on Day 1.

Vincristine is given directly into the vein (IV) over one minute or using a minibag over several minutes by some institutions on Days 1, 8, and 15.

Cisplatin is given directly into a vein over 6 hours on Day 1

Cycle B (This cycle lasts 28 days)

Cyclophosphamide is given into a vein over 1 hour on Days 1 and 2.

MESNA, a drug to protect the bladder from the effects of cyclophosphamide, will be given 15 minutes before each dose of cyclophosphamide and repeated at 3 and 6 hours.

Vincristine is given directly into the vein (IV) over one minute or using a minibag over several minutes by some institutions on Days 1 and 8.

You may also get a supportive care drug called a myeloid growth factor (filgrastim [G-CSF] or pegfilgrastim). This drug will help your blood counts recover after the chemotherapy is given. This drug will be given SubQ.

Review of Diagnosis

Some of the tissue already taken and copies of the films used to make the diagnosis of your disease will be sent to central review centers as part of COG quality control. The central review of tissue and films to confirm a diagnosis helps to make sure that an acceptable standard of expertise is maintained at each institution that is a member of the COG. You will not get any information from these reviews.

If you take part in this study, you will have the following tests and procedures:

**Procedures that are part of regular cancer care and may be done even if you do not join the study.**

Before treatment on this study begins and while receiving treatment, you will be given a series of standard medical tests.

- Physical exam
- Blood tests
- Tests of kidney function
- Tests of liver function
- Tests of hormone function
- Hearing tests
- Magnetic Resonance Imaging (MRI) of brain and spine. (MRI uses magnetic waves to look at soft tissues of the body.)
- Evaluation of cerebral spinal fluid (CSF) obtained by lumbar puncture\*

\*Lumbar puncture: In most cases, you will get medications to numb the pain and blur the memory. A small needle will be inserted between the spine bones and into the spinal fluid and a few teaspoons of spinal fluid will be collected. Lumbar punctures may cause headache. The test is painful and has a small risk of infection or bleeding. The pain usually is brief but occasionally may linger. (If you have had CSF collected at a point after surgery and before entering this study, it may not be necessary to have another lumbar puncture).

### **Optional Neuropsychological Tests**

Because your child is on this study, we would like to do some tests and surveys to see how the treatment on this study is affecting your child's life and the way your child is developing. These tests and surveys are called neuropsychological tests. Subjects who agree to participate in this study will be asked to participate in a separate study of the long-term effects of treatment on brain function (ALTE07C1). If you agree to participate in ALTE07C1, you will be asked to sign a separate consent form for ALTE07C1. Your participation in ALTE07C1 means that you will be asked to complete surveys at several different times during and after your treatment.

### **Optional Quality of Life Tests**

Because your child is on this study, we would like to do some Quality of Life assessments and surveys to see how the treatment on this study is affecting your child's life. Subjects who agree to participate will be asked to complete surveys at several different times during and after your treatment.

These Quality of Life assessments will help us learn about predicting outcomes in children with medulloblastoma, but they will not directly help you. You do not have to agree these extra assessments if you do not want to.

There will be no cost to you for completion of these measures and we will coordinate their administration at a time when you will be seen in clinic.

Please read the instructions and indicate below whether you choose to participate in the quality of life assessments.

Instruction 1. Circle YES to this instruction if you agree complete the quality of life assessments and surveys.

#1:      YES                      NO                      Initials \_\_\_\_\_

### **Optional Biology Tests**

In addition to standard procedures, we would also like to do some extra tests on your tumor tissue. We are requesting a sample of your tumor that was removed during surgery for research related to developing a marker from the tumor's DNA that can predict how a child with medulloblastoma cancer may progress. Participating in these extra tests will not require that you undergo any additional procedures. These tests use tumor tissue left over after diagnostic tests are completed. These extra tests will help us learn about predicting outcomes in children with medulloblastoma, but they will not directly help you. You do not have to agree these extra tests if you do not want to.

Please indicate below whether you choose to participate in the extra test on your tumor tissue.

Please read instructions and indicate whether you choose to participate in extra tests on your tumor tissue.

Instruction 1. Circle YES to this instruction if you agree to let researchers use a sample of your tumor to be used for research related to developing a marker that can predict how a child with medulloblastoma may progress.

#1:      YES                      NO                      Initials \_\_\_\_\_

## HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for about 14 months. However, you will continue to have physical exams, tests of hormone function, MRIs, hearing tests, blood tests and neurological tests for a few years after treatment so that the study doctors can continue to observe any effects of treatment. We would like to continue to find out about your health for about 10 years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study. The study doctor may decide to take you off this study if your cancer gets worse or the side effects from the treatment are too dangerous.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular doctor first.

## WHAT ARE THE RISKS OF THE STUDY?

If you are randomized to receive lower-dose craniospinal radiation and/or a smaller-volume boost dose, there is the risk that the radiation you receive may not be enough to prevent the cancer from coming back.

While on the study, you are also at risk for the side effects described below. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the therapy is completed, but in some cases side effects can be serious or long-lasting or permanent. Other unknown side effects may occur. You will be watched closely and the treatment will be discontinued if serious side effects develop.

Risks and side effects related to the drugs given on this study include the following:

Risks and side effects related to Lomustine include those which are:

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> <li>• Nausea and/or vomiting</li> <li>• Fewer white blood cells, red blood cells and platelets in the blood               <ul style="list-style-type: none"> <li>○ a low number of white blood cells can make it easier to get infections</li> <li>○ a low number of red blood cells can make you feel tired and weak</li> <li>○ a low number of platelets causes you to bruise and bleed more easily</li> </ul> </li> <li>• Loss of Appetite</li> <li>• Weight loss</li> </ul>	<ul style="list-style-type: none"> <li>• Increase in the blood of certain enzymes or bilirubin (a substance that comes from the liver breaking down waste products) which could indicate liver irritation or damage</li> <li>• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)</li> <li>• (Confusion) difficulty in thinking clearly or a sense of not knowing where you are</li> <li>• Tiredness</li> <li>• Unsteadiness when walking</li> <li>• Slurred speech</li> </ul>	<ul style="list-style-type: none"> <li>• Damage and scarring of the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood. This usually occurs only with very large doses over a long period of time.</li> <li>• Damage to the lungs which may can become worse over time and lead to death</li> <li>• Severe kidney damage (which may be permanent)</li> <li>• A decrease in the size of the kidneys</li> <li>• Damage to the nerves of the eye which may decrease vision (the ability to see clearly) and may cause blindness</li> <li>• A new cancer or leukemia resulting from this treatment</li> </ul>

**Risks and side effects related to Cisplatin include those which are:**

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> <li>• Nausea and vomiting</li> <li>• fewer red blood cells and white blood cells and platelets in the blood               <ul style="list-style-type: none"> <li>○ a low number of red blood cells can make you feel tired and weak</li> <li>○ a low number of white blood cells can make it easier to get infections</li> <li>○ a low number of platelets causes you to bruise and bleed more easily</li> </ul> </li> <li>• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or in the vein</li> <li>• Loss of appetite</li> <li>• Damage to the ear causing difficulty in hearing high pitched sounds</li> <li>• Temporary and mild increases in levels of certain chemicals in the blood because the kidney is not working as well as normal</li> </ul>	<ul style="list-style-type: none"> <li>• Abnormal levels of certain salts in the body like sodium, calcium, potassium and phosphate</li> <li>• Metallic taste</li> <li>• Rash</li> <li>• Numbness and tingling in the fingers and toes</li> <li>• Temporary changes in vision</li> <li>• Damage to the ear causing hearing loss, balance problems and ringing in the ears</li> <li>• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage</li> <li>• Inflammation and discomfort in the vein through which the medicine was given</li> <li>• Damage to the skin if the medication leaks from the vein</li> </ul>	<ul style="list-style-type: none"> <li>• Allergic reactions which may be severe and life-threatening, causing difficulty in breathing, rapid heart rate, facial swelling and or a drop in blood pressure</li> <li>• Damage to the kidney which may be permanent</li> <li>• Deafness</li> <li>• Seizures</li> <li>• Damage to the vision which could lead to blurred vision, blue-green color blindness and to loss of vision which usually goes away after stopping the drug</li> <li>• Decrease in muscle and nerve reflexes that may affect normal functions such as walking</li> <li>• Leukemia later in life</li> </ul>

**Risks and side effects related to Cyclophosphamide include those which are:**

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> <li>• Loss of appetite</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Fewer white blood cells in the blood.               <ul style="list-style-type: none"> <li>○ A low number of white blood cells may make it easier to get infections.</li> </ul> </li> <li>• Hair loss</li> <li>• Decreased ability of the body to fight infection</li> <li>• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children</li> </ul>	<ul style="list-style-type: none"> <li>• Abnormal hormone function which may lower the level of salt in the blood</li> <li>• Abdominal pain</li> <li>• Diarrhea</li> <li>• Fewer red blood cells and platelets in the blood               <ul style="list-style-type: none"> <li>○ A low number of red blood cells may make you feel tired and weak.</li> <li>○ A low number of platelets may cause you to bruise and bleed more easily.</li> </ul> </li> <li>• Bleeding and inflammation of the urinary bladder</li> <li>• Absence or decreased monthly periods which may be temporary or permanent and which may decrease the ability to have children</li> <li>• Temporary blurred vision</li> <li>• Nasal stuffiness with IV infusions</li> <li>• Skin rash</li> <li>• Darkening of areas of the skin and finger nails</li> <li>• Slow healing of wounds</li> <li>• Infections</li> </ul>	<ul style="list-style-type: none"> <li>• Heart muscle damage which may occur with very high doses and which may be fatal</li> <li>• Abnormal heart rhythms</li> <li>• Damage and scarring of lung tissue which may make you short of breath</li> <li>• A new cancer or leukemia resulting from this treatment.</li> <li>• Damage or scarring of urinary bladder tissue</li> <li>• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever</li> <li>• Infertility which is the inability to have children</li> </ul>

**Risks and side effects related to Vincristine include those which are:**

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> <li>• Hair loss</li> <li>• Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes</li> <li>• Constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Jaw pain</li> <li>• Headache</li> <li>• Muscle Weakness</li> <li>• Pain and bloating in your abdomen</li> <li>• Numbness and tingling</li> <li>• Wrist or foot drop</li> <li>• Drooping eyelids</li> <li>• Double vision, difficulty seeing at night</li> <li>• Hoarseness of your voice</li> <li>• Difficulty sweating</li> <li>• Abnormal walk with foot slapping</li> <li>• Difficulty with urination or increased desire to urinate</li> <li>• Dizziness and low blood pressure when you stand</li> <li>• Abnormal hormone function which may lower the level of salt in the blood</li> <li>• A mild drop in white blood cells, red blood cells and platelets in the blood               <ul style="list-style-type: none"> <li>○ a low number of red blood cells can make you feel tired and weak</li> <li>○ a low number of white blood cells can make it easier to get infections</li> <li>○ a low number of platelets causes you to bruise and bleed more easily</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Complete stoppage of your intestinal activity which can result in intestinal blockage</li> <li>• If the drug leaks out of the vein when being administered it will cause damage to nearby tissue</li> <li>• Seizures</li> <li>• Vocal cord paralysis</li> <li>• Difficulty breathing</li> <li>• Inability to walk</li> <li>• Decreased ability to hear clearly</li> <li>• Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness</li> <li>• In combination with other chemotherapy drugs: damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger</li> </ul>



All subjects may get a supportive care drug called a myeloid growth factor (filgrastim or pegfilgrastim) if needed to help recover blood counts after chemotherapy. Risks and side effects related to myeloid growth factors (filgrastim (G-CSF) or pegfilgrastim) include those which are:

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> <li>Aching or pain in the bones</li> </ul>	<ul style="list-style-type: none"> <li>Pain, redness, itching, and hardening of the skin and bruising at the site of the injection</li> <li>Headache</li> <li>Higher than normal levels of liver enzymes which may indicate liver irritation or damage</li> <li>Increase of uric acid in the blood</li> <li>A low number of platelets in the blood which may cause you to bruise and bleed more easily</li> <li>Low fever</li> <li>Enlargement of the spleen (an organ in the abdomen/belly which stores blood cells) which may cause pain in the abdomen or left shoulder</li> <li>Higher than normal white blood count</li> <li>Skin condition marked by fever and painful skin lesions that appear mainly on the face, neck, back and arms</li> <li>Rash or worsening of rash<sup>1</sup></li> <li>Inflammation of blood vessels in the skin leading to a raised purple rash and bruising has been seen mainly in patient who are treated for a long time<sup>1</sup></li> <li>Overall reddening with feelings of warmth<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling.</li> <li>Serious allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine, and possibly in the throat or swelling of the tongue which could make it difficult to breath<sup>2</sup></li> <li>If you are known to have sickle cell disease, filgrastim or pegfilgrastim may cause a sickle cell crises.</li> <li>Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening</li> <li>Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim or pegfilgrastim traveling to the lungs when they are inflamed or infected.</li> <li>A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time.<sup>1</sup></li> </ul>

<sup>1</sup> Reported with filgrastim

<sup>2</sup> Reported with pegfilgrastim

**Risks and side effects related to MESNA include those which are:**

<b>Likely</b>	<b>Less Likely</b>	<b>Rare but serious</b>
<ul style="list-style-type: none"> <li>• <b>Bad taste when taken by mouth</b></li> </ul>	<ul style="list-style-type: none"> <li>• Nausea.</li> <li>• Vomiting</li> <li>• Stomach pain</li> <li>• Headache</li> <li>• Pain in arms, legs and joints.</li> <li>• Tired feeling</li> <li>• Rash</li> <li>• Temporary low blood pressure</li> <li>• Diarrhea</li> <li>• Fever</li> <li>• Facial flushing with red cheeks</li> <li>• Nervousness</li> <li>• Dizziness</li> <li>• Confusion</li> <li>• Swelling around the eyes</li> <li>• Coughing</li> <li>• Rapid heart rate</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever</b></li> </ul>

**Possible side effects of radiation therapy to the brain and spinal cord:**

Children that are randomized to receive lower-dose craniospinal radiation and/or a smaller-volume boost dose may experience fewer or less significant radiation-related side effects.

**Short-term side effects:**

- Hair loss (all hair may not grow back after treatment)
- Irritation or redness of the skin with possible peeling of the skin at the site of radiation.
- Areas of the ear canal exposed to radiation may develop inflammation and irritation weeks or months after treatment that may cause plugging of ears, and balance problems.

**Long-term side effects:**

- Changes in hormone function
- Growth failure
- Vision problems
- Partial hearing loss
- Memory loss
- Learning difficulties

**Decrease in red blood cells, white blood cells and platelets:** A decrease in red blood cells may make you feel tired or weak. A decrease in white blood cells may affect your ability to fight off infections.

A decrease in platelets may cause bleeding problems because your blood may be slower to clot.

### **Reproductive Risks**

Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

### **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with medulloblastoma in the future.

If you are randomized to receive lower-dose craniospinal radiation and/or a smaller-volume boost dose, you might benefit from this study by experiencing fewer or less significant radiation-related side effects.

### **WHAT OTHER OPTIONS ARE THERE?**

Instead of being in this study, you have these options:

- Treatment with radiation only and no chemotherapy.
- Treatment with standard doses of radiation and chemotherapy (which is similar to the therapy you would receive on this study if you are randomized to the standard treatment arms).

Please talk to your regular doctor about these options.

### **WHAT ABOUT CONFIDENTIALITY?**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

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. Information about the certificate is attached at end of this consent (Attachment).

**Organizations that may look and/or copy your research records for research, quality assurance and data analysis include:**

- The Children's Oncology Group
- Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA) and other US and international governmental regulatory agencies involved in overseeing research
- Institutional Review Board of this hospital

### **WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If this study included providing tissue specimens to the researcher, there are no plans for you to profit from any new products developed from research done on your specimens.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. There are no plans to pay you for taking part in this study.

### **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care.

You can decide to stop being in the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your doctor will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Whether you participate or not, you will continue to get the best medical care this hospital can provide.

### WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research-related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at ###-###-####

For questions about your rights as a study participant, please call

\_\_\_\_\_  
NAME OF INSTITUTIONAL REVIEW BOARD REPRESENTATIVE\*

at \_\_\_\_\_  
TELEPHONE NUMBER

\*The Institutional Review Board is a group of people who review the research study to protect your rights.

### WHERE CAN I GET MORE INFORMATION?

The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at <http://www.childrensoncologygroup.org/familyhandbook>

Visit the NCI's Web site at <http://www.nci.nih.gov/cancerinfo/>

If you are in the United States, you may call the NCI's *Cancer Information Service* at:  
1-800-4-CANCER (1-800-422-6237)

Information about long term follow-up after cancer treatment can be found at <http://www.survivorshipguidelines.org/>

A description of this clinical trial will be available at <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at anytime.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

**STATEMENT OF CONSENT**

I have been given a copy of all \_\_\_\_\_ *[insert total of number of pages]* pages of this form. The form includes one (1) attachments

I have reviewed the information and have had my questions answered.

I agree to take part in this study.

Participant \_\_\_\_\_ Date \_\_\_\_\_

Parent/Guardian \_\_\_\_\_ Date \_\_\_\_\_

Parent/Guardian \_\_\_\_\_ Date \_\_\_\_\_

Physician/PNP obtaining consent \_\_\_\_\_ Date \_\_\_\_\_

IRB#

IRB Approved:

**Attachment**  
**Certificate of Confidentiality**

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 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, you may choose to voluntarily disclose the protected information. For example, if you request the release of information in writing, the Certificate does not prevent 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 the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.