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CHILDREN'S ONCOLOGY GROUP

ACNS0332

Efficacy of Carboplatin Administered Concomitantly With Radiation and Isotretinoin as a Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients

A Groupwide Phase III Study

CTEP ID / SKION Participating Institution
51075 / Dutch Childhood Oncology Group

[redacted]

Investigator ID
43656

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[redacted]

For Statistics and Data Center Contact Person see: http://members.childrensoncologygroup.org

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>To submit site registration documents:</th><th>For patient enrollments:</th><th>Submit study data</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using 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.</td><td>Data collection for this study will be done exclusively through eRDE system. Please see the Data Submission Schedule in the CRF packet for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> contact the CTSU Help Desk by phone or e-mail:
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<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
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STUDY COMMITTEE

[redacted]

COMMITTEE MEMBERS

[redacted]

[redacted]

AGENT	NSC#
Carboplatin (Paraplatin®)	241240
CISPLATIN	119875
CYCLOHOSPHAMIDE	026271
Filgrastim (G-CSF)	614629
Isotretinoin (13-cis Retinoic Acid)	329481
Vincristine	067574

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, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

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

ABSTRACT

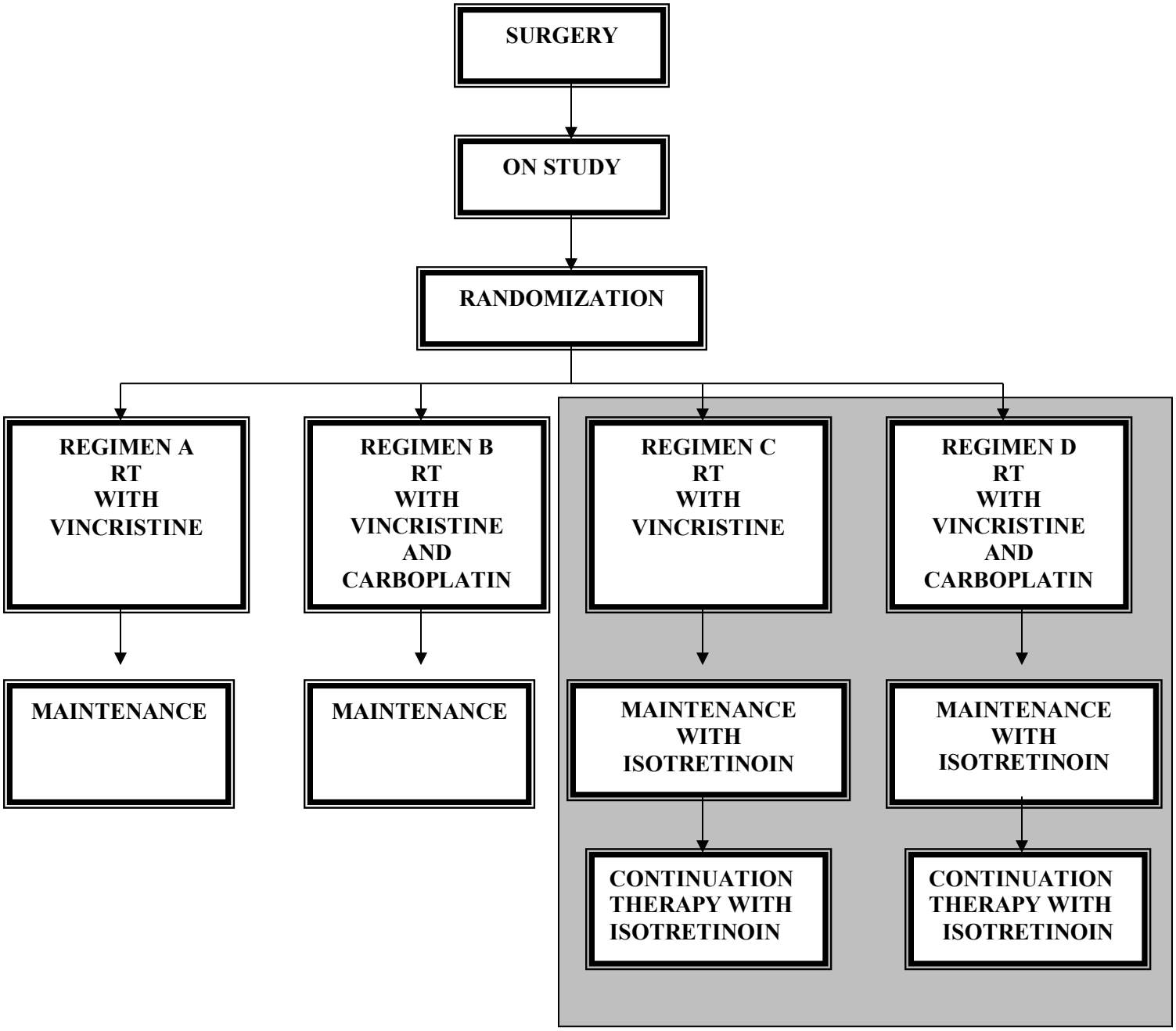
Medulloblastoma is the most common malignant childhood brain cancer. The goal of this study is to determine whether radiosensitization with carboplatin improves cure rates for children with other than average risk medulloblastoma. All patients will receive standard therapy consisting of surgery, radiation therapy and chemotherapy. Subsets of patients will be randomly assigned to receive carboplatin radiosensitization. Carboplatin has activity as a single agent against medulloblastoma and it has been shown to enhance radiation-induced tumor cell kill. A previous study, CCG-99701, demonstrated that it was feasible and safe to administer carboplatin on a daily basis during radiation therapy. Correlative biology studies are incorporated into the research design. ACNS0332 previously included a second randomization to assess whether the addition of Isotretinoin improved suvival. This randomization has been closed because the question has been answered. ACNS0332 previously included supratentorial primative neuroectodermal tumor (PNET) patients in addition to medulloblastoma patients. The PNET component of the trial has concluded.

Note: Enrollment to Regimen C and D on ACNS0332 has been suspended effective January 27, 2015:

Following review of the ACNS0332 study data during the COG Fall 2014 meeting, the DSMC requested a yearly futility analysis to be performed. Based on the most recent analysis and recommendations from the DSMC, it was concluded that treatment of patients with medulloblastoma with isotretinoin as performed in the context of this study will not lead to a significant event free survival advantage. The Study Committee and Group Chair have therefore decided to stop further randomization of patients to isotretinoin (Regimen C and D). The Study Committee recommends that subjects currently receiving protocol therapy on Regimen C or D discontinue administration of isotretinoin.

A futility analysis was also conducted for the carboplatin randomization; the DSMC determined that no changes be made to the carboplatin component of this trial. Therefore, Regimens A and B will remain open for accrual to address this important question. Enrollment of newly diagnosed patients with high-risk medulloblastoma onto this study continues to be strongly encouraged.

EXPERIMENTAL DESIGN SCHEMA



Randomization to arms C and D stopped as of 1/27/15

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1
To determine whether carboplatin radiosensitization increases long term event-free survival for high risk medulloblastoma/PNET patients.

1.1.2
To determine whether Isotretinoin increases long term event-free survival for high risk medulloblastoma/PNET patients.

1.2 Correlative Science Objectives

1.2.1
To compare residual disease response to radiation alone versus radiation plus carboplatin.

1.2.2
To identify molecular prognostic indicators suitable for patient stratification in future trials.

1.2.3
To evaluate the HRQOL during phases of active treatment specific to treatment modalities.

1.2.4
To describe the neuropsychological functioning of the study population and to evaluate the relationship between neuropsychological status and health related quality of life.

2.0 BACKGROUND

2.1 Rationale for Selected Approach and Trial Design

Advances in surgical technique, radiation therapy and chemotherapy have improved the outcome for children with medulloblastoma and other PNETs. Unfortunately, the rate of recurrence, death, and treatment-related morbidity remain unacceptable. [1-4] Therapeutic approaches that improve efficacy with minimal added toxicity are needed.

This study will be conducted in parallel with the ACNS0331 study for standard risk medulloblastoma, thereby completing the therapeutic platform for these tumors. Because the results in patients with high-risk medulloblastoma have historically been substantially inferior to those in patients with standard risk disease, the current study differs from ACNS0331 by maintaining the use of "standard" radiation doses and seeks to test the efficacy of adding radiosensitization and retinoid therapy to the backbone of radiotherapy and moderate intensity adjuvant chemotherapy as a way to improve survival in these high risk patients. In parallel with the ACNS0331 study, the current study will also evaluate the utility of biological parameters as predictors of treatment response and the impact of therapy on quality of life and neuropsychiatric measures. Such approaches, if validated, would then be incorporated in subsequent studies for these tumors.

2.2 Rationale for Concurrent Carboplatin and Radiation Therapy

Carboplatin as a single agent is effective for medulloblastoma/PNET patients, with complete or partial responses observed in 7 out of 15 recurrent disease patients receiving 100-210 mg/m^2/week. [5-7] Most of these patients received 175/mg/m^2/week as a single dose.

In the proposed study, patients will receive 175/mg/m^2/week divided into five daily 35 mg/m^2/day doses. Based on the efficacy data in relapsed patients, co-administration of carboplatin and radiation in the post-surgical period would be justified even in the absence of laboratory studies showing positive interaction between the two modalities. In addition, multiple laboratory and clinical studies show that cancer cell response is greater in the presence of carboplatin and radiation than either modality alone. [8-14]

Early laboratory studies reporting enhancement of radiation effects by platinum agents have been reviewed. [8] The enhancement of radiation-induced cell kill may involve multiple mechanisms including free radical-mediated radiosensitization, inhibition of recovery from potentially lethal or sublethal damage, and direct chemotherapy effects augmented by radiation-mediated enhanced cellular uptake of platinum agents. [8-14]

Concurrent administration of carboplatin and radiation has been well tolerated by adults and elderly patients in clinical trials and has led to improved response rates compared to radiation alone. In patients with advanced head and neck cancer, concurrent administration of carboplatin at AUC of 0.4 per week, docetaxel at 10 mg/m^2 and 64-82 Gy radiotherapy resulted in 81% complete response and 19% partial response rates. [15] Elderly patients with small cell lung cancer were treated with daily carboplatin (30 mg/m^2/day x 4 weeks) and 50-60 Gy radiotherapy and achieved a 50% response rate (1 CR, 18 PR, 38 patients total). [16] A phase III trial of 283 patients with unresectable stage III lung cancer showed an 18% CR rate in patients that received carboplatin (100 mg/m^2/week) plus 60 Gy radiation versus 10% in the radiation only arm (P = 0.1). [17]

Concurrent administration of carboplatin (35 mg/m^2/day x 30 doses) and radiation therapy in high risk medulloblastoma/PNET patients has been shown to be safe in protocol CCG 99701. In that study, carboplatin, rather than cisplatin was selected for reduced toxicities in addition to radiosensitization based primarily on pharmacokinetic properties, as both have been reported to have similar radiosensitizing activity. [18] Because carboplatin binds to plasma proteins more slowly than cisplatin, more free drug is available to cross the blood brain barrier. [19,20] Following intravenous administration of comparable doses in a primate model cerebrospinal AUC levels were 10-fold higher for carboplatin compared to cisplatin. [21] Brain tumor levels of carboplatin sufficient for radiosensitization can be obtained with doses of carboplatin as low as 20 mg/m^2. [22-24]

2.3 Rationale for Concurrent Isotretinoin and Adjuvent Chemotherapy

Pre-clinical studies showed that Isotretinoin and ATRA induced programmed cell death in medulloblastoma cells through a mechanism that involves induction of bone morphogenetic protein 2 (BMP2)-mediated phosphorylation of p38 MAP kinase. [25] Independent studies by Drs Reddy and Phillips at the Children's Hospital of Philadelphia confirmed the pro-apoptotic activity of retinoids in medulloblastoma and demonstrated caspase activation. [26] Fenretinide has also been tested and caused significantly less apoptosis in medulloblastoma cell lines than Isotretinoin or ATRA despite pro-apoptotic effects of fenretinide in other types of cancer (Hallahan and Olson, unpublished data).

Cultured medulloblastoma cells undergo apoptosis as the predominant response to retinoids. In two medulloblastoma cell lines, D283 and D341, Isotretinoin and all-trans retinoic acid (ATRA) induced apoptosis in a dose- and time-dependent fashion at concentrations that are readily achievable in the central nervous system. Efficacy was observed at concentrations ranging from 10 nM to 1 μM. [25] The response increased with duration of treatment so that by 6-8 days, 79% +/- 4% of D283s and 67% +/- 4% of D341s were apoptotic. [25] Because cultured tumor cells do not always faithfully represent primary

tumors, patient-derived medulloblastoma specimens were placed in tissue culture media within 20 minutes of resection from their blood supply, mechanically triturated into near single-cell suspensions and then treated with RA. Eight of 10 primary medulloblastoma/primitive neuroectodermal tumor specimens tested showed significantly increased cell death in response to these retinoids. Only 32 ± 5.2% of cells remained viable after 48 hours of ATRA exposure compared to 70 ± 5.5% of vehicle-treated cells ($P < 0.0006$). In both established cultures and patient-derived specimens, cell cycle arrest and neuronal differentiation was observed in a subset of the cells that failed to apoptose. Importantly, little or no retinoid-induced apoptosis was observed in neuroblastoma or glioma cells indicating that retinoids interfere with a pathway that is uniquely critical for medulloblastoma cell survival. This would suggest that retinoids might have even more efficacy in medulloblastoma patients than has been observed with neuroblastoma patients.

To determine whether the therapeutic window for retinoids was suitable for in vivo medulloblastoma treatment, studies were conducted in athymic mice bearing D283 medulloblastoma xenografts. ATRA or Isotretinoin sharply limited tumor growth. The average volume of treated animals was less than 1/3 that of untreated animals ($p < 0.01$, n = 24 controls, 12 ATRA-treated, 12 Isotretinoin-treated). [25]

A subsequent study also showed that a putative medulloblastoma oncogene is negatively regulated by ATRA. In this study, ATRA repressed OTX2 and induced apoptosis in medulloblastoma cell lines that overexpress OTX2. [27] In contrast to the *ex vivo* data above, these studies indicate that retinoids will be beneficial for treatment of medulloblastomas with anaplastic features. The conflicting preliminary data will be directly addressed as part of the biology correlative studies described in Section 16.

Isotretinoin rather than ATRA was selected for this study because of superior pharmacokinetic properties and comparatively reduced incidence of headaches and pseudotumor cerebri. Isotretinoin crosses the blood brain barrier and achieves parenchymal concentrations that show efficacy in pre-clinical studies. In a phase II clinical trial that measured pharmacokinetic data in 30 children treated with Isotretinoin, the mean serum level ranged from 4.9-8.9 μmol/l at doses of 100-200 mg/m^2/day. [28] The area under the curve was maintained through multiple courses of therapy and clearance of Isotretinoin did not increase during therapy. In this study, the half-life was 5.1 ± 3.2 hours. A study of adults with melanoma similarly showed that serum concentrations greater than 2 μmol/l were achieved with doses much lower than proposed in this study (40 mg every other day). [29] In this study, the plasma half-life averaged 33 hours. Studies of Isotretinoin levels in brain gray and white matter in rats showed that brain concentrations are approximately 30-50% those of serum. [30] Thus, mean serum levels of 4.9-8.9 μmol/l in pediatric patients are expected to provide levels in brain greater than the highest concentration used in pre-clinical studies (1 μmol/l) and over 100 times higher than the minimally effective concentration in pre-clinical studies (10 nmol/l). In the event of disrupted blood brain barrier, the concentration of retinoids in the brain may be even higher.

There is no clinical trial data demonstrating efficacy of retinoids in medulloblastoma, however, Isotretinoin is safe and effective in patients with neuroblastoma. Isotretinoin was tested in a phase III clinical trial of pediatric patients with high risk neuroblastoma. In the cohort that completed the retinoid phase of therapy, 3 year event free survival was increased from 29% to 45% by a six month course of Isotretinoin. [31] Complete responses were also observed in 3 patients with bone marrow metastases as the only site of detectable neuroblastoma in a phase I study. [32] These studies demonstrated that retinoids were

effective and that the dose and schedule proposed for the current study was well tolerated in pediatric patients.

The most compelling reason for providing Isotretinoin concurrently with adjuvant chemotherapy is that medulloblastoma cell apoptosis is significantly higher in the presence of cisplatin and Isotretinoin than either agent alone as described in more detail in the next paragraph. In addition, approximately 29% of medulloblastoma/PNET recurrences occur prior to the completion of adjuvant therapy. If Isotretinoin administration began after adjuvant chemotherapy was complete, there would be no opportunity to improve outcome for this group of patients.

Isotretinoin acts synergistically with cisplatin in cultured medulloblastoma cells. Cisplatin serves as a key agent in medulloblastoma therapy because of its demonstrated efficacy against medulloblastoma cells and because of improved outcomes in clinical trials that utilized platinum-based chemotherapy regimens. Preliminary studies show that Isotretinoin acts synergistically with cisplatin both in vitro and in vivo, increasing apoptosis of D283 cells by as much as three fold compared to either agent alone (Hallahan and Olson, unpublished). In an earlier study, the combination of 1 μg/ml cisplatin and 10 μM/l Isotretinoin led to complete cessation of growth of Med-3 medulloblastoma cells. [33] In other studies, retinoid agonists increased the efficacy of cisplatin against skin squamous cell carcinoma cell lines, oral squamous cell carcinoma xenografts, ovarian adenocarcinoma cells, ovarian caracinoma xenografts, and squamous head and neck cancer cells. [34-37] In addition, durable responses were observed when retinoid agonists and cisplatin were co-administered in patients with recurrent or advanced squamous cell carcinoma of the head and neck, advanced squamous cell carcinoma of the skin, advanced non-small-cell lung cancer. [34,38]

Cisplatin and Isotretinoin have largely non-overlapping toxicities. Prevalent cisplatin toxicities include hearing loss, renal dysfunction, nausea and marrow suppression. Isotretinoin has been safely administered in pediatric neuroblastoma patients. The most common untoward effects of Isotretinoin included dry skin, xerostomatitis, and headache, though the frequency of headache is much lower than seen with other retinoids such as ATRA. In a study of 43 adults treated with Isotretinoin for glioma, there were no instances of headache or pseudotumor cerebri.[39] Because cisplatin and Isotretinoin act synergistically, they have been combined in multiple clinical trials that involved adult patients. In one study, that involved administration of ATRA at 150 mg/m^2 on an every day basis without breaks, ATRA was poorly tolerated and discontinued by some patients. In three other trials that utilized breaks in the Isotretinoin dosing regimen, the combination was well tolerated establishing that the drugs can be safely co-administered.[34,38] The current study follows a two weeks on, two weeks off schedule for Isotretinoin, similar to the schedule that has been well tolerated in children with neuroblastoma.

Following review of the ACNS0332 study data during the COG Fall 2014 meeting, the DSMC requested a yearly futility analysis be performed. Based on the most recent analysis and recommendations from the DSMC, it was concluded that treatment of patients with medulloblastoma with isotretinoin as performed in the context of this study will not lead to a significant event free survival advantage. The Study Committee and Group Chair have therefore decided to stop further randomization of patients to isotretinoin (Regimen C and D) effective 1/27/15. The Study Committee recommends that subjects currently receiving protocol therapy on Regimen C or D discontinue administration of isotretinoin.

A futility analysis was also conducted for the carboplatin randomization; the DSMC determined that no changes be made to the carboplatin component of this trial. Therefore, Regimens A and B will remain open for accrual to address this important question. Enrollment of newly diagnosed patients with high-risk medulloblastoma onto this study continues to be strongly encouraged.

2.4 Rationale for Continued Enrollment of Medulloblastoma Patients and Discontinued Enrollment of PNET Patients

As of Amendment #2, the ACNS0332 protocol has been amended to discontinue enrollment of PNET patients and to extend enrollment of medulloblastoma patients to 300 eligible and evaluable patients. 300 patients have been enrolled on the study. Four (4) of these patients were deemed to be ineligible for the protocol, leaving 296 eligible patients. 211 of the 296 patients had medulloblastoma and the other 85 were diagnosed with SPNET. The SPENT patients enrolled on the trial will be replaced.

Randomization to this study was stratified on dissemination and tumor location (supratentorial PNET vs. medulloblastoma). The study was powered to detect treatment effects among all patients (PNET and medulloblastoma) combined. New data on biological differences between supratentorial PNET and medulloblastoma have become available, raising concern that heterogeneity of treatment effect across tumor type may reduce power. Therefore, the study has been re-powered to detect treatment effects among medulloblastoma patients alone. Accrual of supratentorial PNET patients will be discontinued since power to detect treatment effects in this group, which accounts for less than 30% of enrolled patients, will not be attainable within a reasonable time-frame.

As of June 2014, treatment is complete for all supratentorial PNET patients enrolled on ACNS0332. The diagnoses were made with the best available pathologic tools at the time of diagnosis and it is now clear that these tumors are biologically different than medulloblastomas. PNET patient data will be reported separately from medulloblastoma patient data and each will state the statistical power that accompanies the studies. The genomic studies that will commence on ACNS0332 patient samples will be retrospective and non-CLIA certified. It is being done to advance molecular pathology diagnoses for future patients rather than to alter treatment decisions.

Analyses will be performed separately for medulloblastoma and PNET patients. Statistical power for detecting treatment effects will be unchanged from that reported in the original protocol among medulloblastoma patients. Achieving the same statistical power among PNET patients however, would require more than 10 years of additional accrual, which is not feasible. Therefore outcomes for PNET patients will be reported with a statement regarding the current power.

The study duration is expected to be about 11 years, including the suspension for the amendment, additional 3 years of accrual, and 1 year of follow-up at the end.

2.5 Rationale for Biology Studies

Since the activation of ACNS0332, four molecular subtypes of medulloblastoma have been defined, namely Wnt, Sonic Hedgehog (Shh), Group 3 and Group 4. Within these molecular subtypes, additional prognostic indicators are emerging and some previous inidcators have been disproven as reliable biomarkers of outcome

As of Amendment #2, the biology studies included in Section 16.0 will permit the biology group within the Study Committee to assign each patient to one of the four molecular subclasses of medulloblastoma using fixed tissue, which is available for nearly all patients.

Likewise the PNET patient profiles will be compared to over 800 pediatric patient specimens to help determine the correct molecular subclasses of this disease. While this will not affect the statistical analysis of the study, it will enable the investigators to report patient outcomes in the context of molecular subtypes.

2.6 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.

2.7 Rationale for Continued Enrollment of Medulloblastoma Patients on Carboplatin Randomization and Discontinue Isotretinoin radomization

Amendment #3 incorporates the DSMC request to incorporate interim futility monitoring for both randomizations. We use conditional power as a guide for futility monitoring which is planned to coincide with annual DSMC reports. Prior to the activation of this amendment and in line with a request from the DSMC we conducted an interim futility analysis using the conditional power approach for Isotretinoin randomization based on data frozen as of June 30, 2014. This interim analysis led to the decision that continuing the randomization for Isotretinoin until the end of the trial had a very small chance of leading to a significant difference between the two arms and thus the DSMC recommended closure of the Isotretinoin randomization. At the same time we also conducted a similar interim analysis for the Carboplatin randomization which led to the conclusion that the randomization should continue.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit the supporting documentation to the CTSU Regulatory Office prior to patient enrollment. 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, (1) mark your submissions as 'URGENT,' (2) fax the regulatory documents, and (3) 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.

Sites can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, these sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRB Manager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.2 Patient Registration

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

In order for an institution to maintain COG membership requirements, every 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)* or APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study.*

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

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

3.1.3 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 Neurocognitive Testing
Enrollment onto ALTE07C1 is strongly encouraged.

3.1.5 Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than 10 calendar days after the date of study enrollment. In the event that Day 10 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day.

All patients must begin therapy within 31 days of diagnostic surgery. In the event that Day 31 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day.

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

3.1.7 Randomization
Randomization will take place at the time a patient is entered On Study via RDE. Patients will be assigned to either: Regimen A (RT without Carboplatin), Regimen B (RT with Carboplatin). Randomization will be stratified on the basis of location and dissemination. Six strata will be defined: (1) M0 Medulloblastoma with >1.5 cm^2 residual; (2) M+ Medulloblastoma; (3) M0 Supratentorial PNET with <1.5 cm^2 residual; (4) M0 SPNET with >1.5 cm^2 residual; (5) M+ SPNET, (6) M0 Diffusely Anaplastic Medulloblastoma.

As of Amendment #2, because the accrual of sPNET will be discontinued, only the three strata of medulloblatoma will be defined: (1) M0 Medulloblastoma with >1.5 cm^2 residual; (2) M+ Medulloblastoma; (3) M0 Diffusely Anaplastic Medulloblastoma.

As of Amendment #3, only one randomization will take place to Regimen A or B.

3.1.8 Mandatory Submission of Tissue for Central Pathology Review (See Section 15.0)
All patients must have tissue submitted for central pathology review. Pathology slides from the time of diagnosis must be sent to the COG Biopathology Center within 10 days of study enrollment. See Section 15.0 for information regarding specimen submission.

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.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits

of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

3.2.1 Age

Age greater than or equal to 3 and less than 22 years at the time of diagnosis.

3.2.2 Diagnosis

Newly diagnosed, previously untreated: (1) M0 Medulloblastoma with >1.5 cm^2 residual; (2) M+ Medulloblastoma. Patients with diffusely anaplastic medulloblastoma are eligible regardless of M-stage or residual tumor. See Appendix II for M-Staging.

As of Amendment #2, enrollment of patients with supratentorial PNET has been discontinued.

All patients with M4 disease are not eligible.

3.2.3 Cranial and Spinal MRI

A pre-operative MRI scan of the brain with and without contrast is required. **NOTE: CT scans are NOT sufficient for study eligibility since radiation therapy planning and response will be based on MRI scans only.**

Post-operative head MRI scan with and without contrast (preferably within 72 hours post-surgery). For patients who undergo stereotactic biopsy only, either a pre or post-operative MRI is sufficient. For patients with M2 and M3 disease, a post-op MRI is strongly encouraged, but not mandatory.

Spinal MRI imaging with and without gadolinium is required within 10 days of surgery if done pre-operatively or within 28 days of surgery if done post-operatively. For posterior fossa tumors, pre-operative MRI scans are preferred because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

3.2.4 Evaluation of Lumbar CSF Cytology

Lumbar CSF cytology examination must be obtained pre-operatively or within 31 days following surgery. The optimal time for obtaining CSF is prior to surgery or 1-3 weeks following surgery. Ventricular CSF (either pre- or post-op) may be used only if a post-operative spinal tap is contraindicated. 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_3). Patients who are categorized as M_1 must have either an intra-operative positive CSF (via lumbar puncture at the end of the procedure) or a positive lumbar CSF obtained > 7 days post-operatively (to rule out surgically induced false positives).

3.2.5 Performance Level (See Appendix I)
Patients must have a Karnofsky performance level of ≥ 30 for patients > 16 years of age or a Lansky performance scale of ≥ 30 for patients ≤ 16 years of age and life expectancy > 8 weeks.

3.2.6 Prior Therapy
No previous chemotherapy or radiation therapy.

3.2.7 Concomitant Medications Restrictions

3.2.7.1
Corticosteroids should not be used during chemotherapy administration as an antiemetic because of their effect on the blood-brain barrier.

3.2.7.2
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, phenobarbitol, carbamazepine, and St. John's wort. The use of these drugs should be avoided with vincristine.

3.2.7.3
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/.

3.2.7.4
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.

3.2.7.5
No other experimental therapy is permitted while on study.

3.2.8 Organ Function Requirements:

3.2.8.1 Adequate renal function defined as:
- Creatinine clearance or radioisotope GFR ≥ 70mL/min/1.73m^2 OR
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

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

3.2.8.2 Adequate liver function defined as:
- Total bilirubin < 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.
- For patients on anti-seizure medications, SGOT (AST) or SGPT (ALT) must be < 5 x ULN.

3.2.8.3 Adequate bone marrow function defined as:
- ANC ≥ 1,000/μL
- Platelets ≥ 100,000/μL (untransfused)
- Hemoglobin ≥ 8 g/dL (may be transfused)

3.2.9 Pregnancy

There is information indicating a risk of fetal or teratogenic toxicity with this treatment.

Female patients who are post-menarchal must have a negative pregnancy test. Lactating female patients must agree not to breast-feed while on this trial. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

3.2.10 Regulatory

3.2.10.1
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.10.2
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).

Overview of Treatment Plan
Following neurosurgical procedure and staging, patients will be randomized to receive either 36 Gy craniospinal irradiation with appropriate boost to the tumor bed or the same radiation regimen with addition of carboplatin as a radiosensitizing agent. All patients must begin therapy within 31 days of surgery. The dose of carboplatin will be 35 mg/m^2/day for 30 doses over 6 ½ weeks based on the dose finding phase of COG 99701. All patients will receive vincristine 1.5 mg/m^2 once per week during radiation therapy for a total of 6 doses.

Following radiation and a 6 week rest period, patients will then undergo Maintenance chemotherapy with cisplatin, vincristine, and cyclophosphamide in 28 day cycles for a total of 6 cycles (according to COG 99701, Regimen B). Note: Maintenance may be delayed up to 8 weeks based on experience from 99701. Approximately 10% of patients will drop counts between 4-6 weeks after completing radiation therapy and Maintenance should not be initated until counts recover.

Radiation Therapy
All patients will receive craniospinal radiation therapy (CSRT) to doses of:
36 Gy CSRT

55.8 Gy Posterior fossa (cumulative dose)

See Section 18.0 for details regarding technique and doses to the brain, spine and boosts to known sites of metastases depending on disease stage and tumor response.

ALL PATIENTS WILL REQUIRE REVIEW OF THEIR RADIATION THERAPY TREATMENT PLAN. THE RADIATION TREATMENT PLAN FOR THE CRANIOSPINAL FIELDS MUST BE SUBMITTED TO IROC RI (QARC) FOR QA REVIEW WITHIN 3 DAYS OF INITIATION OF RADIATION THERAPY (SECTION 18.9). THE TREATMENT PLAN FOR THE BOOST VOLUME MUST BE SUBMITTED BEFORE THE START OF THE BOOST TREATMENT.

4.1 Regimen A Administration Schedule for Radiation Therapy

All patients must begin therapy within 31 days of diagnostic surgery. In the event that Day 31 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day.

VinCRIStine: IV push over 1 minute (or infusion via minibag as per institution policy) 1.5 mg/m^2/day (maximum single dose 2 mg) once weekly Weeks 1-6 during radiation for a total of 6 doses. Vincristine should be started within the first week of starting radiation

therapy and given weekly thereafter. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg.
Avoid extravasation; the use of a central line is suggested.

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®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Myeloid Growth Factor: Subcutaneous (preferred) or IV
Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day to be administered during Radiation Therapy as needed. CBCs will be obtained weekly. If ANC ≥ 1500/μL, no myeloid growth factor is needed and weekly CBCs will continue. If ANC ≤1500/μL at any point, then the following regimen should replace weekly CBCs. If ANC ≤1500/μL on any Friday, myeloid growth factor will be administered subcutaneously or IV on Friday, Saturday, and Sunday. Myeloid growth factor should not be given until after the radiation treatment on Friday has been delivered. If the ANC >1500/μL, no myeloid growth factor will be administered that weekend. On any Monday or Wednesday, if the ANC <1000/μL, myeloid growth factor will be administered on that day and the following day after the radiation treatment. If the ANC ≥1000/μL on Monday or Wednesday, myeloid growth factor will not be administered (see Table below). Family members should be taught to administer myeloid growth factor. Myeloid growth factor guidelines are tabulated below:

Guidelines for Myeloid Growth Factor Administration During Radiotherapy

DAY	CBC with diff, plts	ANC 1000-1500	ANC < 1000
Friday	x	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Fri., Sat., Sun.	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Fri., Sat., Sun.
Monday	x	No myeloid growth factor	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Mon., Tues.
Wednesday	x	No myeloid growth factor	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Wed., Thur..

There is to be no dose escalation of myeloid growth factor **for neutropenia alone. In the event of a potentially life-threatening infection with neutropenia,** filgrastim or biosimilar **may be increased to 10 micrograms/kg/day. There will be no dose escalations of sargramostim.**

Significant myelosuppression is likely to occur, particularly during the last two-three weeks of radiation. **However, radiation should not be withheld for myelosuppression alone. Radiation should be continued even if the patient is hospitalized with fever and neutropenia as long as the patient is clinically stable. Administration of the boost should not be substituted for craniospinal radiation in the face of low counts.**

Myeloid growth factor following the completion of radiotherapy (Week 7-12) should only be used in the setting of fever and/or infection with neutropenia (i.e. not prophylactically) but should be stopped 24 hours prior to starting Maintenance.

4.1.1 ACNS0332: Regimen A Radiation Therapy

Six weeks of radiation therapy (Weeks 1-6) and 6 weeks of rest (Weeks 7-12) 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 12 is a rest period (6 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^2 (maximum dose 2 mg)	Administer once weekly Weeks 1-6 during radiation for a total of 6 doses	Vincristine should be started within the first week of starting radiation therapy and given weekly thereafter and can be administered any day during the week. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg.	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets *- 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_3). *See Section 7.1 for a complete list of observations.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Myeloid Growth Factor	SubQ or IV (SubQ preferred)	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day	See Administration Guidelines (Section 4.1)	Should be administered during Radiation Therapy as needed. See Administration Guidelines (Section 4.1).	

Regimen_____ Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	VCR ____mg	Myeloid Growth Factor Used _____ _____mcg	Studies	Comments (Include any held doses, or dose modifications) Indicate days myeloid growth factor given on each week
				Enter calculated dose above and actual dose administered below			
		1	1	____mg#	____mcg$	a ,f	
		2	8	____mg#		a ,f	
		3	15	____mg#		a ,f	
		4	22	____mg#		a ,f	
		5	29	____mg#		a ,f	
		6	36	____mg#		a ,f	
		7	43			a,f	
		8				a,f	
		9				a,f	
		10				b%,c%,d%,e%,	
		11					
		12					Indicate last day of myeloid growth factor dose _____
				To begin Maintenance, the ANC must be ≥ 750/µL, platelets ≥ 75,000/µL and the patient must have been off myeloid growth factor for at least 24 hours. If ANC < 750/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.

$ - Administer myeloid growth factor as needed and according to table in Section 4.1.

% - Obtain during Weeks 10-12. Obtain Spinal MRI and cytology only if initially positive.

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

4.2 **Regimen B Administration Schedule for Radiation Therapy**

All patients must begin therapy within 31 days of diagnostic surgery. In the event that Day 31 falls on a Saturday, Sunday or Holiday, therapy must begin the following business day.

VinCRIStine: IV push over 1 minute (or infusion via minibag as per institution policy) 1.5 mg/m^2/day (maximum single dose 2 mg) once weekly Weeks 1-6 during radiation for a total of 6 doses. Vincristine should be started within the first week of starting radiation therapy and given weekly thereafter. Administer prior to CARBOplatin. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg.
Avoid extravasation; the use of a central line is suggested.

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®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

CARBOplatin: IV over 15 minutes
35 mg/m^2/day given daily during radiation therapy for a total of 30 doses. The first dose of CARBOplatin should be administered on the first day of radiation therapy. CARBOplatin will be over 15 minutes 1-4 hours prior to radiation therapy. This should be sufficient time for patients who may require sedation or who travel to another facility. **If a radiation treatment is not given, CARBOplatin should be held as well. If a dose of CARBOplatin is given and radiation therapy is NOT administered due to sedation or technical issues, the CARBOplatin dose should not be made up (i.e. no more than 30 doses of CARBOplatin should be given). Since there are 31 fractions of radiation, the last radiation treatment will not be preceded by a dose of CARBOplatin.**

Avoid use of aluminum containing needles or administration sets.
Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).

Myeloid Growth Factor: Subcutaneous (preferred) or IV
Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day 5 micrograms/kg/day to be administered during Radiation Therapy as needed. CBCs will be obtained every Monday, Wednesday, and Friday. If ANC ≤1500/μL on any Friday, myeloid growth factor will be administered subcutaneously or IV on Friday, Saturday, and Sunday. Myeloid growth factor should not be given until after the radiation treatment on Friday has been delivered. If the ANC > 1500/μL, no myeloid growth factor will be administered that weekend. On any Monday or Wednesday, if the ANC <1000/μL, myeloid growth factor will be administered on that day and the following day after the radiation treatment. If the ANC ≥1000/μL on Monday or Wednesday, myeloid growth factor will not be administered (see Table below). Family members should be taught to administer myeloid growth factor. Myeloid growth factor guidelines are tabulated below:

Guidelines for Myeloid Growth Factor Administration During Radiotherapy

DAY	CBC with diff, plts	ANC 1000-1500	ANC < 1000
Friday	x	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Fri., Sat., Sun.	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Fri., Sat., Sun.
Monday	x	No myeloid growth factor	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Mon., Tues
Wednesday	x	No myeloid growth factor	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day Wed., Thur.

There is to be no dose escalation of myeloid growth factor **for neutropenia alone. In the event of a potentially life-threatening infection with neutropenia,** filgrastim or biosimilar **may be increased to 10 micrograms/kg/day. There will be no dose escalations of sargramostim.**

Significant myelosuppression is likely to occur, particularly during the last two-three weeks of radiation. **However, radiation should not be withheld for myelosuppression alone. Radiation should be continued even if the patient is hospitalized with fever and neutropenia as long as the patient is clinically stable. Administration of the boost should not be substituted for craniospinal radiation in the face of low counts.**

Filgrastim following the completion of radiotherapy (Week 7-12) should only be used in the setting of fever and/or infection with neutropenia (i.e. not prophylactically).

4.2.1 **ACNS0332: Regimen B Radiation Therapy**
Six weeks of radiation therapy (Weeks 1-6) and 6 weeks of rest (Weeks 7-12) 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 12 is a rest period (6 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^2 (maximum dose 2 mg)	Administer once weekly Weeks 1-6 during radiation prior to CARBOplatin dose that day for a total of 6 doses	VinCRIStine should be started within the first week of starting radiation therapy and given weekly thereafter and can be administered any day during the week. The absolute dose of vinCRIStine should be rounded down to the nearest 0.1 mg.	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus *- 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_3). *See Section 7.2 for a complete list of observations.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
CARBOplatin (CARBO)	IV over 15 minutes	35 mg/m^2/day	Daily during RT for a Total of 30 Doses	CARBOplatin and VinCRIStine will be given 1-4 hours prior to RT. See Adminitration Guidelines (Section 4.2).	
Myeloid Growth Factor	SubQ or IV (SubQ prefered)	Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day		Should be administered during Radiation Therapy as needed. See Administration Guidelines (Section 4.2).	

Regimen_____ Ht_____cm Wt_____kg BSA_____m^2

Date	Date	Week	Day	Time CARBO Finished	Time XRT Started	CARBO ____mg	VCR ____mg	Myeloid Growth Factor Used _____ ____mcg	Studies	**Comments** (Include any held doses, or dose modifications) Indicate days myeloid growth factor given on each week
						Enter calculated dose above and actual dose administered below				
		1	1			____mg	____mg#	____mcg$	a ,f, g	
			2			____mg				
			3			____mg			f	
			4			____mg				
			5			____mg			f	
		2	8			____mg	____mg#		a,f	
			9			____mg				
			10			____mg			f	
			11			____mg				
			12			____mg			f	
		3	15			____mg	____mg#		a ,f, g	
			16			____mg				
			17			____mg			f	
			18			____mg				
			19			____mg			f	
		4	22			____mg	____mg#		a,f	
			23			____mg				
			24			____mg			f	
			25			____mg				
			26			____mg			f	
		5	29			____mg	____mg#		a,f, g	
			30			____mg				
			31			____mg			f	
			32			____mg				
			33			____mg			f	
		6	36			____mg	____mg#		a,f	
			37			____mg				
			38			____mg			f	
			39			____mg				
			40			____mg			f	
		7							f&, g	
		8							f&	
		9							f&	
		10							b%,c%,d%,e%,f&	
		11							f	
		12							f	Indicate last day of myeloid growth factor dose _____
					To begin Maintenance, the ANC must be ≥ 750/µL, platelets ≥75,000/µL and the patient must have been off myeloid growth factor for at least 24 hours. If ANC < 750/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.
$ - Administer myeloid growth factor as needed and according to table in Section 4.2.
% - Obtain during Weeks 10-12. Obtain Spinal MRI and cytology only if initially positive.
& - If counts are low, CBC should be performed twice weekly.

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

4.3 **Regimen A or Regimen B Maintenance**

Begin each cycle of Maintenance on Day 29 and when ANC ≥ 750/μL, platelets ≥ 75,000/μL and the patient must have been off myeloid growth factor for at least 24 hours for a total of 6 Cycles.

CISplatin: IV over 6 hours
75 mg/m^2 on Day 1

Suggested hydration and supportive care: Prehydration should begin at least 2 hours prior to CISplatin infusion with normal saline and mannitol (7.5 g/L) at 125 mL/m2/hr. After the completion of the CISplatin infusion, begin D5NS and mannitol (7.5 g/L) and 8 mEq Magnesium sulfate/L at 125 mL/m^2/hr x 8 hours. IV fluids should then be changed to D5 1/2 NS + 20 mEq KCl/l + 8 mEq Magnesium sulfate/L at 125 mL/m^2/hr to complete 24 hours of hydration (until first dose of cyclophosphamide). Urine output of at least 3 mL/kg/hr should be achieved prior to CISplatin infusion and maintained for at least 8 hours following completion of the infusion. Mannitol 0.5 g/kg may be used to maintain urine output. If a mannitol bolus fails to increase urine output over the ensuing hour, then furosemide 1 mg/kg IV should be given as a bolus. Four hour input and output totals should be maintained within 20% of each other.

Oral magnesium supplementation following CISplatin administration may be necessary. Electrolytes (i.e., Mg, Ca, PO_4, K) should be followed closely thereafter.

Avoid use of aluminum containing needles or administration sets. 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®).

VinCRIStine: IV push over 1 minute (or infusion via minibag as per institution policy)
1.5 mg/m^2/day (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.

Avoid extravasation; the use of a central line is suggested.

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®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide: IV over 1 hour
1000 mg/m^2 on Day 2 and Day 3. On Day 2, cyclophosphamide should be given at least 24 hours after CISplatin.

Suggested hydration and supportive care: Urine output should be maintained at a minimum of 3 ml/kg/hr. Hydration is continued with D_5 1/2NS plus 20 mEq/L KCl at 100 mL/m^2 per hour. After second dose of cyclophosphamide, hydration should be continued for a minimum of 8 hours and until patient maintains normal PO intake. Note: nausea and vomiting are likely and prolonged IV fluids may be necessary to prevent dehydration and maintain electrolyte balance.

Myeloid Growth Factor: Subcutaneous (preferred) or IV
Filgrastim or biosimilar 5 micrograms/kg/day OR sargramostim 250 micrograms/m^2/day daily starting on Day 4 and continue for at least 10 days until post-nadir ANC > 1500μL. Myeloid Growth Factor must be discontinued for a minimum of 24 hours prior to next chemotherapy cycle if counts have recovered.

Do not start the next cycle of chemotherapy until at least 24 hours after myeloid growth factor has been stopped. Myeloid growth factor may be given concomitantly with vincristine.

4.3.1 **ACNS0332: Regimen A and Regimen B Maintenance** Four consecutive weeks (28 days) will constitute one cycle. Use one copy of the TDM for each cycle (please note cycle number).	_____ Patient name or initials	_____ DOB

Begin each subsequent cycle of Maintenance on Day 29 and when count criteria are met. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	75 mg/m^2	Day 1	See Administration Guidelines (Section 4.3)	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus h. SGOT, SGPT, Alkaline Phosphate, Bilirubin i. Creatinine Clearance or GFR j. Urinalysis k. Thyroid Function *- 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_3). *See Section 7.3 for a complete list of observations.* **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
VinCRIStine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m^2 (maximum dose 2 mg)	Days 1 and 8	The absolute doses of vincristine to be delivered are a function of body seruface area, rounded down to the nearest 0.1 mg.	
Cyclophosphamide (CPM)	IV over 1 hour	1000 mg/m^2	Days 2 and 3	See Adminitration Guidelines (Section 4.3)	
Myeloid Growth Factor	SubQ or IV (SubQ preferred)	Filgrastim or biosimilar 5 microgram/ kg/day OR sargramostim 250 micrograms/ m^2/day	Start on Day 4 and continue for at least 10 days until post-nadir ANC > 1500µL.	Do not start the next cycle of chemotherapy until at least 24 hours after myeloid growth factor has been stopped. Myeloid growth factor may be given concomitantly with vincristine.	

Regimen_____ Cycle _____ Ht_____cm Wt_____kg BSA_____m^2

Date Due	Date Given	Week	Day	CDDP ____mg	VCR ____mg	CPM ____mg	Myeloid Growth Factor Used _____ ____mcg	Studies	Comments (Include any held doses, or dose modifications)
				Enter calculated dose above and actual dose administered below					
		1	1	____mg	____mg			a, e, f, g, h, i%, j (b, c@, d#)##,	
			2			____mg			
			3			____mg			
			4				____mcg		
		2	8		____mg			f+,g	
		3	15					f+,g	
		4	22					f+,g	Indicate last day of Myeloid Growth Factor dose_____
			28					f+,g (a, b, c@, d#, e, f, g, h, k)&	
			29	To begin next cycle of Maintenance, the ANC must be ≥ 750/µL, platelets ≥ 75,000/µL and the patient must have been off myeloid growth factor for at least 24 hours. If ANC < 750/µL or platelets < 75,000/µL then repeat CBC and differential at least twice a week until criteria are met. See Section 5.2.2.1					

\+ If counts are low and while on myeloid growth factor, it is recommended that CBCs be performed twice weekly.
@ Spinal imaging is only necessary for patients with M_1 – M_3 disease.
# Required only for patients who are positive at diagnosis.
% Obtain if creatinine is greater than normal for age (see Section 3.2.8.1)
& Obtain within 1 month of completing Maintenance.
Obtain prior to Cycle 4.

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

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Modifications During Radiation Therapy

5.1.1 Vincristine

5.1.1.1 Neurotoxicity

For Grade 3/4: foot drop, severe paresis, disabling paresthesias, ileus or cranial neuropathy hold vincristine and resume at 1 mg/m^2 (1.5 mg maximum) when symptoms resolve.

5.1.1.2 Jaw Pain

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

5.1.1.3 Hepatotoxicity

If total bilirubin is greater than 1.9 mg/dL, hold vincristine dose. If total bilirubin is 1.5 - 1.9 mg/dL, administer vincristine at 1 mg/m^2 (1.5 mg maximum).

5.1.2 Carboplatin (Regimen B)

5.1.2.1 Hematologic Toxicity

It is likely that patients will develop myelosuppression during the last two-three weeks of radiation therapy. See Section 4.2 for myeloid growth factor guidelines during radiation. Red cell and platelet transfusions should be used to maintain the Hct >30% and platelets >30,000/μL during chemoradiotherapy. **No dose modifications of Carboplatin will be made.**

5.1.2.2 Nephrotoxicity

If the serum creatinine increases to greater than twice the baseline value, a creatinine clearance or GFR should be done. If the creatinine clearance or GFR falls below 60 ml/min/1.73m^2, reduce carboplatin dose by 25% to 26 mg/m^2. A serum creatinine should be checked three times a week thereafter. If the creatinine returns to less than twice the baseline value and the creatinine clearance or GFR to > 60 ml/min/1.73m^2, return to full dosage.

5.2 Dose Modifications during Maintenance Chemotherapy

5.2.1 Vincristine

5.2.1.1 Neurotoxicity

For Grade 3/4: foot drop, severe paresis, disabling paresthesias, ileus or cranial neuropathy hold vincristine and resume at 1 mg/m^2 (1.5 mg maximum) when symptoms resolve.

5.2.1.2 Jaw Pain

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

5.2.1.3 Hepatotoxicity

If total bilirubin is greater than 1.9 mg/dL, hold vincristine dose. If total bilirubin is 1.5 - 1.9 mg/dL, administer vincristine at 1 mg/m^2 (1.5 mg maximum).

5.2.2 Cyclophosphamide

5.2.2.1 Hematological Toxicity

If chemotherapy is due and the absolute neutrophil count is below 750/µL or the platelet count is less than 75,000/µL, the next cycle of chemotherapy should be delayed. Repeat CBC and platelet count twice-weekly. The next cycle of therapy should be administered when the ANC >750 and the platelet count >75,000, but the dose of cyclophosphamide should be reduced by 25% to 750 mg/m^2/dose (i.e. each daily dose should be reduced by 25%).

If the ANC is above 750/µL but below 1,000/µL or the platelet count is > 75,000/µL but below 100,000/µL, the next cycle of therapy should be administered, but the dose of cyclophosphamide should be reduced by 25% to 750 mg/m^2/dose (i.e. each daily dose should be reduced by 25%).

Subsequent cycles should be given at full dose as long as counts recover on time.

5.2.2.2 Bladder Injury

If microscopic (> 10 RBC/hpf on at least 2 urine analyses) or gross hematuria occurs (hemorrhagic cystitis), give hydration to 3000 mL/m²/day (3500 to 4000 mL/m²/day for gross hematuria) using fluid containing at least 0.45% NaCl. Achieve urine specific gravity ≤1.010 prior to start of cyclophosphamide. May use diuretics (like furosemide) to increase urine output. For microscopic hematuria, give mesna 360 mg/m^2 with the cyclophosphamide and administer mesna for 24 hours after each cyclophosphamide dose at 120 mg/m^2/hr by continuous infusion. For gross hematuria give mesna at 100% of the cyclophosphamide dose by continuos infusion. If gross hematuria persists or recurs, delete subsequent cyclophosphamide doses.

5.2.2.3 Renal Dysfunction

If estimated creatinine clearance (by Schwartz formula for children or radioisotope GFR) is < 10 ml/min/1.73 m^2, reduce the dose of cyclophosphamide by 25% to 750 mg/m^2/dose (i.e. administer 75% of the full dose.)

5.2.3 Cisplatin

5.2.3.1 Nephrotoxicity

If the creatinine clearance or GFR is < 60 ml/min/1.73 m^2, then the cisplatin should not be given. If the creatinine clearance or GFR improves to >60 ml/min/1.73 m^2, cisplatin should be reinstituted at 50% (37.5mg/m^2/dose) dosage for the next two cycles of chemotherapy. After two cycles of therapy with stable creatinine clearance (>60 ml/min/1.73 m^2), cisplatin should be given at full doses.

5.2.4 Ototoxicity

PLEASE SEE TOXICITY SCALE BELOW. NOTE: THIS IS A DIFFERENT TOXICITY SCALE THAN USED IN PREVIOUS COG STUDIES

GRADE 1	**> 25 db loss at > 4 KHz, Asymptomatic**
GRADE 2	**> 25 db loss at 4 KHz, tinnitus**
GRADE 3	**≥ 25 db loss at ≥ 2 KHz**
GRADE 4	**≥ 40 db loss at ≥ 2 KHz**

If there is a disparity between ears, the grading should reflect the better ear. For Grade 0 ototoxicity, no dose modification should be made. For Grade 1 ototoxicity (defined as a > 25 db loss at > 4 KHz, asymptomatic) a 25% reduction to 56 mg/m^2/dose should be made in cisplatin dosage. For Grade 2 ototoxicity (defined as a > 25 db loss at 4 KHz, tinnitus) an additional 25% reduction (to 42 mg/m^2/dose) in cisplatin should be made if previously reduced or a 50% reduction (to 37.5 mg/m^2/dose) in cisplatin dose should be made. For Grade 3 and 4 ototoxicity (defined as a > 25 db loss at ≥2 KHz and ≥ 40 db loss at ≥ 2 KHz) cisplatin should be deleted and not restarted.

5.2.5 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 or seizures. If hypomagnesemia develops, 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 under **Standard Sections for Protocols**.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

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 Observations, Pre-Treatment and During Radiation Therapy for Regimen A

Evaluation	Pre-Study	Weeks 1-6	Weeks 10-12 (After XRT)
CBC with diff, platelets	X	Weekly	
Physical/Neuro exam, weight	X	Weekly	
Electrolytes, Ca, Creatinine, BUN, magnesium, phosphorus, SGOT (or SGPT), bilirubin	X		
Serum Creatinine, Creatinine Clearance or GFR	X		
Audiogram (See Section 5.2.4 for Grading Scale)	X		X
MRI of the Head (T2-weighted imaging and T1-weighted imaging pre- and post-contrast) and Spine with and without Contrast	X#		X+
Lumbar CSF cytology	X@		X+
Pregnancy Test (For Females who are Post-Menarchal)	X		
Central Pathology Review (Section 15.0)	X		
Optional Biology Studies (Section 16.0)	X		

\+ Spine MRI and cytology to be done only if initially positive

\# Post-op MRI should be done within 72 hours of surgery. For patients who undergo stereotactic biopsy only, post-op MRI is not required. For patients with M2 and M3 disease, a post-op MRIis encouraged, but not mandatory. Spinal MRI is required within 28 days of surgery if done post-operatively and within 10 days of surgery if done pre-op. (If MRI scan is performed within 10 days prior to surgery, then only a post-contrast examination is required). A pre-operative spinal MRI scan is preferable for patients with posterior fossa tumors because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. 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_3).

7.2 Required Observations, Pre-Treatment and During Radiation Therapy for Regimen B (With Carboplatin)

Evaluation	Pre-Study	Weeks 1-6	Weeks 7-9 (After XRT)	Weeks 10-12 (After XRT)
CBC with diff, platelets	X	3x/Week	Weekly[%]	Weekly
Physical/Neuro exam, weight	X	Weekly		
Electrolytes, Creatinine, BUN, Ca, magnesium, phosphorus	X	q o week	Week 7	
Serum Creatinine, Creatinine Clearance or GFR	X			
Audiogram (See Section 5.2.4 for Grading Scale)	X			X
MRI of the Head (T2-weighted imaging and T1-weighted imaging pre- and post-contrast) and Spine with and without Contrast	X[#]			X[+]
Lumbar CSF cytology	X[@]			X[+]
Pregnancy Test (For Females who are Post-Menarchal)	X			
Central Pathology Review (Section 15)	X			
Optional Biology Studies (Section 16)	X			

\+ Spine MRI and cytology to be done only if initially positive

\# Post-op MRI should be done within 72 hours of surgery. For patients who undergo stereotactic biopsy only, post-op MRI is not required. For patients with M2 and M3 disease, a post-op MRIis encouraged, but not mandatory. Spinal MRI is required within 28 days of surgery if done post-operatively and within 10 days of surgery if done pre-op. (If MRI scan is performed within 10 days prior to surgery, then only a post-contrast examination is required). A pre-operative spinal MRI scan is preferable for patients with posterior fossa tumors because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

% If counts are low, CBC should be performed twice weekly.

@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. 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_3).

7.3 Required Observations During Maintenance Chemotherapy for Regimens A and B

Evaluation	Prior to Each Cycle	During Each Cycle	Prior to Cycle 4	1 Month After Cycle 6	Relapse/Disease Progression
Physical (Ht, Wt, BSA)/Neurologic exam	X			X	X
CBC with Diff, Platelets,	X	Weekly+		X	X
Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus	X	Weekly		X	
SGOT, SGPT, Alkaline Phosphate, Bilirubin	X			X	
Creatinine Clearance or GFR	X##				
Urinalysis	X				
Audiogram (See Section 5.2.4 for Grading Scale)	X			X	
MRI of the head (T2-weighted imagining and TI-weighted imagining pre-and post- contrast) and spine with contrast			X*	X*	X
CSF cytology			X #	X #	X
Thyroid Function Evaluation (Free T_4 and TSH)				X	

* Spinal imaging is only necessary for patients with $M_1 – M_3$ disease.
\# Required only for patients who are positive at diagnosis.
\+ If counts are low and while on Filgrastim, it is recommended that CBCs be performed twice weekly.
Obtain if creatinine is > normal for age see Section 3.2.8.1.

7.4 Required Observations Following Therapy

Evaluation	3 mos	6 mos	9 mos	12 mos	15 mos	18 mos	21 mos	2.0 yrs	2.5 yrs	3.0 yrs	3.5 yrs	4.0 yrs	Annually	At Relapse Disease Progression
History, Physical with Neurologic Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Liver Function, BUN, Creatinine, Electrolytes (Ca, Mg), CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI of head (with contrast)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spinal MRI (with contrast)*	X$	X$	X$	X$	X$	X$	X$	X$	X$	X$	X$	X$	X$	X
Lumbar CSF Cytology#														X
Audiogram		X		X		X		X		X		X	X	
Thyroid Function Evaluation (Free T_4 and TSH)		X		X				X		X		X	X	
LH, FSH, estradiol or testosterone				X				X		X		X	X	
Serial Measurment of Height (Stature)%		X		X				X		X		X	X	

* Spinal MRI should include complete spine (cervical, thoracic, lumbar and sacral)
% Refer to endocrinologist if a growth below the 3rd percentile, drop in height percentile on growth grid, growth velocity <4-5cm/yr in childhood or lack of pubertal growth spurt
$ Obtain if initially positive. Patients with M1-M3 disease require the more frequent scans.
# Obtain per institutional standard of care.

7.5 Optional Studies

7.5.1 Neuropsychologic Evaluations

Patients who consent to participate on ALTE07C1 will be assessed at three times points: at 9 months (± 3 months) post cancer diagnosis; at 30 months (± 3 months) post diagnosis, and again at 60 months (± 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.

8.0 SUPPORTIVE CARE GUIDELINES

These are provided for institutional consideration. Investigator discretion should be used, and individual considerations made for specific patient situations and institutional practices. Patients may receive supportive care as clinically indicated. Supportive care for any reason, including care of complications arising from the cancer, adverse reactions, or other underlying diseases, must be recorded through resolution of the event. The Study Chair may be called with any questions or problems. Please also see the COG Supportive Care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp and the *Supportive Care of Children with Cancer, 2004 ed., Arthur R. Altman, M.D.*

8.1 Venous Access

Patients are required to have an indwelling central venous access catheter.

8.2 Antiemetics

Antiemetics and use of serotonin antagonists should be used according to institutional guidelines. **Corticosteroids should not be used during chemotherapy administration as an antiemetic because of their effect on the blood-brain barrier.**

Dexamethasone may be used for delayed nausea and vomiting.

8.3 Fever and Neutropenia

Patients who develop a fever greater than 38.5°C should be evaluated for neutropenia and infection. 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.

Significant myelosuppression is likely to occur, particularly during the last two-three weeks of radiation. **However, radiation should not be withheld for myelosuppression alone. Radiation should be continued even if the patient is hospitalized with fever and neutropenia as long as the patient is clinically stable. Administration of the boost should <u>not</u> be substituted for craniospinal radiation in the face of low counts.**

8.4 Prophylactic Antibiotics

Patients who receive chemotherapy should be started on trimethoprim/sulfamethoxazole (TMP/SMZ) at trimethoprim 2.5mg/kg/dose twice daily on 2 or 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 been discontinued. Patients with TMP/SMZ allergy should be treated with dapsone or pentamidine. Additional treatments and information can be found in the COG Supportive Care Guidelines (see above).

8.5 Azole Anti-fungal Agents

Avoid co-administration of vincristine and azole anti-fungal agrents such as fluconazole, itraconazole and voriconazole whenever possible. The risk of vinca alkaloid toxicity (eg constipation, myalgia, neutropenia) may be increased. If co-administration is necessary and vinca alkaloid toxicity increases, it may be necessary to alter vincristine dosing as described in sections 5.1.1 and 5.2.1.

8.6 Blood Products

8.6.1 Irradiation

Blood products should be irradiated following the current FDA guidelines found at: http://www.fda.gov/cber/gdlns/gamma.htm

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at http://www.shopcsa.ca.

8.6.2 Platelets

Patients will be transfused as necessary with platelets. It is suggested that the platelet count be maintained > 30,000/μL. 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.

8.6.3 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 megestrol (Megace) at 5 mg/kg/dose twice daily or nutritional support either enterally or via a central venous catheter with parenteral hyperalimentation. Patients should have their magnesium checked frequently and be supported with magnesium supplementation if necessary.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
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) Development of a second malignant neoplasm (SMN)
f) Repeated eligibility studies outlined in the protocol are outside the parameters required for eligibility.

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 was withdrawn.

9.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
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) The tenth anniversary of the date the patient was enrolled on this study.

10.0 STATISTICAL CONSIDERATIONS

This is a randomized, phase III, factorial-designed study comparing induction radiation therapy (XRT) alone to XRT + carboplatin (XRT+CBCDA) both followed with maintenance therapy ± Isotretinoin, for the treatment of supratentorial PNET or disseminated infratentorial PNET (medulloblastoma). The primary objective of the statistical analysis will be to test whether the addition of CBDCA to XRT or the addition of Isotretinoin to maintenance therapy results in an increase in the proportion of patients who are long-term event-free survivors.

Prior to Amendment 2, randomization to this study was stratified on dissemination and tumor location (supratentorial PNET vs. medulloblastoma). The study was initially powered to detect treatment effects among all patients (PNET and medulloblastoma) combined. However emergence of new data on biological differences between supratentorial PNET and medulloblastoma raised the concern that heterogeneity of treatment effect across tumor types may reduce power. Therefore, as of Amendment 2, the accrual goals of the study were adjusted to detect treatment effects among medulloblastoma patients alone. Accrual of supratentorial PNET patients was discontinued since power to detect treatment effects in this group, which accounts for less than 30% of enrolled patients, would not be attainable within a reasonable time-frame. At the conclusion of the study the analyses will be performed separately for medulloblastoma and PNET patients.
As of Amendment 3, the isotretinoin randomization was closed effective 1/27/15 following a futility analysis. As noted in the original study design, detailed below, since a factorial design approach was used to power the study, closure of one of the randomizations does not affect the power considerations for the remaining randomization, based on the original design assumptions.

10.1 **Design Considerations**

Since the administration of CBDCA as a radiation sensitizer and Isotretinoin as a pro-apoptotic agent occur at different times during therapy, it is considered extremely unlikely that the addition of CBDCA to XRT in induction will qualitatively change the effect on efficacy of Isotretinoin in maintenance, or similarly, that the addition of Isotretinoin in maintenance will qualitatively change the effect on efficacy of the addition of CBDCA during XRT. Hence, the study is not designed with, nor is it considered necessary to provide, high power to detect these unlikely qualitative interactions.

This trial consists of factorial randomization: one addressing a carboplatin question and the other addressing an Isotretinoin question. If one of the two randomizations is closed (whether due to efficacy, toxicity or other considerations), then the trial will continue accrual and randomization to the other randomization during the time that an amendment is being prepared and processed to modify the protocol. Continuing accrual until the amendment is prepared is appropriate because the two clinical questions being tested through these randomizations are independent of each other, and because the study design remains valid if one of the randomizations is stopped.

If this circumstance arises, the following procedure will be used for consenting patients until the new protocol and consent form is available. Patients will sign the exiting consent form, and may be enrolled provided that the enrolling physician documents in the medical record that: (1) the randomization to one of the randomization factors has been closed, but the other randomization remains open per the protocol; (2) since the randomizations and study questions are independent as stated in the protocol, the patient can be enrolled on the study as the official amendment to change the study is being processed; and (3) this has been explained to the patient and he/she understands the changes in the study and agrees to enter the study. When the amended consent form is approved, the patient will be re-consented to complete the record.

As of Amendment 3, the isotretinoin randomization was closed following a futility analysis. As noted in the original study design, detailed below, since a factorial design approach was used to power the study, closure of one of the randomizations does not affect the power considerations for the remaining randomization, based on the original design assumptions.

10.2 **Patient Accrual**

Accrual of eligible, supratentorial PNET or disseminated infratentorial PNET (medulloblastoma) patients to the pilot study CCG-99701 has averaged approximately 25 patients per year (after accounting for temporary suspensions). Given that this study targetted 75% of patients in former CCG institutions, and that during the COG A9961 study in medulloblastoma, former POG institutions enrolled approximately 77% of the total number of patients enrolled by CCG institutions, the projected COG accrual of these patients is expected to be 60 per year. A similar estimate results from the older CCG-9931 study, which enrolled supratentorial PNET and disseminated MBL patients at a rate of 39 per year. This is considered an underestimate, since CCG-9931 was open only to patients with measurable residual disease. Adjusting for groupwide participation, this results in an estimated accrual of 66 per year in COG. Hence, it is reasonable to expect that accrual rate of at least 60 per year will be observed, with higher rates possible.

As of Amendment #2, it is estimated that about 35 medulloblastoma patients could be enrolled every year according to the accrual history of the study.

10.3 **Study Duration**

The planned study duration will be 5 years of accrual and 1 year of follow-up. This study will accrue for 5 years provided that total number of eligible, correctly randomized and followed patients is projected to be at least 300. If annual accrual is slower than the required 60 patients per year, accrual will be extended until a minimum of 300 patients has been accrued, with final analysis one year after the end of accrual. If annual accrual is greater than 60 per year, the accrual can continue for the full 5 years of accrual, depending on the need for patients in successor studies at this time, and at the discretion of the disease committee, in order to increase precision and power. Much of the remaining discussion will refer the minimum nominal accrual goal of 300 patients accrued over 5 years and followed for 1 year.

The accrual rate of eligible, correctly randomized and followed patients will be evaluated at month 18 of the study using the average accrual rate achieved between months 7 and 18. Accrual rates of 50/year or less at this time will be of concern.

As of Amendment #2, 300 patients have been enrolled on the study. Four (4) of these patients were deemed to be ineligible for the protocol, leaving 296 eligible patients. 211 of the 296 patients had medulloblastoma and the other 85 were diagnosed with SPNET. The SPENT patients enrolled on the trial will be replaced. Patients who do not have metastatic disease or residual disease >1.5 cm^2 by central neuroradioloty review, patients with localized medulloblastoma and < 1.5 cm^2 residual disease who were enrolled because of diffuse large cell anaplasia, but were found not to have this diagnosis, and patients who are found to have a histologic diagnosis other than medulloblastoma (e.g., ATRT) by central pathology review will be excluded from the final data set used to address the primary objectives. We expect approximately 10% of the patients falling in this category. Therefore, the study will accrue additional 100 medulloblastoma patients to ensure about 280 ((211+100)*0.9) eligible and evaluable patients for the analysis of primary objectives. Due to the extended accrual time and longer follow-up for the patients who have been enrolled, similar power can be obtained with this target number of eligible and evaluable patients.

With these changes the maximum accrual becomes 400 (300+100) targeting 280 eligible and evaluable medulloblastoma patients for the primary objectives of the study. The study duration is expected to be about 11 years, including the suspension for the amendment, additional 3 years of accrual, and 1 year of follow-up at the end.

10.4 **Study Endpoints for Analysis of Treatment Efficacy**

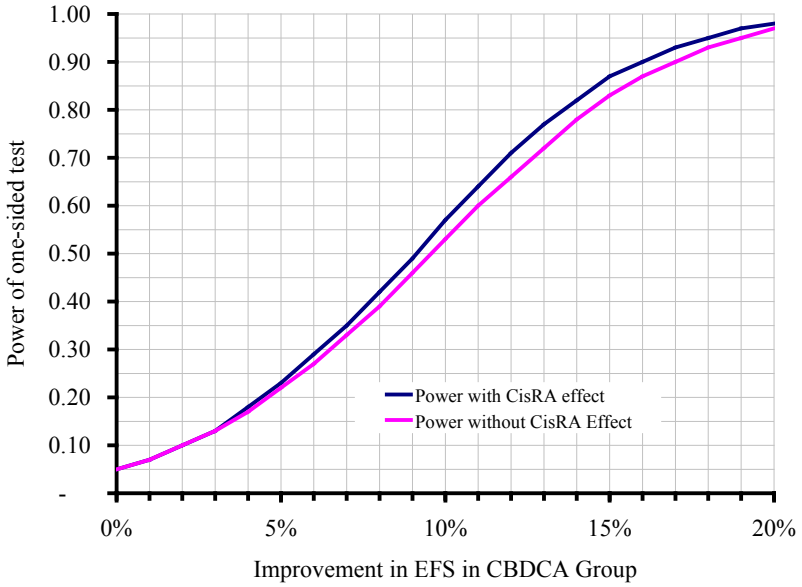
The primary endpoint for the evaluation of treatment efficacy will be time to an event, which will be used to compute the event-free survival (EFS) percentage. An event comprises disease progression or recurrence, occurrence of a second malignant neoplasm, or death from any cause. Secondary endpoints in this analysis will be tumor response to radiation therapy ± carboplatin, and time to death, from which the survival (S) percentage will be computed.

10.5 **Statistical Analysis of Difference in Long-Term EFS Rate**

The main study analysis will be based a stratified logrank test, [40] with stratification on all randomization stratifiers (below) as well as on the factorial treatment group not the subject

of the analysis. Good approximation to the power of these test are obtained using the methods of Sposto and Sather. [41]

It is expected that 300 eligible medulloblatoma patients are accrued over eight years with one year additional follow-up, with an annual 1% censoring rate. The reference group (XRT alone, no Isotretinoin) is best represented by a PCM with long-term EFS (cure) rate of 56%, and two-year EFS of 61%, based on the most recently available COG data in a similar cohort of patients (R Sposto, personal communication). Based on a one-sided test with 5% Type I error, the test of the CBDCA effect, under the assumption that Isotretinoin has no effect, will have at least 80% power to detect a 15% increase in long-term EFS (56% to 71%, RFR=0.591), and at least 90% power to detect a 17% increase (56% to 73%, RFR=0.543). Under the assumption that Isotretinoin results in a halving of the failure rate, the test of the CBDCA effect will have at least 80% power to detect a 14% increase in long-term EFS (65% to 79%, RFR=0.547), and at least 90% power to detect a 16% increase (65% to 81%, RFR=0.489). The problem is symmetrical, so that these figures apply to the test of the Isotretinoin effect. No adjustment for multiple comparison will be made in this comparison. The figure below illustrates the power under these two scenarios.



10.6 Interim Monitoring

Monitoring for differences in long-term EFS will be based on the same one-sided likelihood ratio test as described above. Interim monitoring rules will be devised according to the methods of Lan-Demets. [42] To detect substantial *increases* in efficacy due to the addition of either CBDCA or Isotretinoin, the 5% Type I error will be spent at a rate of αt^2, where t is the appropriate information-time scale. To detect substantial *decreases* in efficacy due to either of these additions, a 20% Type I error rate will be used, with error spent at a rate of αt.

Initially interim monitoring analyses were planned at least after 2, 3, 4, and 5 years of the study. Monitoring after 5 years was not planned, because all patients on the trial were expected to have completed treatment. As of Amendment #2, interim monitoring analyses were to be conducted yearly until the accrual of the study is completed.

Amendment #3 is in response to the DSMC comments following the Fall 2014 COG Meeting. In their comments the DSMC requested that the protocol be amended to reflect interim monitoring of the results for medulloblastoma patients only, as a result of the fact that the primary cohort of the study was limited to medulloblastoma patients as of the last amendment of the study. The DSMC also requested that futility monitoring is added for the two randomizations.

Revised monitoring rule for efficacy for medullablastoma patients only (inactive as of Amendment #4):

The number of events observed to date in medulloblastoma cohort is different from the combined Medulloblastoma+PNET cohort and it is clear that the interim monitoring rule for the medulloblastoma cohort needs to take this difference in the number of events into account. We propose to do this by following the second approach in Anderson (2014, unpublished manuscript) which accounts for the alpha-spending that has already occurred in planning future interim analyses. Not surprisingly the number of events in the combined Medulloblastoma/PNET cohort is larger than the number of events in the Medulloblastoma only cohort hence the alpha already spent in the previous analyses is larger than what would be suggested by the information present in the Medulloblastoma cohort. Anderson (2014, unpublished manuscript) suggests accounting for this by skipping one or more of the planned interim analyses until the accumulated information can catch up to the alpha already spent based on the previous design parameters. Based on the data available as of Amendment 3, this approach suggests that the first interim analysis we can perform for the medulloblastoma cohort will be in Fall 2017, which is expected to be very close to the end of accrual. We will then perform what will likely be the final analysis in Fall 2018.

Updated monitoring rule for efficacy for medullablastoma patients only (Amendment #4)):

In response to DSMC comments following Fall 2015 COG meeting, the monitoring rule for efficacy for medulloblastoma patients only was further updated. Consistent with the discussions and the consensus that followed between the DSMC and CTEP statisticians, we propose to use the number of events, which was calculated based on the original study design for the combined medulloblastoma/sPNET cohort, as the full information for the medulloblastoma cohort as well since the assumptions in the original design are reasonable and valid for medulloblastoma cohort as well. The following points were agreed upon and will be used in all future analyses of the data from the medulloblastoma cohort:

- The full information will be defined as 110 events, which was calculated based on the original design parameters in the protocol.
- The alpha already spent in the previous interim analyses of the trial will be calculated based on the data from medullablastoma cohort alone. Furture interim analyses will be conducted based on the leftover alpha following this approach.
- The final analysis for the trial will be conducted once 280 eligible and evaluable medulloblastoma patients have been enrolled and all have been followed for at least 1 year as specified in Amendment #2, regardless of the number of events observed at that time.

The last interim analysis was conducted in Fall 2014. No interim analysis was conducted in Fall 2015 per the analysis plan specified in Amendment #3A. Following the above described approach, we will implement interim analyses to correspond with the Fall 2016 and Fall 2017 DSMC reports. Based on the observed number of events at these scheduled interim analyses, we will calculate the % of information, interim monitoring boundary for

efficacy and overall alpha expended according to the methods of Lan and Demets. The 5% type I error will be spent at a rate of αt^2, where t is the % of information. The 100% information is defined as the 110 events. The same approach will be implemented to find the boundary for efficacy for the final analysis which is expected to be conducted in Fall 2018.

Updated monitoring rule for efficacy for medullablastoma patients only (Amendment #5):

- The final analysis for the trial will be conducted once 280 eligible and evaluable medulloblastoma patients have been enrolled and all have been followed for at least 1 year as specified in Amendment #2. The interim analysis as described as in Amendment #4 will be implemented annually until the final analysis point is reached as described above.

Interim futility monitoring for Carboplatin randomization
We will use conditional power as a guide for futility monitoring at interim monitoring time points. The following outlines the steps we will follow to conduct the interim futility monitoring: First, the design is mimicked in East 6.4. Consistent with the original design this design assumes that the 2-year EFS rate is 61% and long-term EFS rate is 56% in the control group. Based on a sample size of 300 patients and a one sided log-rank test with 5% type I error, the test of the Carboplatin effect was estimated to have at least 80% power to detect a 15% increase in long-term EFS (56% for control vs. 71% for carboplatin). Second, the test-statistic for one-sided stratified log rank test is calculated to compare the two treatment groups based on most recently frozen data. Thrid, this test statistic is used as the basis for calculating conditional power for interim monitoring via East 6.4. Fourth, the conditional power estimate would then be communicated to the DSMC at each interim analysis point with our recommendations on the futility of continuing this randomization. Though it is difficult to come up with a strict cut-off, we will consider recommending stopping the carboplatin randomization if the conditional power estimate falls below 10%.

Interim futility monitoring for Isotretinoin randomization
A similar approach to the one described above was used to assess futility based on data frozen on June 30, 2014 which led to the conclusion that the likelihood of reaching a statistically significant result at the end of the study for the Isotretinoin randomization was very small. Thus this randomization was suspended as of Amendment 3.

Interim Monitoring for Ototoxicity:
Previous studies that utilized full dose craniospinal irradiation followed by cisplatin-based maintenance therapy showed approximately 25% to 30% grade 3 and 10% grade 4 ototoxicity (personal communication with Dr. Roger Packer). The occurrence of excessive grade 4 ototoxicity rates at any time during therapy will constitute a primary endpoint for safety monitoring. A grade 4 ototoxicity rate that exceeds p0=15% will be considered unacceptable. A Bayesian monitoring rule with prior density Beta (2,12) on the probability p of ototoxicity rate will be used as a trigger for careful assessment of excess hearing loss. The prior has median p=0.125 and mean p=0.14, with approximately 95% of support less than p=0.32. A posterior probability P (p> p0|data)>85% will satisfy the monitoring criterion. This represents 85% certainty that the ototoxicity rate exceeds p0 given the data and the assumed prior density. Ototoxicity rates will be monitored separately in each of the two chemotherapy induction groups. Operationally, the monitoring criterion will be

satisfied if 4 patients develop Grade 4 ototoxicity in the first 10 patients, or ≥6/20, ≥8/30, etc. If the monitoring criterion is satisfied, an immediate clinical review of the cause and timing of the hearing loss will be undertaken. In frequentist viewpoint, this criterion will be satisfied 9% of time if p=11% and 94% of time if p=20% assuming we have n=150 patients.

10.7 Statistical Analysis of the Post-RT Response

In CCG-99701, 50/146 patients (34%) had residual tumor measuring at least 1.5 cm^2. These are the patients who will be evaluable for post-RT response assessment. Hence, approximately 100 patients in the current study, 50 each receiving XRT alone or XRT+CBDCA, will be evaluable for this endpoint. Using a two-sided test of proportions with Type I error 5%, this sample size will provide at least 80% power to detect a 30% difference in post-RT response rate between the two treatment groups. There will be no interim monitoring based on this endpoint.

10.8 Stratification

Randomization will be stratified on the basis of location and dissemination. Six strata will be defined: (1) M0 Medulloblastoma with >1.5 cm^2 residual; (2) M+ Medulloblastoma; (3) M0 Supratentorial PNET with <1.5 cm^2 residual; (4) M0 SPNET with >1.5 cm^2 residual; (5) M+ SPNET, (6) M0 Diffusely Anaplastic Medulloblastoma.

As of Amendment #2, because the accrual of sPNET will be discontinued, only the three strata of medulloblatoma will be defined: (1) M0 Medulloblastoma with >1.5 cm^2 residual; (2) M+ Medulloblastoma; (3) M0 Diffusely Anaplastic Medulloblastoma.

10.9 Neuropsychological and Quality of Life

The primary objective of this part of the study is to assess the quality of life (QOL) and neuropsychological (NP) outcome of the study population.

Descriptive statistics, including means, standard errors, medians, inter-quartile ranges, proportions, will be used to characterize the overall QOL and NP outcome for patients. Descriptions at baseline will estimate the acute effects of the tumor before the onset of treatment effects, and descriptions at follow up periods will estimate the long-term effects of the tumor and its treatment. The raw scores obtained in this study population, for example, the Processing Speed Indices from the WISC-IV or WAIS-III, will be compared with established population test norms provided in the scoring tables of the manuals. Test variables of the instruments, for example, nonverbal skills and processing speed, will be compared on the basis of intercorrelations. Using two-sample t tests for continuous variables and Pearson's χ test for categorical variables, the intervention and the control arms will be compared in terms of clinical characteristics at the time of randomization, and in terms of baseline QOL and NP scores. Data-reduction strategy, such as factor analysis can be used to reduce the overall number of statistical comparisons and thus minimize inferential errors associated with multiple univariate tests of dependent variables.

For patients who have baseline and at least two follow up evaluations, a growth curve model, which is a particular variant of random-effects models, will be utilized. This approach treats data from different patients as statistically independent and data from the same patient as correlated. Growth curve models emphasize the explanation of within-person variation over time by a natural developmental process. The growth curve model allows an estimation of the average rate of change (or slope) over time for patients within

the total group, as well as an estimation of the differences in the slopes between subgroups. Growth curves for patients will be averaged, and comparisons will be made between those who receive intervention and those who do not, controlling for variables such as age at diagnosis, sex, race/ethnicity and treatment related factors.

10.9.1 Sample Size Calculation

The primary interest of this study is on long-term effects of treatment on QOL and NP outcomes, so that the sample size calculation will be based on a comparison of the two-year QOL and NP assessment between the treatment groups, the Isotretinoin vs. the standard chemotherapy arms. The calculation also applies to detecting significant CBDCA effect. It is assumed that 300 patients will be accrued over five years with two-additional follow-up. Of the approximately 61% of patients who are alive and free from progression at three years, we will assume that at minimum 80% (73 patients per treatment arm) will have QOL and NP assessments at three years. Using a two-sided two-sample t-test with Type I error 0.05, we have 80% power to detect a 0.46 standard deviation (SD) difference in the mean change between the two treatment groups. We assume that a difference in mean QOL and NP scores between different treatment groups as small as one-half of one standard deviation will be considered to be clinically significant.

10.9.2 Subject Attrition and Missing Data

We want to plan the study in a manner that avoids missing data. It is proposed that each participating institution will be asked to identify one person (i.e. nurse, CRA, psychologist) who will be responsible for monitoring the data collection/submission. This individual will serve as the institution's "contact person" regarding this portion of the protocol. If the above procedure is carried out, we can anticipate that the loss to follow-up in this study will be minimal. We will collect covariates that explain variability in the outcome and missing data patterns. We will document the reasons for missing data. These missing values are expected to be missing at random and not associated with any outcome of the study. When there is any suspicion that the missing data will be related to events or outcomes that will affect QOL, appropriate models such as selection models, and mixture models will be utilized in longitudinal data analyses to deal with such issues.

10.10 **Gender and Ethnicity Considerations**

Review of outcome data from previous CCG medulloblastoma studies indicates that treatment effects are consistent within gender and ethnicity. That is, no one treatment examined has proven superior for one gender or ethnic group. Because of this, the study size will not be adjusted to ensure high power to detect differences in outcome in groups defined by ethnicity or gender.

Expected Accrual by Sex and Race/Ethnicity for the Additional 100 Medulloblastoma Patients

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	18	25	43
Not Hispanic or Latino	138	217	355
Unknown	1	1	2
Ethnic Category: Total of all subjects	157	243	400
Racial Category			
American Indian or Alaskan Native	2	2	4
Asian	5	7	12
Black or African American	9	17	26
Native Hawaiian or other Pacific Islander	1	2	3
White	137	209	346
Other	2	4	6
Not Reported	1	2	3
Racial Category: Total of all subjects	157	243	400

11.0 EVALUATION CRITERIA

11.1 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

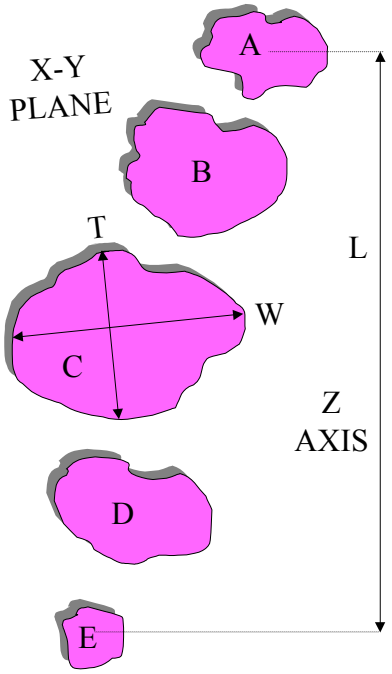
In order to completely document the assessment of response, the three-dimensional tumor measurements for all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up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

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)

Figure 11.1: COG Guidelines for Measurement of Tumor Size



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

Table 11.1: RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")
(Modified from Appendix II, Table 2, JNCI 92:213, 2000)

Response	Diameter, 2R Decrease	Product, $(2R)^2$ Decrease	Volume, $4/3\pi R^3$ Decrease
	30%	50%	65%
	50%	75%	87%
Disease Progression	**Increase**	**Increase**	**Increase**
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

4. 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.

Table 11.2 Overall Response Assessment

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

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:

$$\frac{\text{LxWxT (current scan)}}{\text{LxWxT (reference scan)}}$$

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): ≥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): ≥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***

Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome

- Treatment related secondary malignancy

12.3 **Reporting of Adverse Events for Commercial Agents – via CTEP-AERS**

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

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

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- COG requires the CTEP-AERS report to be submitted **within 7 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 revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]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 not due to cancer recurrence must be reported via CTEP-AERS.

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 CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all Grade 3 and higher Adverse Events.

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 and Surgical Reports. These forms are submitted through the Imaging Document System in the eRDES.

2. Reference Labs' required reports, and IROC RI (QARC) data: These data accompany submissions to these centers, which forward their review 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 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.

14.1.1 Types of Surgery

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

14.1.2 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.

14.1.3 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.

14.1.4 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.

14.1.5 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 for histologic diagnosis (see Neuropathology Guidelines, Section 15.0).

14.1.6 Biology Studies

Please note that the biology studies in this protocol request approximately 2 grams (2 cc) of tissue, divided into fixed, snap frozen, and fresh tissue shipped in tissue culture media. Because the fresh tissue must remain sterile, please coordinate tissue handling with the pathology service and refer to tissue submission guidelines in Section 16.1. In many institutions, the responsibility for obtaining consent for biology studies will be the responsibility of the surgeons because it is necessary to obtain consent prior to surgery.

14.1.7 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.

14.2 **Shunts**

Children whose preoperative MRI scans indicate the possibility of a medullo-blastoma/PNET may need precraniotomy external CSF shunts (external ventricular drain (EVDs)), if they are primarily symptomatic because of tumor induced hydrocephalus. A third ventriculostomy can be used as an alternative to a shunt.

14.3 **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.

14.3.1 Size of Post-Surgical Residual Tumor

The size of residual tumor present after surgery will be based on post-surgical MRI as dileneated 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 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 after surgery, preferably within 72 hours post surgery.

14.6 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.

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

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.

15.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

15.1 Neuropathology Goals

Precise histopathological diagnosis of tumors of primitive neuroepithelium.

15.2 Requirements for Handling Biopsy or Surgical Resection Tissue

15.2.1 Light Microscopy

A portion of tumor tissue should be fixed and processed in the usual manner.

15.2.2 Biology Studies

Two grams (2 cc) of tissue should be requested from the operating room for biology studied in addition to the tissue needed for pathologic diagnosis. Instructions for sending fixed and frozen tissue to the Biopathology Center and fresh tissue to Dr. Martine Roussel's laboratory are provided in Section 16.0.

15.2.3 Autopsy Tissue

If necropsy tissue becomes available it should be submitted on APEC14B1.

A complete autopsy report along with representative sections of residual tumor and/or metastases should be sent to the primary review pathologist. If available, snap frozen and fixed specimens of non-neoplastic cerebellum, cerebral cortex (frontal, parietal, occipital), basal ganglia, and pons should be sent to the Biopathology Center using guidelines in APEC14B1. These tissues are valuable controls for biology studies

15.3 Pathology Review Materials

All patients must be centrally reviewed and the diagnosis consistent with Medulloblastoma or CNS PNET. Slides and pathology reports must be sent to the Biopathology Center for Pathology Review within 10 days of study enrollment.

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 Patient ID Number. If blocks are unavailable, send all of the following slides of tumor:

- Two (2) H&E stained slide of each representative lesion
- Four (4) unstained slides from one representative tumor block

Pathology Reports or Forms: Write the patient's COG patient identification number on all reports submitted to the BPC.

- Institutional pathology report
- Operative report
- 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 unless the institution requests their return. 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.

15.4 **Central Review Process**

The primary review pathologist, will be the reviewer of record. For any questions regarding review submission, contact the Biopathology Center at 614-722-2894.

Shipping

Send all materials for pathology review by regular mail or using the institution's courier account to:

COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, Ohio 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
Email:BPCParaffinTeam@nationwidechildrens.org

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

16.0 SPECIMEN REQUIREMENTS FOR BIOLOGY STUDIES

16.1 **Optional Biology Studies**

Institutions are encouraged to enroll and submit specimens for APEC14B1.

Fixed and snap **frozen** tissue is to be sent to the Biopathology Center and **fresh** tissue is to be sent directly to Dr.Roussel's laboratory.

16.1.1 Materials for Submission:

The following materials must be sent to the Biopathology Center at the time of **diagnosis for consenting patients**:

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 cm^2 is preferred. Label with the COG Patient ID Number, collection date and specimen type.

Peripheral Blood: 5 cc of peripheral blood in a green top tube (sodium heparin) and 5 cc of blood in a purple top tube (EDTA) should be sent at room temperature any time before the initiation of therapy. Do not send if the patient has had a whole blood transfusion. Label blood with COG Patient number, collection date and specimen type.

Formalin Fixed Tissue: Submit 10 tissue sections fixed in 10% buffered formalin; two of which should be on positively charged slides for possible immunohistochemistry. Label with the Patient ID Number, surgical pathology ID number, block number, collection date and specimen type.

Pathology Reports and Transmittal Forms. Send the institutional pathology report and include a specimen transmittal form with each shipment. Write the patient's COG Patient ID Number on all reports submitted

The following materials must be sent to Dr. Roussel's laboratory at the time of **diagnosis**:

Fresh surgical tissue: Submit at least 0.5 grams (0.5 cc) **sterile fresh** tissue in tissue transport media packed on ice packs by overnight "First a.m." delivery as described in 16.1.3.

16.1.2 Shipment Of Fixed and Frozen Specimens

Biological specimens (other than fresh tissue which is sent to Dr. Roussel) can be shipped to the BPC in a Specimen Procurement Kit. Specimen Procurement Kits must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday since Saturday delivery is only available for fresh blood or bone marrow. The specimen procurement kit is constructed to allow shipment of frozen (**on dry ice**) and ambient temperature tissues in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both.** This kit contains most of the supplies necessary for shipping specimens to the BPC. To request a specimen procurement kit, go to the BPC Kit Management link (https://ricapps.nationwidechildrens.org/KitManagement).

Before specimens are placed into the Specimen Procurement Kit, they need to be placed in several layers of packaging. Package the frozen and room temperature specimens separately so that they can be placed into separate compartments of the kit for shipping. First place specimens into a biohazard envelope with absorbent material. Next, place the secondary biohazard envelope into the white Tyvek envelope. Expel as much air as possible before sealing each envelope

Snap frozen tissue is shipped in one of the kit compartments filled with approximately 4 lbs. of dry ice. Layer dry ice on the bottom of the compartment until the compartment is about half full. Place the frozen tissue on top of the dry ice. Cover the tissue with more dry ice until the compartment is almost completely full. Set the foam lid on top of the kit compartment to secure specimens during shipment.

Formalin fixed tissue and blood are shipped at room temperature in the second compartment of the kit. Place the specimens (already packaged in the biohazard and Tyvek envelopes) into the kit compartment. Insert the transmittal form, pathology report and any other required documents. Place the foam insert on top to secure specimens during shipment.

Close the outer lid of the Specimen Procurement Kit and secure it with filament or other durable sealing tape. Print shipping label via the BPC Kit Management system

and attach to the top of the kit. Complete the dry ice label (UN 1845). Place the dry ice and Exempt Human Specimen labels to the side of the kit.

Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355.

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
Email: BPCBank@nationwidechildrens.org

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

16.1.3 Shipment Of Fresh Specimens

Complete the Specimen Transmittal Form on the RDE and print a copy to send with the specimen. Label specimens with COG patient identification and the BPC Number (if available). Fax a copy of the transmittal form to Dr. Marine Roussel at (901) 595-2381. Transport of fresh primary brain tumors should abide by the following guidelines to maximize the viability after transport. First, all fresh tumors should be sent *ON ICE OR ICE PACKS*. Also, while RPMI media is acceptable, DMEM-F12 with 10% FBS and Antibiotics and Antimycotics is far preferable. Please contact the Roussel Lab at martine.roussel@stjude.org to obtain frozen aliquots of this media. **Also, please notify the lab (martine.roussel@stjude.org, li.lu@stjude.org, barbara.rhodes@stjude.org) as soon as possible that a tumor is resected or ready for shipment; this allows time to make the necessary preparations for specimen processing.** Any further questions should be addressed to martine.roussel@stjude.org .

Ship specimens ON ICE PACKS, PRIORITY OVERNIGHT for first a.m. delivery. Specimens may be sent 7 days a week to the address below:

Martine F Roussel, PhD
Member
Endowed Chair in Molecular Oncogenesis
Co-Leader of the Cancer Genetics, Biochemistry and Cell Biology Cancer Center Program
Department of Tumor Cell Biology, MS# 350
Danny Thomas Research Center, D-5006C St Jude Children's Research Hospital
262, Danny Thomas Place Memphis, TN, 38105
Phone: (901) 595-3481
Fax: (901) 595-2381
E-mail: martine.roussel@stjude.org

Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355.

16.2 **Specific Aims**

Biology studies are critical to the development of more effective and less toxic therapies and for the purpose of stratifying patients to the most appropriate treatment regimens. In the period since this clinical trial was first proposed, extensive collaboration between members of the ACNS0332 biology group and colleagues has clearly defined four consensus molecular subtypes of medulloblastoma, namely Wnt-driven, Sonic Hedgehog (Shh)-driven, Group 3 and Group 4. Within these molecular subtypes, additional candidate prognostic indicators are emerging and some previous candidates have been disproven as reliable biomarkers of outcome.

Genomic analyses have also shown that sPNETs are clearly different than medulloblastomas. Approximately 1/3 of sPNETs are genomically aligned with high grade gliomas raising the possibility that in the future, some sPNET patients should perhaps no longer be treated per protocols that have been optimized for medulloblastoma patients. In other instances, sPNET patients were shown to have genomic profiles consistent with various medulloblastoma molecular subclasses, atypical teratoid rhabdoid tumors (ATRTs), or low grade astrocytomas. In several of these instances, re-analysis of tissue from the patient in question revealed pathognomonic mutations (e.g, INI1/hSNF5 gene in ATRT).

The specific aims of the biology studies are:

1. To determine the molecular subtype of each medulloblastoma patient.
2. To describe the genomic profiles of sPNET patients in the context of >800 reference samples from pediatric brain tumor patients
3. To *confirm* prognostic indicators of therapy failure in high-risk medulloblastomas
4. To *identify* prognostic indicators of therapy failure in high-risk medulloblastomas
5. To generate patient-derived resources that help prioritize targeted therapies for future clinical trials
6. Tissue banking

Tissue utilization will be prioritized in order of the Specific Aims.

16.3 **Aim 1. To determine the molecular subtype of each medulloblastoma patient.**

At the 2013 Global Summit on Pediatric Brain Tumors, an interdisciplinary internationally renowned group of experts reached consensus that 1) the next WHO guidelines should reflect the four established molecular subclasses of medulloblastoma as primary criteria for diagnosis, 2) that the concordance between subgroup classification by 850K Illumina analyses or Nanostring platform was superior to immunohistochemistry and on par with or superior to gene expression profiling, 3) that 850K Illumina analyses were least susceptible to batch effects and were more robust than competing platforms when performed on formalin fixed paraffin-embedded (PPFE) tissue. Since snap frozen tissue has been submitted on about 1/3 of patients enrolled in ACNS0332 and PPFE tissue was submitted on nearly 100%, the ACNS0332 biology group recommended using PPFE unstained slides as the source of DNA for evaluation on the 850K Illumina platform as the primary means for molecular subclassification. This will be performed first on a test batch, then on tissue from 3-4 unstained slides for all ACNS0332 patients. In rare instances, where tissue was not submitted in any form, attempts will be made to retrieve tissue from the institutions involved in patient enrollment.

For this aim, the 850K data set from each patient will be compared to a reference set of hundreds of pediatric brain tumor specimens. Those cases that clearly fall within one of the four established medulloblastoma subclasses will be designated as such. Outliers will be identified and best efforts will be made using remaining tissue samples to clearly define the correct molecular subclass of medulloblastoma, or if indicated, an alternative diagnosis. In such cases, the final determination will be made by the biology group in consultation with study neuropathologists. The final designations will be the basis for reporting molecular subclass results. In the event that the neuropathologists and biologists conclude that a patient has a disease that is not eligible for ACNS0332, appropriate eligibility actions will be taken by the study chair.

The biology committee will meet and review all cases in the context of molecular subclass, age, 850K data and other available information to determine whether additional molecular studies are required for proper molecular diagnoses prior to tissue being released for other biology studies described below.

16.4 **Aim 2. To describe the genomic profiles of sPNET patients in the context of >800 reference samples from pediatric brain tumor patients**

In the 1980s, the World Health Organization adopted a diagnostic classification system that “lumped” all primitive neuroectodermal tumors of the central nervous system. Using genome wide analyses, two competing hypotheses have recently emerged. The first, advanced by Dr. Annie Huang, suggests that about 1/3 of sPNETs are molecularly similar to high grade gliomas and very distinct from medulloblastomas. The remaining 2/3 of patients classify into 4 molecular subtypes by cluster analyses. In unpublished data, Stefan Pfister analyzed over 50 cases diagnosed as sPNETs in the context of approximately 800 pediatric brain tumor specimens. Like Dr. Huang, Dr. Pfister’s group observed that about 1/3 of these cases cluster with high grade gliomas. The remaining cases, however, do not cluster together but rather cluster individually or in small groups with various molecular subclasses of medulloblastoma, ATRTs, low grade gliomas, or other central nervous system malignancies. Dr. Pfister has raised the question of whether an entity of sPNET exists.

Neuropathologists frequently experience difficulty in distinguishing sPNET from high grade glioma at the time of diagnosis – and often tumors diagnosed as one of these recur with predominant features of the other. We hypothesize that a subclass of tumors exist that have both glioma and PNET features, that respond poorly to either glioma- or sPNET-therapy, and may represent a biphenotypic or stem-cell origin. We further wish to distinguish between the two hypotheses stated above for the remaining cases – and entertain a third possibility in which some of the sPNET cases share genomic signatures with medulloblastoma or other pediatric brain tumors and there are also distinct subset(s) of sPNET tumors. To accomplish this, we will generate a reference data set from approximately 100 sPNET cases submitted to ACNS0332 using the 850K Illumuna platform as described in Aim 1. These data, data from approcximately 200 medulloblastoma cases from ACNS0332 and approximately 800 reference pediatric brain tumor cases analyzed by Dr. Pfister's group will be made available to 3 groups of scientists skilled in genomic analyses of pediatric brain tumors (Pomeroy/Cho; Taylor/Huang; and Pfister). The ACNS0332 biology committee will meet with these investigators to review analysis methods, findings, similarities, and discrepancies. The consensus will be the basis for subgroup analyses of patient outcomes for those patients enrolled as sPNET patients in ACNS0332.

16.5 **Aim 3. To confirm prognostic indicators of therapy failure in high-risk medulloblastomas**

We hypothesize that certain children can be prospectively identified as patients who will likely fail therapy even with 36 Gy craniospinal irradiation, combination chemotherapy, and augmentations such as carboplatin radiosensitization or isotretinoin. If this hypothesis is correct, children with a very high risk of death due to medulloblastoma may be considered for therapeutic options other than typical high risk therapeutic protocols in the future.

Certain gene amplifications or deletions, particularly in the context of molecular subclass designation, are evolving as candidate prognostic indicators based on very large genomic studies of previously treated patients. Likewise, mutations in certain genes may confer prognostic information. Amplifications, deletions and sequence mutations can all be determined by multiple different methods, can be determined on FFPE tissue, and are not subject to "batch effect" variation.

In some cases, prognostic indicators have been validated in large "test sets" after being identified in large "training sets". Unfortunately, none of these studies were prospective and most involved "community" patient populations, meaning that treatment and data collection were not standardized. Even so, it is difficult to find survivors with some of these mutations across multiple data sets and raises the possibility that we will be able to identify children who are at high risk of failing therapeutic regimens such as those used in ANCS0332. We will use a combination of gene expression analyses, exome sequencing, targeted candidate sequencing, 850K methylation analyses, immunohistochemistry, and other methods to screen for and validate potential prognostic indicators and potential variants from existing medulloblastoma molecular classifiers.

16.6 **Aim 4: To *identify* candidate prognostic indicators of therapy failure in high-risk medulloblastomas**

It is possible that additional important DNA- or RNA-based prognostic markers will be identified in this study. Because of statistical considerations of multiple comparisons and

small genetically defined prognostic subgroups, the only candidate prognostic indicators that will be tested prospectively are those listed in section 16.5. Once Aims 1-3 are completed to the ANCS0332 biology group's satisfaction, then data sets and remaining unstudied tissue will be provided to researchers for the purpose of identifying additional candidate prognostic indicators or other biologic features that provide insight into medulloblastoma genesis or behavior.

16.7 **Aim 5: To generate patient-derived resources that help prioritize targeted therapies for future clinical trials**

Approximately 20 genetically engineered mouse models of medulloblastoma have been generated worldwide to date. Unfortunately, nearly all of these represent Shh-driven medulloblastomas and there are few models that represent other types of medulloblastoma and none that represent sPNET. Due to medulloblastoma incidence rates, it is possible for COG to run a major Phase III study about once every 6-9 years. For this reason, it is critical to prioritize candidate therapeutics in the best available mouse models before initiating human clinical trials. Through ACNS0332, ACNS02B1 and related studies, over 50 malignant pediatric brain tumors have been orthotopically transplanted into the brains of immunocompromised mice. Approximately half of these have generated tumors in mice that survive serial transplantation and are suitable for non-clinical in vivo pharmacology studies. Though far less successful, attempts to generate stable cultures of these cells under serum free conditions has yielded a small number of cell lines that are suitable for in vitro studies. All of these patient derived resources are currently being genomically analyzed and compared to the initial specimen from the patient of origin.

Generation of these resources will continue under ACNS0332 with the ultimate goal of generating multiple mouse models that represent each of the major medulloblastoma molecular subtypes to the extent that each grows under these conditions. All patient-derived resources are made available to researchers world-wide in a manner consistent with informed consent. Investigators using the models or cell lines are encouraged to share data with the COG Central Nervous System and New Agents committees as early as reasonable to enable the data to be considered in clinical trial strategy.

16.8 **Aim 6. Tissue Banking**

Snap frozen and fixed tissue specimens that are not used for the experiments described above will be banked through the COG Biopathology Center as described in protocol ACNS02B3. In addition, primary cultures of enriched medulloblastoma cells derived from patients in this study will be cryopreserved and stored for future use.

17.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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**

A pre-operative MRI scan of the brain with and without contrast is required. **NOTE: CT scans are NOT sufficient for study eligibility since radiation therapy planning and response will be based on MRI scans only.**

To document the degree of residual tumor postoperative cranial MRI with and without contrast must be done. Post-operative head MRI scan with and without contrast (should be done within 72 hours post-surgery). For patients who undergo stereotactic biopsy only, a post-operative MRI is not required. For patients with M2 and M3 disease, a post-op MRI is strongly encouraged, but not mandatory. Patient eligibility by imaging criteria requires demonstration of residual tumor > 1.5 cm^2 or metastatic disease.

(Note: all quoted slice/skip thicknesses are maximal; thinner slices/skip are encouraged, [and may be necessary if the lesion imaged is very small] allowing for signal to noise and cross talk limitations depending on the particular platform employed)

Required sequences:

1. Sagittal T1 localizer; 4 mm skip 0.4 mm
2. Axial FSE T2; 4 mm, skip 0.4 mm
3. Axial T2 FLAIR; 4 mm skip 0.4
4. Axial diffusion; 4-5 mm skip 0 (single shot, matrix 128 x 128 or 128 x 192, B=1000)
5. Axial T1; 4 mm skip 0.4 mm
6. Axial T1 with contrast; 4 mm skip 0.4 mm
7. Sagittal T1 with contrast; 4 mm skip 0.4 mm
8. Axial T2 FLAIR with contrast; 4 mm skip 0.4

Optional sequences

Precontrast :

1. Axial susceptibility weighted imaging (SWI) or
gradient echo (susceptibility sequence); 4-5 mm skip 1-2 mm. TE=20, flip angle =20.
2. Sagittal or coronal FSET2; 4 mm skip 0.4 mm, depending on tumor configuration/orientation
3. Axial T2 FLAIR; 4 mm skip 0.4
4. Diffusion Tension Imaging (DTI) sequence: 12 – 30 direction (depending upon scanner) 2.5-5
mm skip 0, b=1000

Post contrast :

1. Coronal T1 : 4mm skip 0.4
2. T1-weighted gradient echo volume sequence (SPGR or equivalent)

Notes:

1. DO NOT INTERLEAVE T1 weighted sequences
2. Flow compensation should not be used (or al least not on all T1 enhanced sequences)
3. Fat Saturation not necessary

17.2 **MR Spine With and Without Contrast**

Spinal MRI (T-1 weighted imaging with and without gadolinium) is required within 28 days of surgery if done post-operatively and within 10 days of surgery if done pre-operatively. If an MRI scan is performed within 10 days prior to surgery, than only a post-

contrast examination is necessary. For posterior fossa tumors, pre-operative MRI scans are preferred because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

If there is significant motion artifact and/or hemorrhage, then the scan is not evaluable and must be repeated or the patient is not eligible for study.

1. Whole spine sagittal T1; 3 mm skip 0 – 0.3 mm.

Technical notes:

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

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 msecs)
- DO NOT INTERLEAVE

<u>For primary tumors of the spinal cord, add:</u>

1. Whole spine sagittal T2; 3 mm skip 0 mm.

Technical notes:

- Can keep Phase direction AP, frequency direction SI, with anterior saturation pulses; or switch phase direction SI, frequency direction AP, with inferior and superior saturation pulses if that produces better images (less CSF pulsation artefacts)
- Pixel size 1 mm^2 or less (example: for 26 cm FOV, use 256 x 256 matrix)

2. Axial FSE T2, 4-5mm skip 0-1 mm, through tumor

NOTE:

In the routine evaluation for subarachnoid metastatic dissemination from brain tumors to the spine:

1. High quality T1 images are essential - without artifacts from physiologic motion (cardiac,

respiratory) or from CSF pulsation.

2. T2 weighted sequences (sagittal or axial) are not needed. They are optional.

17.3 Central Review

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

- Pre-operative Cranial MRI with and without contrast
- Post-operative Cranial MRI with and without contrast
- Pre <u>OR</u> Post-operative Spinal MRI with contrast
- Cranial and Spinal MRI with and without contrast at the end of Radiation Therapy (Week 10 Prior to Start of Maintenance)
- Cranial and Spinal MRI with and without contrast 4 weeks following the end of Maintenance or best response if relapse during therapy
- Cranial MRI at progression (relapse) with and without contrast
- Spinal MRI at progression (relapse) with contrast
- Copies of all Operative Reports

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information.

Imaging studies submitted on CD should be sent to:
IROC RI (QARC)
Building B, Suite 201
640 George Washington Highway,
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

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).

18.0.1 General Guidelines

Radiation therapy for patients on COG protocols can only be delivered at approved COG RT facilities (see COG's Policies and Procedures). Contact IROC RI (QARC) for questions or further 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 infants 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. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons or proton beam therapy and electronic data submission is required.

For treatment planning and delivery all collaborating investigators should have general anesthesia and/or deep-sedation capabilities as needed, and customized immobilization that provides for treatment that is both reproducible and safe.

18.0.2 Credentialing Requirements

Radiation therapy will be administered using protons or photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and craniospinal radiation therapy. Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; those using IMRT and not previously credentialed for use of IMRT

in COG trials must successfully irradiate IROC Houston's IMRT head and neck phantom and must update their Facility Questionnaire on IROC Houston's website. All centers must have completed the IROC craniospinal radiation therapy benchmark. All centers participating in this protocol must complete the IROC CT/MR image fusion benchmark. Benchmark materials may be obtained from IROC RI (QARC) (www.irocri.qarc.org) and must be submitted and approved before case reviews can be finalized. Use of both scanned and scattered proton techniques are allowed, but each proton beam line used to treat patients on this study must be credentialed prior to clinical trial use by IROC Houston. For information regarding the IMRT phantoms and proton credentialing, please contact IROC Houston (http://rpc.mdanderson.org/rpc).

18.0.3 Guidelines and Requirements for the Use of IMRT

Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored cooperative group trials. These guidelines are available through www.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

18.0.4 Guidelines and Requirements for the Use of Proton Beam Therapy

Investigators using proton beam therapy will be required to comply with current guidelines for the use of protons in National Cancer Institute sponsored clinical group trials. These guidelines are available through www.qarc.org.

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

Use of either photons or protons is allowed on this study. If IMRT is used, photon energy should be no greater than 10 MV.

Equipment/Method	Photons (any energy)	IMRT (4-10MV)	Protons
Linear Accelerator	X	X	
Proton Beam			X

18.2.1 Modality

X-rays with a nominal energy ≥ 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 ≥ 4 MV, as long as dosimetric constraints are accomplished. Electron beams of suitable energy to treat the spinal cord may be allowed if prior documentation has been reviewed and approved by IROC RI (QARC). Proton beams may be used by credentialed centers and will require digital submission of treatment planning data to IROC RI for QA review.

18.2.2 Calibration

The calibration of therapy machines used in this protocol shall be verified by IROC Houston (formerly the RPC).

18.2.3 Equipment

Patients enrolled on this study must be treated using conformal radiation therapy treatment planning and delivery techniques at a minimum for the primary. IMRT or Proton Therapy will be allowed if appropriate credentialing requirements have been met.. 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 beams are used, prior approval from the study radiation therapy coordinator is necessary. 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. Allowable treatment techniques are 3D conformal, IMRT, and proton therapy provided that all credentialing requirements have been met for the technique in use.
- 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 ICRU Report 62 definitions 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 Photon 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$_1$ (CTV_1) is the entire craniospinal axis. The craniospinal axis Planning Target Volume (PTV_1) 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_1 margin should be considered due to inexactness of repositioning for the spinal fields.

Although conventional simulation will be allowed for the craniospinal axis PTV_1 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_1): The whole-brain field shall extend anteriorly to include the entire frontal lobe and cribriform plate region. Coverage of the CTV takes precedence over protection of the lenses or eyes. Inferiorly, the CTV_1 shall be at least 0.5 cm below the base of the skull at the foramen magnum. PTV_1 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.

Spine (CTV_1): 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_1 should be defined to account for setup error.

For proton therapy, the spinal target volume will include the vertebral bodies for skeletally immature patients to minimize the risk of unequal vertebral growth. Skeletal maturity can be estimated with a wrist x-ray to determine bone age. Dose to the thyroid gland can be attenuated by allowing incomplete coverage of the lower cervical vertebra. The spinal target volume in skeletally mature

patients will include the spinal subarachnoid space with a margin of 3-5 mm into the vertebral body to allow for inter-fraction set up variation.

The dose prescription for the brain and spine will be daily fractions of 1.80 Gy. See Table 18.4 for doses required by initial disease stage and early RT response.

Posterior Fossa Boost (CTV_{PF}): This volume refers to patients with posterior fossa primaries. 3D-based treatment planning is mandatory for these volumes. IMRT is allowed for the PTV_{PF}. The CTV_{pf} should encompass the entire posterior fossa. The posterior fossa must be defined on the planning CT scan. It is strongly recommended that a sagittal and or coronal MRI be used to assist in identification of the position of the tentorium. The CTV_{PF} 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_{PF}) is a 0.3cm to 0.5cm margin around the CTV to account for day-to-day setup variation. The PTV_{PF} should not extend beyond the external bony confines of the skull except at the foramen magnum to C1-C2. The PTV_{PF} 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 55.8 Gy must encompass at least 95% of the PTV_{PF} (the posterior fossa) as shown by DVH. No part of the PTV_{PF} should receive less than 50 Gy. Treatment techniques for the PTV_{PF} may include parallel opposed laterals or other 3D CRT methods to limit dose to the supratentorial brain, hypothalamus, pituitary or middle ear.

Metastasis Site Boost (CTV_M):

Patients with M1 disease will receive no additional boost.

Patients with M2 disease (intracranial subarachnoid disease) will receive boosts to areas of supratentorial or posterior fossa metastatic disease.

Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease.

Diffuse spinal disease is defined as radiographically visible multiple sites of disease in each of at least 3 out of 4 spinal regions (i.e., cervical, thoracic, lumbar or sacral). If there is diffuse involvement of the spine, the entire spine will be treated in the boost volume.

The CTV_m margin for boosting metastatic deposits will be 0.5 to 1.0 cm encompassing the lesion within the anatomic compartment. Another 0.3 to 0.5 cm margin will be added for the PTV_M. Field shaping may be conformal and consideration may be given for normal organ sparing and abutment of other high dose or boost sites.

18.3.2.1 Proton Definitions for GTV, CTV and PTV

- *GTV* is the same for protons and photons.
- *CTV* is the same for protons and photons.

- PTV is the same as photons and will be used to select the appropriate beam size and beam arrangements to achieve lateral coverage of the targeted volume and to minimize heterogeneity. The PTV will not be used to determine the distal range for the individual proton beams but will be used to report dose according to ICRU Report-78. The proton distal target margin will be determined per beam using the guidelines in Section 18.4.5.

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 C2)
- Skin (non-specified tissues)

A Web based atlas with normal organ contours is available at www.QARC.org under Resources.

18.4 Dosimetry

18.4.1 Prescription Point

The prescription point for the neuroaxis (PTV_1, 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 55.8 Gy isodose covers at least 95% of the respective planning target volumes. The minimum dose to the PTV_{PF}, PTV_{ST} or PTV_{boost} shall not be < 50 Gy.

18.4.2 Dose Definition

Dose is to be specified in Gray (Gy)-to-muscle. For proton beam, the absorbed dose shall be specified in CGE, which is the same as ICRU 78 DRBE using a standard RBE of 1.10 with respect to water.

18.4.3 Prescribed Dose and Fractionation

36.0 Gy CSRT (PTV_1)
55.8 Gy Posterior fossa boost, ***cumulative dose*** (PTV_{PF} or PTV_{ST})
Patients with M1 disease will receive no additional boost.
Patients with M2 disease (intracranial subarachnoid disease) will receive boosts to areas of supratentorial or posterior fossa metastatic disease. (Table 18.4)

Patients with M3 disease (spinal deposits of disease) are subdivided into those with diffuse disease and those with focal disease. Patients with diffuse disease will have their entire spine boosted to 39.6 Gy. (Table 18.4)

Table (18.4) Radiation Dose for Craniospinal Axis Radiation Therapy

M-Stage at Diagnosis	CSRT Dose	Metastasis location	Dose to PTV_M	Total Dose to PTV_M	Dose to PTV_{PF}/ PTV_{ST}	Total Dose to PTV_{PF} /PTV_{ST}
M0, M1	36 Gy	None	NA	NA	19.8 Gy	55.8 Gy
M2	36 Gy	Intracranial	19.8 Gy	55.8 Gy	19.8 Gy	55.8 Gy
M3	36 Gy	Diffuse	3.6 Gy	39.6 Gy	19.8 Gy	55.8 Gy
		Focal, above terminus of spinal cord	9 Gy	45 Gy	19.8 Gy	55.8 Gy
		Focal, below terminus of spinal cord	14.4 Gy	50.4 Gy		

*note: if M3 and has intracranial metastatic disease, follow schema for M2 cranial dosage as well

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_{PF}, PTV_{ST} or PTV_{boost} should be encompassed within 95% of the 55.8 Gy isodose surface and no more than 5% of the PTV 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.

18.4.5.1 Proton Dose Uniformity

For protons, at least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. The PTV; however, will be only be used to select the appropriate beam size and beam arrangements to achieve lateral coverage of the targeted volume and to minimize heterogeneity. The lateral margin for proton beam therapy should be 3 to 5mm. The PTV will not be used to determine the distal range for the individual proton beams. The proton distal target margin will be determined per beam based on the distal aspect of the CTV and additional margin(s) meant to account for range uncertainty and the SM and IM components of the PTV which are understood for this group of patients and which may affect the proton distal range.‡

Proton Distal Target Range † = CTV(d) + Square root ((Range Uncertainty)^2 + (Set-up Margin)^2 + (Internal Margin)^2)

- CTV(d) = the distal aspect of the CTV

- Range Uncertainty = 1.5% of the water-equivalent range of the CTV at max depth
  - ≥ 1mm
- Set-up Margin = set-up, mechanical and dosimetric uncertainties
  - Protons are relatively unaffected by set-up uncertainty in axis of beam
  - Uncertainty in hardware and software – no assigned value available
- Internal margin = compensates for all variations in site, size and shape of the tissues contained in or adjacent to the CTV
  - ≥ 1mm

Proton Proximal Target Range † = CTV(p) - Square root ((Range Uncertainty)^2 + (Set-up Margin)^2 + (Internal Margin)^2)

- CTV(p) = the proximal aspect of the CTV
- Range Uncertainty = 1.5% of the water-equivalent range of the CTV at max depth
  - ≥ 1mm
- Set-up Margin = set-up, mechanical and dosimetric uncertainties
  - Protons are relatively unaffected by set-up uncertainty in axis of beam
  - Uncertainty in hardware and software – no assigned value available
- Internal margin = compensates for all variations in site, size and shape of the tissues contained in or adjacent to the CTV
  - ≥ 1mm

†The proton distal range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns.
‡The uncertainty of distal margin has been estimated to be as large as 4mm.

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 that 2 treatment days, please notify Dr. Jeff Michalski.

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. 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:

$$\textit{The angle} = \tan^{-1} \frac{\textbf{Error! Bookmark not defined.}\ \textit{spine length}/2}{\text{SAD}}$$

If asymmetric collimator jaws are used:

$$\textit{The angle} = \tan^{-1} \frac{\textbf{Error! Bookmark not defined.}\ \textit{upperspine length}}{\text{SAD}}$$

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 900 cGy. Custom blocking may be required at the inferior border of the spine.

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 at least twice during treatment of the cranio-spinal axis (e.g. after each 9Gy). 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) 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.

18.5.1.6 Selection of Proton Beam Arrangements

Proton beams have two uncertainties at the distal edge of the beam that affect planning. The first is the physical uncertainty of the exact location of the stopping edge. This is accounted for in Sect. 18.4.5. The second is the biologic uncertainty of the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in a critical organ will not be allowed. Individual proton beams which are a component of a multi-field proton beam and which stop within such an organ will be allowed but are not encouraged. It is preferable to stop the proton beam beyond the critical organ.

18.5.1.7 Field Shaping

Field-shaping is required. Shielding shall be at least 5 HVL thick. Multi-leaf collimation may be used. The field shaping for protons will be done with either brass apertures or proton-specific multileaf collimation.

18.5.1.8 Example Cases

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

18.5.1.9 Imaging

CT (3 mm - 5 mm section thickness from the thoracic inlet to the base of the skull, 3 mm for the entire 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

Normal tissue dose recommendations are the same for photons and protons (proton dose measured in CGE).

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 of this volume shall be submitted.

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 the PTV_{pf} prescription dose.

18.7 Dose Calculations and Reporting

Institutions using conventional 3D treatment planning must have an approved 3D Conformal Benchmark on file with IROC. If IMRT or Protons are to be used, credentialing requirements specific to those modalities must be satisfied. See Section 18.0.2 for details regarding credentialing requirements.

18.7.1 Prescribed Dose

The dose prescription and fractionation shall be reported on the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose shall be reported on the RT-2 Radiotherapy Total Dose Record form.

18.7.2 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 C2). Dose volume histograms will be calculated and submitted for the GTV, CTV and PTV of each volume treated. Dose volume histograms will be calculated and submitted in composite form whenever possible. If IMRT is used, a DVH must be submitted for a category of tissue called "**unspecified tissue**," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

18.8 **Quality Assurance Documentation**

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.

Digital Submission:

Submission of treatment plans in digital format as DICOM RT 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 IROC RI (QARC) web site at 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.

Data to be Submitted:

External beam Treatment Planning System

- Digitally reconstructed radiographs (DRR) each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. DRR's are not required for IMRT.
- RT treatment plan 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. A DVH shall be submitted for the organs at risk specified in Section 18.3.3. 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. DVH's are included in the digital plan.
- 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 all diagnostic materials and surgical reports used in defining the target volume including (i) preoperative MRI and postoperative cranial MRI with and without contrast; (ii) pre or postoperative spinal MRI with and without contrast; sagittal imaging should be included for both brain and spine; (iii) copies of the all op reports, pathology reports, and copies of the results for the Lumbar CSF cytology examination must also be submitted. DICOM format is required for all imaging
- Portal images for the craniospinal fields
- Prescription Sheet for Entire Treatment
- For protons, a description of the rationale for the PTV margins.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the IROC RI (QARC) and the radiation oncology reviewers.

Forms

- RT-1 Dosimetry Summary Form.
- Proton Reporting Form (if applicable).

Within 1 week of the completion of radiotherapy, the following data shall be submitted for all patients:

- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points
- Documentation listed above showing any modifications from original submission.

The data should be sent to:

IROC RI (QARC)
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Telephone: (401) 753-7600
FAX: (401) 753-7601

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

COG Protocol Dosimetrist
IROC RI (QARC)
Building B, Suite 201
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Telephone: (401) 753-7600
FAX: (401) 753-7601

18.9 Definitions of Deviation in Protocol Performance

18.9.1 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.

18.9.2 Dose Uniformity

Minor Deviation
The variation of dose in one of the target volumes exceeds + 10%, - 5%, but is within ± 15%.

Major Deviation
The variation of dose in one of the target volumes exceeds ± 15%.

18.9.3 Volume

Minor Deviation
Margins less than specified, or field(s) excessively large. Major incorrect definition of Organs At Risk volumes.

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

19.0 QUALITY OF LIFE AND NEUROPSYCHOMETRIC GUIDELINES

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.

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
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_0	No evidence of subarachnoid or hematogenous metastasis.
M_1	Microscopic tumor cells found in CSF.
M_2	Gross nodular seeding demonstrated in the intracranial subarachnoid space or ventricular system distant from the primary site.
M_{3a}	Gross nodular seeding in the spinal subarachnoid space without evidence of intracranial seeding.
M_{3b}	Gross nodular seeding in the spinal subarachnoid space as well as intracranial seeding.
M_4	Extraneural metastasis

APPENDIX III: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0332
(for children from 7 through 12 years of age)

A Trial to Compare Two Ways of Treating Patients with High Risk Medulloblastoma/PNET

1. We have been talking with you about your medulloblastoma. Medulloblastoma is a type of cancer that grows in the brain. Sometimes cancer is called "high risk" because it is more likely to come back after treatment. High risk cancer is treated with stronger medicine to make it less likely to return. After doing tests, we have found that you have high risk medulloblastoma.

2. We are asking you to take part in a research study because you have a type of brain cancer called high risk 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 the type of brain cancer that you have. We want to find out if adding 1 drug to the usual therapy can improve the treatment for the type of brain cancer that you have. The drug we are testing is carboplatin (the 'C' drug). We will do this by comparing 2 ways to treat the cancer. We don't know which way is better. That is why we are doing this study.

3. Children who are part of this study will be treated with radiation therapy and chemotherapy. Radiation therapy is the use of high-energy x-rays to kill cancer cells. Chemotherapy is medicine that destroys cancer cells. When a chemotherapy drug is given along with radiation therapy this is called chemoradiotherapy.

4. On this study, everyone will be given the usual treatment for your type of cancer. But some patients will have 1 drug added to that therapy. This means that you will be treated in 1 of 2 ways:

    * The usual therapy.

    * The usual therapy plus the 'C' drug.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that if you are given the 'C' drug this will improve the treatment and your cancer will be less likely to return. But we don't know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that if you are given the 'C' drug then you may have more side effects than you would on the usual therapy. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

8. We would also like to do research 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 research tests. You can choose to be on the study but not to allow us to use extra tumor cells for research.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0332
(for teens from 13 through 17 years of age)

A Trial Using Chemotherapy and Radiation Therapy to Compare Two Ways of Treating Patients with High Risk Medulloblastoma/PNET

1. We have been talking with you about your medulloblastoma. Medulloblastoma is a type of cancer that grows in the brain. Sometimes cancer is called "high risk" because it is more likely to come back after treatment. High risk cancer is treated with stronger medicine to make it less likely to return. After doing tests, we have found that you have high risk medulloblastoma.

2. We are asking you to take part in a research study because you have high risk 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 find out if adding 1 chemotherapy drug to the standard therapy will improve the treatment for young people with high risk medulloblastoma.

   Standard therapy for medulloblastoma includes surgery, radiation therapy and chemotherapy. Radiation therapy is the use of high-energy x-rays to kill cancer cells. Chemotherapy is medicine that destroys cancer cells. When a chemotherapy drug is given along with radiation therapy this is called chemoradiotherapy.

   This study deals with treatment after surgery. The standard treatment for high risk medulloblastoma after surgery is chemoradiotherapy followed by "Maintenance" chemotherapy. In this study, we want to find out if adding a drug called carboplatin to the chemoradiotherapy can improve the outcome of patients.

3. Children and teens who are part of this study will all be treated with the standard therapy for high risk medulloblastoma but some patients will have 1 drug added to that therapy. This means that you will be treated in 1 of 2 ways:

   * Standard therapy (chemoradiotherapy followed by Maintenance chemotherapy)

   * Standard therapy with the addition of carboplatin during chemoradiotherapy

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that if you receive carboplatin this will improve the treatment and your cancer will be less likely to return. But we don't know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." The risks to you from this study are that if you receive carboplatin then you may have more side effects than you would on standard therapy. Other things may happen to you that we don't yet know about.

6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

7. Another part of the 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 research tests. If there are any leftover samples from these tests, we would like your permission to store them for use in future research. This is called banking. This part of the study is optional.

8. You can still be treated for your tumor if you decide not to be on this study. You can also decide to be on the study but not to allow us to use extra tumor cells for research.

APPENDIX IV: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Downloading Site Registration Documents:

Site registration forms may be downloaded from the ACNS0332 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the COG link to expand, then select trial protocol ACNS0332
- Click on the Site Registration Documents link

Requirements for ACNS0332 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the IROQ Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.
ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX V: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

Some drugs, food, and supplements may interact with carboplatin. Examples include:

Drugs that may interact with carboplatin*
• Antibiotics like gentamicin or tobramycin • Anti-seizure medications like fosphenytoin or phenytoin • Arthritis medications like leflunomide, tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like clozapine or natalizumab

Food and supplements that may interact with carboplatin**
• Echinacea

**Sometimes these drugs are used with carboplatin on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Some drugs, food, and supplements may interact with cisplatin. Examples include:

Drugs that may interact with cisplatin*
• Antibiotics like gentamicin or tobramycin • Anti-seizure medications like fosphenytoin or phenytoin • Arthritis medications like leflunomide or tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like bumetanide, clozapine, furosemide, natalizumab

Food and supplements that may interact with cisplatin**
• Echinacea

**Sometimes these drugs are used with cisplatin on purpose. Discuss all drugs with your doctor.*
***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Some drugs, food, and supplements may interact with cyclophosphamide. Examples include:

Drugs that may interact with cyclophosphamide*
• Allopurinol • Chloramphenicol • Cyclosporine • Digoxin • Etanercept • Hydrochlorothiazide • Indomethacin • Nevirapine • Pentostatin • Warfarin

Food and supplements that may interact with cyclophosphamide**
• St. John's Wort • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Sometimes these drugs are used with cyclophosphamide on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Some drugs, food, and supplements may interact with vincristine. Examples include:

Drugs that may interact with vincristine*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Aripiprazole, nefazodone, trazodone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tocilizumab, tofacitinib
• Anti-rejection medications
  • Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir
• Anti-seizure medications

- Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
- Heart medications
  - Amiodarone, digoxin, dronedenarone, propranolol, verapamil
- Some chemotherapy (be sure to talk to your doctor about this)
- Many other drugs, including the following:
  - Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin

Food and supplements that may interact with vincristine**

- Echinacea
- St. John's Wort
- Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with vincristine on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

REFERENCES

1. Geyer J, et al: Survival of infants with primitive neuroectodermal tumors or malignant ependymomas of the CNS treated with eight drugs in 1 day: a report from the Children's Cancer Group. J. Clin. Oncol 12:1607-1615, 1994
2. Duffner PK, Horowitz ME, Krischer JP, et al: Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. NEJM 328(24):1725-31, 1993
3. Zeltzer M, Boyett JM, Finlay JL, et al: Metastasis stage, adjuvant treatment, and residual tumor are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921 randomized phase III study. J Clin Oncol 17:832-845, 1999
4. Ris MD, Packer R, Goldwein J, et al: Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group study. Journal of Clinical Oncology 19:3470-6, 2001
5. Allen JC, Walker R, Luks E, et al: Carboplatin and recurrent childhood brain tumors. J Clin Oncol 5:459-463, 1987
6. Mastrangelo R, Lasorella A, Riccardi R, et al: Carboplatin in childhood medulloblastoma/PNET: Feasibility of an in-vivo sensitivity test in an "up-front" study. Med Ped Oncol 24:188-196, 1995
7. Gaynon PS, Ettinger LJ, Baum ES, et al: Carboplatin in childhood brain tumors. Cancer 66:2465-2469, 1990
8. Douple EB, Richmond RC, O'Hara JA, et al: Carboplatin as a potentiator of radiation therapy. Cancer Treat Rev 12:A111-24, 1985
9. O'Hara JA, Douple EB, Richmond RC: Enhancement of radiation-induced cell kill by platinum complexes (carboplatin and iproplatin) in V79 cells. Int J Radiat Oncolo Biol Phys 12:1419-22, 1986
10. Yang LX, Douple EB, O'Hara JA, et al: Production of DNA double-stranded breaks by interactions between carboplatin and radiation: a potential mechanism for radiopotentiation. Radiat Res 143:309-15, 1995
11. Begg AC, van der Kolk PJ, Emont J, et al: Radiosensitization in vitro by cis-diammine (1,1-cyclobutanedicarboxylato) platinum (II) (carboplatin, JM8) and ethylenediammine-malonatoplatinum (II) (JM40). Radiother Oncol 9:157-65, 1987
12. Yang LX, Douple EB, Wang HJ: Irradiation enhances cellular uptake of carboplatin. Int J Radiat Oncol Biol Phys 33:641-6, 1995
13. Caffo O: Radiosensitization with chemotherapeutic agents. Lung Cancer 34:S81-90, 2001
14. Geldof AA, Slotman BJ: Radiosensitizing effect of cisplatin in prostrate cancer cell lines. Cancer Lett 101:233-9, 1996
15. Karasawa K, Shinoda H, Katsui K, et al: Radiotherapy with concurrent docetaxel and carboplatin for head and neck cancer. Anticancer Res 22:3785-8, 2002
16. Atagi S, Kawahara M, Ogawara M, et al: Phase II trial of daily low-dose carboplatin and thoracic radiotherapy in elderly patients with locally advanced non-small cell lung cancer. Jpn J Clin Oncol 30:59-64, 2000
17. Clamon G, Herndon J, Cooper R, et al: Radiosentization with carboplatin for patients with unresectable stage III non small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group and the Eastern Cooperative Oncology Group. J Clin Oncol 17:4-11, 1999
18. Skov K, MacPhail S: Interaction of platinum drugs with clinically relevant x-ray doses in mammalian cells: a comparison of cisplatin, carboplatin, iproplatin and tetraplatin. Int J Radiat Oncol Biol Phys 20:221-225, 1991
19. Patton TF, Himmelstein KJ, Belt R, et al: Plasma levels and urinary excretion of filterable platinum species following bolus injection and IV infusion of cis-diachlorodiammineplatinum in man. Cancer Treat Rep 62:1359, 1978
20. Alberts DS, Mason-Liddil N: Carboplatin in the treatment of ovarian cancer. Semin Oncol 16:19-26, 1989

21. Patel M, Godwin K, McCully C, et al: Plasma and cerebrospinal fluid pharmacokinetics of carboplatin and cisplatin. ProcAACR 37:403-404, 1996
22. Alverez MV, Cobreros G, Heras A, et al: Studies of cisdichlorodiammineplatinum (II) as a radiosensitizer. Br J Cancer 3 (S3):68-72, 1978
23. Dritschilo A, Piro AJ, Kelman AD: The effect of cis-platinum on the repair of radiation damage in plateau phase Chinese hamster cells. Int J Radiat Oncol Biol Phys 5:1345-1349, 1979
24. Stewart DJ, Leavens M, Maor M, et al: Human central nervous system distribution of cisdiamminedichloroplatinum and use as a radiosensitizer in malignant brain tumors. Can Res 42:2474-2479, 1982
25. Hallahan AR, Pritchard JI, Chandraratna RA, et al: BMP-2 mediates retinoid-induced apoptosis in medulloblastoma cells through a paracrine effect. Nat Med 9(8):1033-8, 2003
26. Gumireddy K, et al: All-trans-retinoic acid-induced apoptosis in human medulloblastoma: activation of caspase-3/poly(ADP-ribose) polymerase 1 pathway. Clin Cancer Res 9(11):4052-9, 2003
27. Di C LS, Adamson DC, Parrett TJ, et al: Identification of OTX2 as a Medulloblastoma Oncogene Whose Product can be Targeted by All-Trans Retinoic Acid. Cancer Res 65(3):919-24, 2005
28. Khan AA, Villablanca JG, Reynolds CP, et al: Pharmacokinetic studies of 13-cis-retinoic acid in pediatric patients with neuroblastoma following bone marrow transplantation. Cancer Chemother Pharmacol 39(1-2):34-41, 1996
29. Formelli F, Cavadini E, Mascheroni L, et al: Pharmacokinetics and effects on plasma retinal concentrations of 13-cis-retinoic acid in melanoma patients. Br J Cancer 76:1655-60, 1997
30. LeDoze F, Debruyne D, Albessard F, et al: Pharmacokinetics of all-trans retinoic acid, 13-cis-retinoic acid, and fenretinide in plasma and brain of Rat. Drug Metab Dispos 28:205-208, 2000
31. Matthay KK, Villablanca JG, Seeger RC, et al: Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. N Engl J Med 341:1165-1173, 1999
32. Villablanca JG, Khan AA, Avramis VI, et al: Phase I trial of 13-cis-retinoic acid following bone marrow transplantation. J Clin Oncol 13:894-901, 1995
33. Liu J, Guo L, Luo Y, et al: All trans-retinoic acid suppresses in vitro growth and down-regulates LIF gene expression as well as telomerase activity of human medulloblastoma cells. Anticancer Res 20:2659-2664, 2000
34. Shin DM, et al: Phase II and biologic study of interferon alpha, retinoic acid, and cisplatin in advanced squamous skin cancer. J. Clin. Oncol. 20 (2):364-370, 2002
35. Shalinsky DR, et al: Enhanced antitumor efficacy of cisplatin in combination with ALRT1057 (9-cis retinoic acid) in human oral squamous carcinoma xenografts in nude mice. Clin Cancer Res 2:511-520, 1996
36. Aebi S, et al: all-trans retinoic acid enhances cisplatin-induced apoptosis in human ovarian adenocarcinoma and in squamous head and neck cancer cells, Clin. Cancer Res. 3:2033-2038, 1997
37. Formelli F, Cleris L: Therapeutic effects of the combination of fenretinide and all-trans-retinoic acid and of the two retinoids with cisplatin in a human ovarian carcinoma xenograft and in a cisplatin-resistant subline . 2000
38. Recchia F, Lalli A, Lombardo M, et al: Ifosfamide, cisplatin, and 13-Cis retinoic acid for patients with advanced or recurrent squamous cell carcinoma of the head and neck: a phase I-II study. Cancer 92:814-21, 2001
39. Yung WK, Kyritsis P, Gleason MJ, et al: Treatment of recurrent malignant Gliomas with High Dose 13-cis Retinoic Acid. Clin Cancer Res 2:1931-35, 1996
40. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data, 2nd Edition. New York: Wiley. 36:2411-2419, 2002
41. Sposto R, Sather HN: Determining the duration of comparative clinical trials while allowing for cure. Journal of Chronic Diseases 38(8):683-90, 1985

42. DeMets DL, Lan KKG: "Interim analysis: The alpha spending function approach". Statistics in Medicine 13:1341-1352, 1994