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**CHILDREN'S ONCOLOGY GROUP**

**ACNS0831**

# Phase III Randomized Trial of Post-Radiation Chemotherapy in Patients with Newly Diagnosed Ependymoma Ages 1 to 21 years

**A Groupwide Phase III Study**

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| CONTACT INFORMATION | | |
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| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
| Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.<br>Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.)<br><br>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.<br><br>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance. | 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. | Data collection for this study will be done exclusively through the eRDE system. Please see the Data Submission Schedule in the CRF packet for further instructions. |
| 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. | | |
| **For clinical questions (i.e., patient eligibility or treatment-related)** contact the Study PI of the Lead Protocol Organization. | | |
| **For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Website is located at** https://www.ctsu.org. | | |

## TABLE OF CONTENTS

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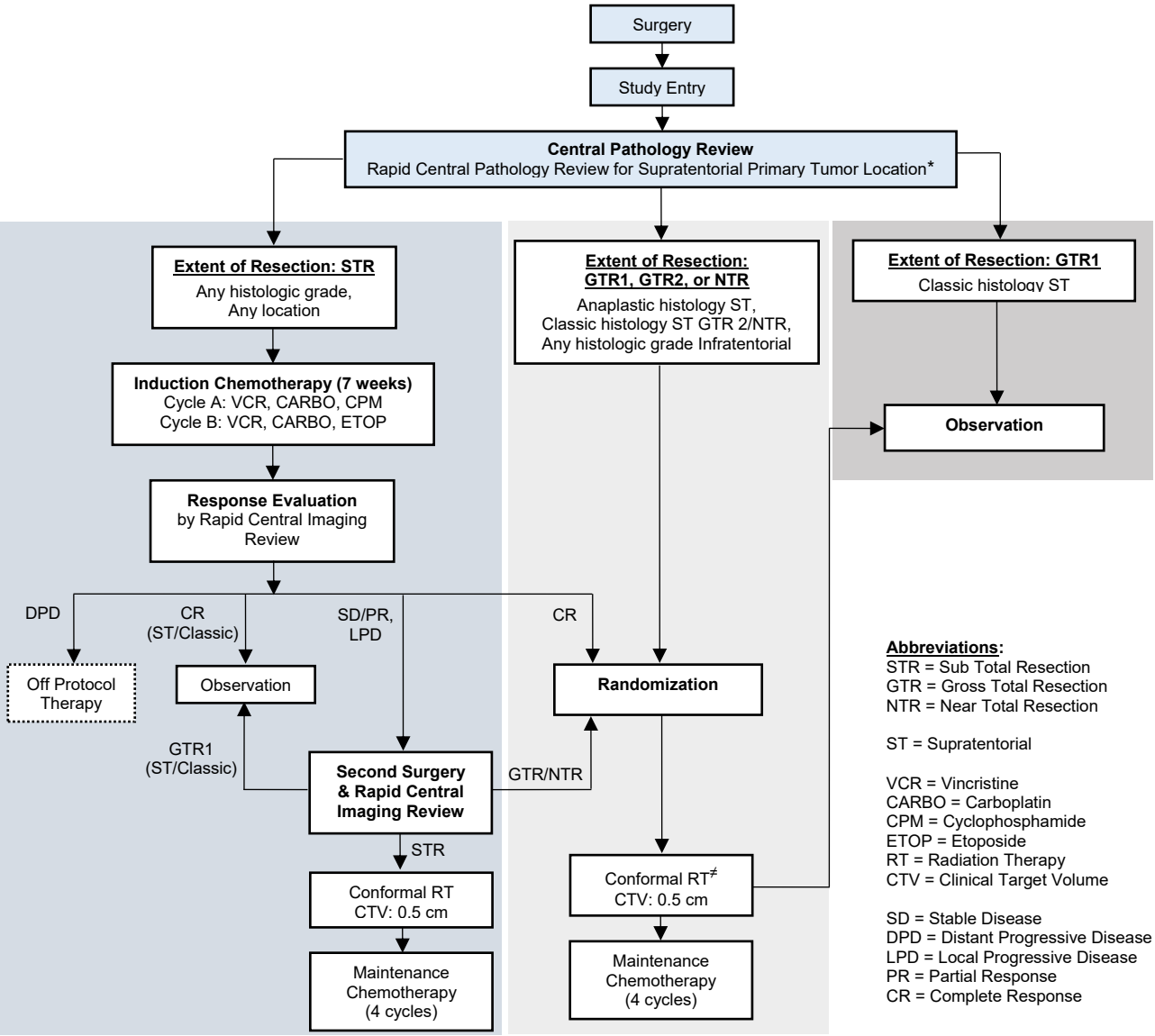
| AGENT | NSC# | IND # |
|---|---|---|
| Carboplatin | 241240 | Exempt |
| Cisplatin | 119875 | Exempt |
| Cyclophosphamide | 026271 | Exempt |
| Etoposide | 141540 | Exempt |
| Filgrastim (G-CSF) | 614629 | Exempt |
| Mesna | 113891 | Exempt |
| Vincristine | 067574 | Exempt |

SEE **SECTION 14.0** AND **SECTION 15.0** FOR SPECIMEN SHIPPING ADDRESSES

## ABSTRACT

Ependymoma accounts for 8-10% of all childhood CNS tumors with fewer than 170 new cases diagnosed in the United States each year in children and adults less than age 25 years.[1] The mean age at diagnosis ranges from 51-71 months,[2-5] and 25 to 40% are diagnosed in children less than 3 years of age.[6] Survival statistics for ependymoma are generally disappointing with 5-year survival and progression-free survival estimates of 50-64% and 23-45%, respectively[2,4,7-9] Recurrences are typically local with a median time to recurrence of 13-25 months [2-4,7,8,10], however, 20% of failures have isolated distant recurrence.[11] Late recurrences are not uncommon. The standard of care for ependymoma is maximal surgical resection compatible with an acceptable neurologic outcome followed by post-operative radiation therapy directed at the primary site. The application of immediate post-operative irradiation for children younger than 3 years of age remains controversial, however, the feasibility and efficacy of this approach is currently being examined prospectively in ACNS0121 for children as young as 12 months of age. Although multi-agent chemotherapy has been given in previous studies in an effort to delay or avoid irradiation, the small size of such studies and their non-randomized design has precluded definitive conclusions regarding the role for chemotherapy in ependymoma.[12-14] Data from the last CCG ependymoma study, CCG-9942, presented at ISPNO in June 2004 (manuscript published in September 2012)[15] argues that chemotherapy may play an important role in ependymoma. This study showed that patients with incomplete resections who received pre-radiation chemotherapy had a very similar outcome (55% 5-year event free survival [EFS]) compared to those who underwent a complete resection initially followed by immediate post-operative local radiation (58% 5-year EFS). A significant concern regarding pre-radiation chemotherapy is the risk of progression prior to radiation, which occurred in 15% of patients on CCG-9942. Other "baby brain" studies have also shown that a delay in radiation results in unacceptable progression rates. However, several studies have also shown good response rates to chemotherapy. Since surgical resection remains a critical prognostic factor, ACNS0121 addressed the question of whether a short course of chemotherapy given to those with incompletely resected tumors would increase the number of patients who can achieve a complete resection at second surgery prior to receiving conformal radiation (cRT). This should theoretically translate to an improved outcome in that subset, but those data have not yet been released. The current study proposes to answer the question of whether the administration of maintenance chemotherapy following radiation will improve event free and overall survival or whether it will only result in additional toxicity. Neurologic, neuropsychological and endocrine long-term sequelae of surgery, cRT, and maintenance chemotherapy will be assessed. This study will use a comprehensive genetic approach in order to create a molecular classification for ependymoma and to identify the genetic alterations underlying the biological and clinical behavior of various subsets of this tumor.

## ACNS0831 EXPERIMENTAL DESIGN SCHEMA




**IMPORTANT NOTES:**

* Rapid Central Pathology Review will be performed on all Supratentorial patients. See Section 14.2.1 for details.

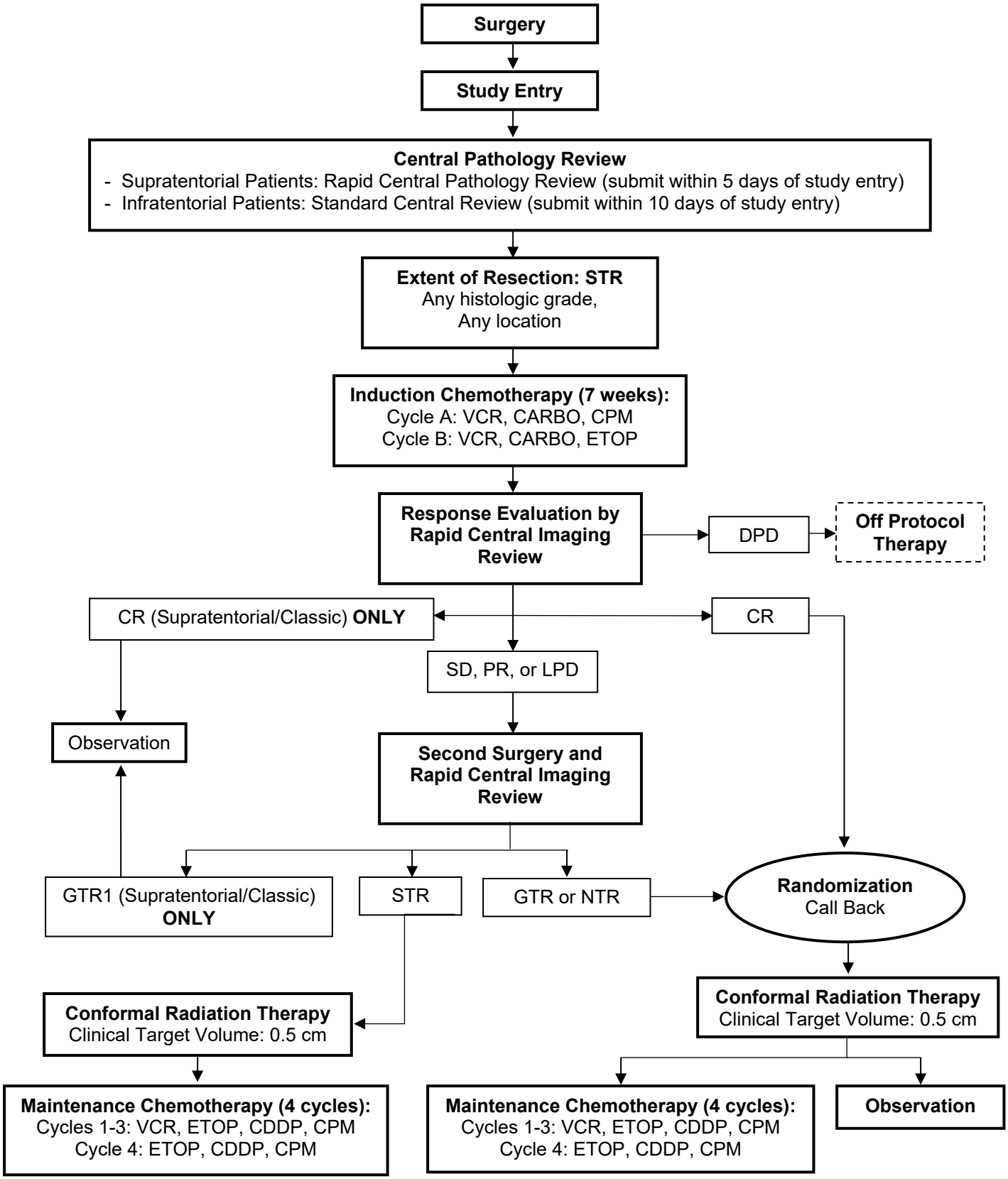
Guidelines for extent of resection can be found in Section 4.1.

- All patients with a sub total resection (STR), regardless of tumor location and histology, will receive **Induction**.
- All patients with an infratentorial tumor GTR 1, GTR 2, or NTR will be **Randomized**.
- All other GTR 1, GTR 2, and near total resection (NTR) supratentorial patients will be **Randomized**.
- Only Supratentorial patients who have classic histology confirmed by Rapid Central Pathology Review and gross total resection 1 (GTR 1) will be assigned to **Observation**.

≠ Under the condition that the extent of resection is indeterminate because the surgeon cannot unequivocally report that microscopic disease is not present OR the information necessary to determine extent of resection at the time of the operation is not available, the patient will be randomized to either (a) conformal radiation therapy (cRT) and maintenance chemotherapy OR (b) cRT and observation.

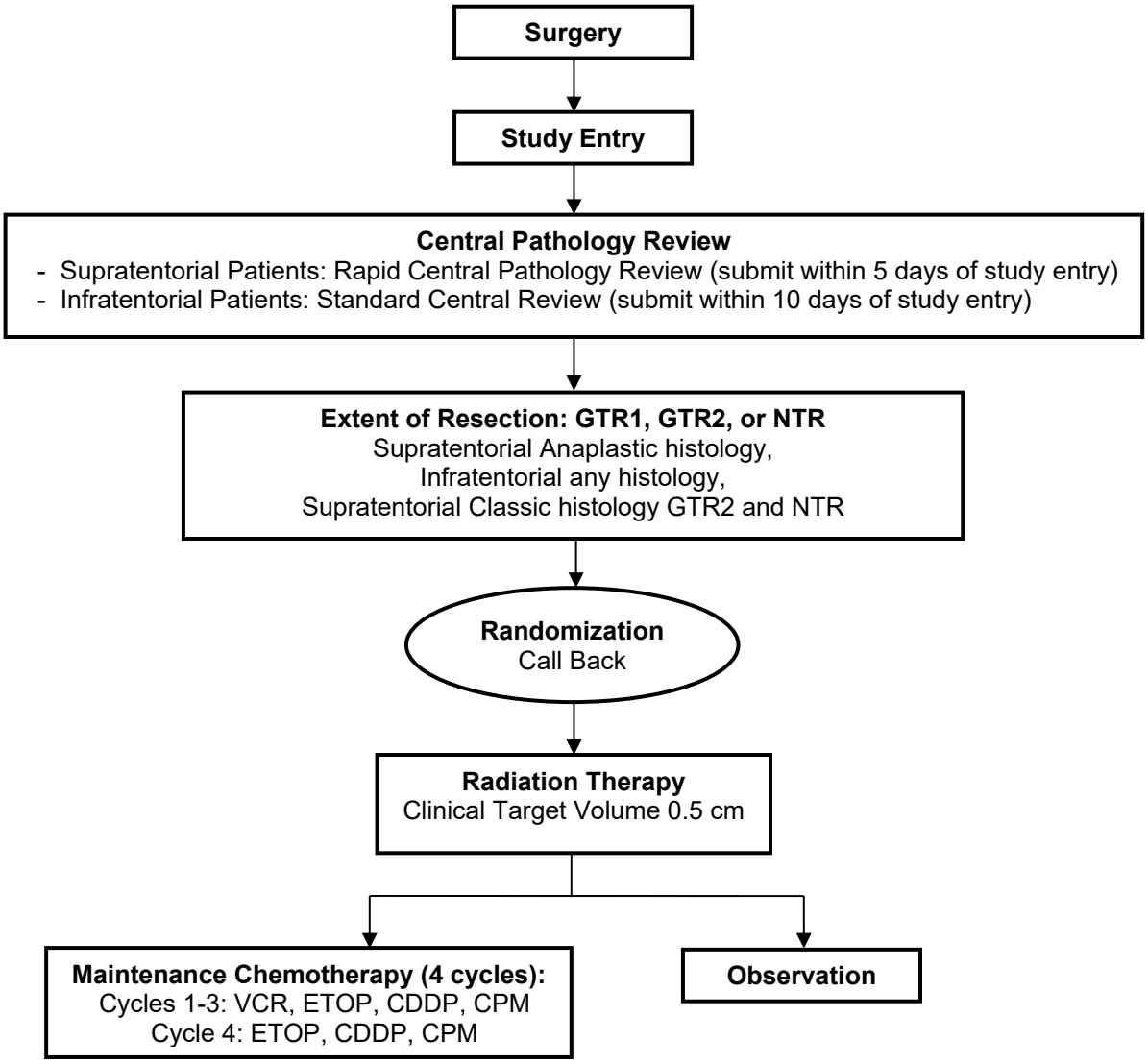
**SCHEMA FOR INDUCTION (For patients with STR)**

See abbreviations on Experimental Design Schema.



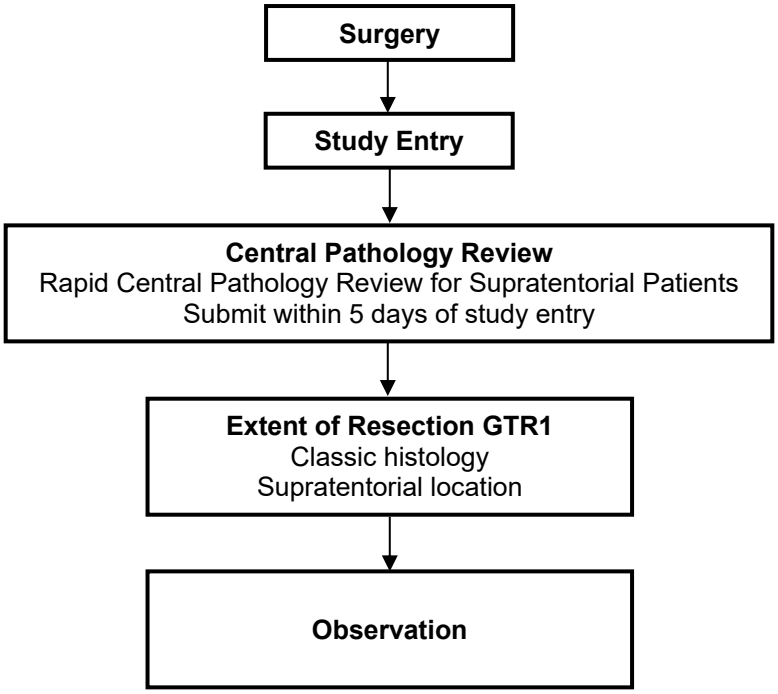
**SCHEMA FOR RANDOMIZATION (For patients with GTR 1, 2 or NTR)**

See Abbreviations on Experimental Design Schema.



**SCHEMA FOR OBSERVATION (For patients with GTR1 CLASSIC HISTOLOGY ST LOCATION)**

See Abbreviations on Experimental Design Schema.



# 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

## 1.1 Primary Objectives

To determine the event free survival (EFS) and overall survival (OS) of children with *completely* resected ependymoma treated with post-operative conformal radiation therapy (cRT) and then randomized to receive or not receive four cycles of post-radiation maintenance chemotherapy (vincristine, cisplatin, etoposide, and cyclophosphamide [VCEC]).

## 1.2 Exploratory Objectives

1.2.1 To estimate the EFS and OS of children with *incompletely* resected ependymoma who are unable to achieve a complete response (CR) by a) post-operative induction chemotherapy or by b) second surgery who will then be non-randomly assigned to cRT followed by four cycles of maintenance chemotherapy (VCEC).

1.2.2 To further evaluate the EFS and OS of children with supratentorial classic ependymoma who achieve a complete resection at first or second resection OR children who achieve a CR to short course induction chemotherapy following first surgery.

1.2.3 To evaluate whether the addition of maintenance chemotherapy post-radiation therapy contributes to neurobehavioral morbidity and reduced functional outcomes over time, compared to patients treated with radiation therapy followed by observation alone.

1.2.4 To examine differences in neurobehavioral outcomes and quality of life of children treated with proton beam radiation therapy compared to children treated with conventional radiation delivery techniques.

1.2.5 To evaluate biologic prognostic factors in childhood ependymoma by studying molecular groups as defined by DNA methylation profiling and immunohistochemistry, copy number variants to identify 1q gain in posterior fossa ependymomas, CDKN2A loss (homozygous deletion) in supratentorial ependymomas and specific genetic alterations such as RELA fusions, YAP1 fusions and the H3 K27M mutation on initial tumor samples and correlating these data with clinical outcome.

1.2.5.1 To explore prognostic molecular signatures and genomic alterations in ependymomas by building upon the data derived from ACNS0121 to correlate biomarkers listed above with WHO grade, location, extent of resection, treatment, EFS and OS.

# 2.0 BACKGROUND

## 2.1 Rationale for selected approach and trial design

### 2.1.1 Rationale for Surgery

Surgical resection appears to be the most important prognostic factor for children with ependymomas.[2-5,7-10,16,17] Patients with complete resection and radiation therapy have a 5-year survival estimate of 67-80% and a 5-year progression-free survival estimate of 51-75%, compared to a 5-year survival estimate of 22-47% and progression-free survival estimate of 0-26% for patients with incompletely resected tumors treated with radiation therapy. Even though complete resection is considered instrumental for long-term event-free and overall survival, historically, complete resection is achieved only for 42 to 62% of patients.[4,5,7,9] Complete resection is more easily achieved for tumors in supratentorial locations and from the roof of the fourth ventricle; tumors in other locations, including those intimately associated with the lower cranial nerves, have more morbidity associated with aggressive attempts at resection. Despite the high rate of incomplete resection after an initial surgery, a few studies have reported the use of second look surgery for patients with residual disease.[18,19] ACNS0121 addressed this issue, and was primarily concerned with whether second surgery would increase the surgical morbidity to an unacceptable level. Overall, surgical complications in patients on ACNS0121 were noted in 110 out of the 378 patients enrolled with 4 patients who experienced a complication at the time of second look surgery. On ACNS0121 there were 25 patients who had second look surgery after chemotherapy and 4 patients had a surgical complication. The complications included vocal cord weakness in one patient, right vocal cord paresis, and right facial paresis which was delayed in the second patient. The third patient had deficits noted in cranial nerves.[6-8] The fourth patient experienced a pseudomenigocele post-operatively with vomiting. The ACNS0121 Study Committee does not think that this is an unreasonably high surgical complication rate and they would expect a similar surgical complication rate on ACNS0831. Additionally, there has been a more recent publication reporting the complete resection rate at initial surgery is approximately 70%, which is much higher than previously reported.[20]

### 2.1.2 Rationale for Conformal Radiation Therapy (cRT)

Conformal radiation therapy (cRT) may be used to increase the dose to the primary site and at the same time decrease the side effects of treatment. Reducing the dose of radiation administered to normal tissue is a logical approach for treating childhood ependymoma, but requires systematic evaluation and planning, treatment-failure monitoring, and assessment of CNS effects. Merchant et al.[21] reported the preliminary results of a St. Jude Children's Research Hospital study (RT-1) that treated 64 pediatric patients with localized ependymoma after July 1997. This study used cRT with an anatomically defined clinical target volume margin of 1.0 cm surrounding the postoperative residual tumor and tumor bed. Only six failures occurred after a median follow-up period of 17 months (range: 3 to 43 months). This group included very young children with a median age of 3.0 years (range: 1.1 to 22.9 years). The majority of patients received a total dose of 59.4 Gy. Longer follow-up of this study reveals that at a median follow-up of 38.2 months, 20 out 88 patients have failed with a median time to progression of 14

months. The 3-year progression-free survival (PFS) was 74.7% (+/- 5.7%) for patients with gross total resection and cRT versus 42.9% (+/- 16.2%) for patients who underwent near total/subtotal resection and cRT18, which are nominally comparable to results reported in prior studies that used substantially larger treatment fields. These results are promising and suggest that the volume of irradiation may be substantially reduced without compromising disease control in pediatric patients with ependymoma. ACNS0121 administered radiation in this fashion and we plan to continue the same dose with additional volume reduction in the current study.

2.1.3 Rationale for Chemotherapy

The role of chemotherapy for intracranial ependymoma remains uncertain. However, recent data from CCG-9942 presented at the International Society of Pediatric Neuro-Oncology in June 2004 by Dr. James Garvin[22] demonstrates compelling information in support of a potentially important role for chemotherapy. This study was fully published in September 2012 in Pediatric Blood and Cancer.[15] In this study, patients without postoperative residual disease were treated with radiation alone. Between 1995 and 1999, there were 84 children ages 3-21 years enrolled on the CCG 9942 Phase II trial. Forty one patients with residual disease received four cycles of pre-irradiation chemotherapy with cisplatin, vincristine, cyclophosphamide, and etoposide. Of 35 evaluable patients, 40% had a complete response, 17% partial response giving a 57% objective response rate. The 5 year OS and EFS for the whole group was 71 ± 6% and 57 ± 6%, respectively. Interestingly, there was no difference in OS or EFS between patients assigned to pre-irradiation chemotherapy (5 yr EFS 55% ± 8%) because of post-operative residual tumor compared to the patients assigned to radiation alone because of no post-operative residual (5 yr EFS 58% ± 9%). This is a striking result since children with incomplete resections previously had fared much worse than those with complete resections. This strongly suggests a real benefit for chemotherapy in the incompletely resected patients. 5-year EFS was 65+/- 12% for complete response/partial response (CR/PR) compared to 50% +/- 16% for SD/MR. The 5-year OS after the end of induction chemotherapy for patients with CR/PR was 87+/- 9%, compared to 62+/- 18% for patients with MR/SD (P = 0.25). Although the patient numbers are small, these figures suggest that patients with a CR/PR to chemotherapy had an OS at 5 years better than the children who had complete resection plus radiation alone. However, because 15% of children progressed on chemotherapy, a delay in radiation seems an unwarranted risk in patients who have already achieved a CR with surgery. Delay in the delivery of radiation for ependymoma has previously been cited as a cause of increased recurrence rates in some "baby brain" studies of ependymoma.[13,14,23] On the other hand, these studies also demonstrated a significant response rate, which again supports a role for chemotherapy.

Ependymoma has been shown to be responsive to certain chemotherapeutic regimens. Cisplatin has response rates of approximately 33% (18% complete responses).[24] Phase 2 data on the use of carboplatin by Gaynon et al.[25] report 14 evaluable patients with ependymoma with 2/7 patients having received prior cisplatin with stable disease and no objective responses. Of the 5 patients without prior cisplatin exposure there were 2 PRs, no CRs, and 3 progressive diseases (PDs). In addition to the results from CCG-9942, there are data from several

studies using adjuvant combination chemotherapy in children with newly diagnosed ependymoma which have shown encouraging responses. White et al. found an 86% response rate to four cycles of vincristine, etoposide and cytoxan in seven children younger than 4 years of age with newly diagnosed ependymoma.[26] Mason et al. found a 16% response rate in 10 children younger than 6 years of age with newly-diagnosed ependymoma treated with 4-5 cycles of cisplatin, vincristine, etoposide, and cytoxan.[27] Duffner et al.[12] reported a 48% CR/PR response rate to two cycles of cyclophosphamide/vincristine. Geyer et al. reported a 36% CR/PR response rate to chemotherapy: 44% to a regimen of vincristine, cisplatin, etoposide, cyclophosphamide and 30% to a regimen of vincristine, carboplatin, ifosfamide, etoposide, and cyclophosphamide.[14] Selection of the chemotherapy agents, delivery schedule, and duration of treatment necessary to achieve these aims is difficult given the range of responses, differences in toxicity profiles, and lack of data from which to model such a study. However, given the favorable response rate to the combination of VCEC in a group-wide setting, there is a strong rationale to build upon the results of CCG-9942 by incorporating the VCEC regimen in the proposed study.

2.1.4 Rationale for Observation Only for Supratentorial GTR1 Differentiated Patients

There are isolated reports in the literature of some supratentorial ependymoma patients treated with surgical resection alone who have done well.[28] Therefore, this was the approach taken in ACNS0121 to test this prospectively. The preliminary results for patients who were observed only are available from ACNS0121. The group was defined to be only classic histology supratentorial ependymoma patients who had achieved a microscopic gross total resection (GTR1). Thirteen patients were enrolled. Two were declared ineligible based on central pathology and radiology review as not having ependymoma. Two of the remaining eleven patients experienced local relapses within 12 months of enrollment. Both patients were salvaged with additional surgery and radiation therapy and remain without evidence of disease at 18 and 30 months after salvage therapy. The investigators have recommended continuing this approach (observation only) for children with supratentorial classic ependymoma following microscopic gross total resection using central pathology and radiology review.

| Study | # pts | Age) | Histology | Overall Schema | Response to CT | EFS | OS |
|---|---|---|---|---|---|---|---|
| *BBSFOP* | 73 pts | < 5 years | 65 Grade III<br>8 Grade II | Surgery then chemo | None responded > 50% | 2 yr PFS 33%<br>4 yr 22% | 2 yr 79%<br>4 yr 59% |
| *Baby POG '93 Duffner* | 46 pts | < 3 years | | Surgery then chemo VCR/CTX (eval after 2 cycles) | 48% CR/PR | 2 yr 42%<br>4 yr 20% | 2 yr 74%<br>4 yr 35% |
| *CCG 9921 '2005 Geyer* | | < 3 years | Grade II & III, unclear breakdown | Surgery then chemo<br>A: Vcr/CisEtop/CTX<br>B: Vcr/Carbo/ICTX/E | A:44%<br>B:30% | 3 yr 26% | |
| *SFOP* | 73 pts | < 5 yrs | 60 (88%)<br>Grade III<br>8 (12%)<br>Grade II | Surgery + Chemo only (RT @ recurrence/prog)<br>A: Carbo, procarbazine,<br>B: Etop/cis<br>C: Vcr/CTX | Eval after A,B,C<br>Response not reported | 2 yr 33%<br>4 yr 22% | 2 yr 79%<br>4 yr 59% |
| *UKCCSG* | 89 pts<br>80 local | < 3yrs | 59 (66%)<br>Grade II | Surgery + Chemo only (RT@ recurrence/prog)<br>1: Vcr/Carbo<br>2: Vcr/MTX<br>3: Vcr CTX<br>4: Cis | Not reported | 2 yr 60 %<br>4 yr 45% | 2 yr 85%<br>4 yr 65% |
| *CCG 9942 J. Garvin 2006* | 84 pts<br>39 CT | 3-21 years | 28 Grade I<br>33 Grade III<br>14 Mixed<br>5 Unknown | Surgery + chemo + RT Vcr/CTX/Etop/Cis | 42% CR<br>18%PR | 3 yr 59.5% | 3 yr 80% |

## 2.2 Rationale for Correlative Biological Studies

Since ACNS0831 opened, there have been significant advances in our understanding of the biology of ependymoma that prompt reconsideration of the correlative biologic studies proposed in the original protocol. In particular, there are published findings that are relevant to the trial's primary aims, because they indicate that ependymomas with specific molecular characteristics could be expected to have different biologic behaviors and to be associated with distinct patient outcomes. A complete understanding of the trial aims will therefore require assessment of these molecular genetic characteristics, which fall into three categories: (i) molecular groups as defined by DNA methylation profiling, (ii) copy number variants, and (iii) specific genetic alterations.

These new biologic studies directly relating to trial aims test a central hypothesis: **ependymoma biomarkers among molecular groups, copy number variants, and specific mutations are associated with clinical and pathologic variables, including patient outcome.**

The discovery of molecular groups with distinct clinical, pathologic, and genetic characteristics among medulloblastomas has been critical to our understanding of this disease and has suggested novel therapeutic approaches based around patient stratification with conventional therapies, including irradiation dose reduction for WNT-activated

medulloblastomas and targeted chemotherapy for SHH-activated medulloblastomas with PTCH1 or SMO mutations.[29]

Medulloblastoma molecular groups were defined first by gene expression profiling and subsequently by DNA methylation profiling. Both methods have been used to define molecular groups of ependymoma. In the most comprehensive study to date, DNA methylation profiling was used to discover nine molecular groups of ependymomas drawn from a patient population chosen to represent the entire disease.[30] Three molecular groups were identified in each of the three major CNS anatomic compartments: supratentorial, infratentorial (posterior fossa), and spinal. One molecular group from each anatomic compartment was enriched with tumors showing the histopathologic features of subependymomas, which generally occur in adults. One spinal molecular group was enriched with adult myxopapillary tumors. Four molecular groups were shown to be particularly relevant to childhood disease and thus to the ACNS0831 cohort: supratentorial RELA (ST-RELA), supratentorial YAP1 (ST-YAP1), posterior fossa group A (PFA), and posterior fossa group B (PFB). A tumor from each of these four groups can present in childhood; childhood ependymomas rarely occur in the other five groups, and ependymomas in the PFA and supratentorial ST-YAP1 groups almost always occur in children.

Each of the four pediatric molecular groups is associated with a characteristic genetic or epigenetic alteration, although not all supratentorial tumors in one molecular group might have the specific alteration. ST-RELA and ST-YAP1 group tumors have RELA and YAP1 fusion genes, respectively,[30,31] but YAP1 fusion genes occur in only a minority of ST-YAP1 group tumors (Ellison, unpublished observation). PFA ependymomas are characterized by high expression of CXorf67 and reduced H3 K27-trimethylation (H3K27--me3),[32] while PFB ependymomas show the reverse, i.e., high levels of H3K27-me3.[33]

Several studies have demonstrated associations between ependymoma molecular groups and clinical variables, aside from anatomic site. Age has been mentioned above and focuses attention on four 'pediatric' molecular groups. Several studies have highlighted a difference in outcome between PFA and PFB ependymomas; PFA tumors, which mainly present in infants, have a relatively poor outcome.[30,34,35] Fewer data are available for supratentorial ependymomas, but ST-RELA ependymomas have been reported to have a worse outcome than ST-YAP1 tumors.[30] However, anecdotal evidence is emerging to suggest that the supratentorial groups might not have a significantly distinct outcome and, importantly, the prognostic value of ependymoma molecular groups has not yet been reported in a clinical trial cohort.

Multiple studies have shown that copy number status of chromosome 1, specifically 1q gain, is associated with poor outcome in pediatric PF ependymoma.[36,37] 1q gain is detected in approximately 15% of PF ependymomas, but at much lower frequencies in supratentorial or spinal ependymomas. The association with poor outcome is frequently independent of other variables.

Homozygous deletion of CDKN2A, which is detected in a small proportion (<10%) of mainly supratentorial ependymomas, has been shown to be an adverse prognostic indicator in some gliomas, e.g., pleomorphic xanthoastrocytoma and anaplastic astrocytoma with piloid features. While less is known about this copy number alteration in ependymoma, in

one study CDKN2A loss was shown to be an important prerequisite for modeling human ependymoma in the mouse,[38] and in another it was associated with a poor prognosis.[39]

As indicated above, ependymomas at different anatomic sites and in different molecular groups are characterized by specific genetic alterations. The first genomic studies of the tumor suggested that recurrent mutations were not a feature of PF ependymomas. However, subsequent studies have demonstrated that H3 K27M mutations do occur in a small proportion (4%) of PFA ependymomas.[32,40] An H3 K27M mutation has been associated with a particularly poor survival in several tumor types. It occurs in a large proportion of diffuse midline gliomas, which have a particularly poor prognosis. In addition, when an H3 K27M mutation occurs (rarely) in a WHO grade I/II glioma, patient outcome is poorer than expected.

2.2.1 Molecular groups as defined by DNA methylation profiling and immunohistochemistry

The molecular groups will be determined by DNA methylation profiling using DNA extracted from FFPE tissue and Illumina EPIC (850K) arrays. Immunohistochemistry for H3K27-me3 will also be used to identify PFA and PFB tumors.[33] The groups that will be defined are listed below.

- RELA (ST-RELA)
- YAP1 (ST-YAP1)
- PFA
- PFB

2.2.2 Copy Number Variants

The copy number variants 1q gain and CDKN2A loss can be assessed as part of the analysis of data from DNA methylation profiling arrays and will also be evaluated by interphase fluorescence in situ hybridization (iFISH).[36]

- 1q gain in posterior fossa ependymomas
- CDKN2A loss (homozygous deletion) in supratentorial ependymomas

2.2.3 Specific Genetic Alterations

iFISH with break-apart probes to RELA and YAP1 loci on 11q13 and 11q22, respectively, can be used to detect gene rearrangements and is a surrogate marker of RELA and YAP1 gene fusions in supratentorial ependymomas.[31] H3 K27M mutation can be detected by immunohistochemistry with a mutation-specific antibody that has found significant utility in diagnostic laboratories for identifying diffuse midline gliomas.[32]

- RELA fusions, specifically C11orf95-RELA fusions
- YAP1 fusions
- H3 K27M mutation

## 2.3 Rationale for Neuropsychologic Studies

As survival rates among children treated for pediatric ependymoma continue to improve with advances in treatment regimens, increased attention must be paid to the late effects of treatments and the functional outcomes of these children. Neurocognitive late effects are an important outcome to examine, as poor neurologic functioning may contribute to

limitations in age-appropriate activities of daily living such as school performance, employment, independent living, and quality of life.

It is well established that total radiation dose and volume of irradiated brain contribute to neurocognitive outcome in pediatric brain tumor survivors, with studies asserting that radiation dosimetry is the most clinically significant determinant of intellectual outcomes.[11] Several studies have found that lower doses of cranial radiation are associated with less intellectual impairment, providing evidence for the merits of reducing radiation dose and volume for localized pediatric brain tumor cases, when tumor control can be maintained.[41,42] One study of cRT found stable intellectual functioning (IQ) in children up to three years post therapy,[11] with another study showing no significant longitudinal decline in the intellectual ability of patients with infratentorial tumors who received local radiation therapy as compared to conventional craniospinal irradiation.[43]

Recent studies have begun to extend evaluation of neurocognitive outcome beyond global measures of IQ to capture specific neurocognitive domains and academic performance. Conklin and colleagues found that children with ependymoma who were treated with cRT generally performed well academically many years post-treatment.[44] However, reading skills appeared to be more vulnerable than math and spelling performance, which remained stable over time. Younger age at start of cRT was predictive of a significant decline in reading over time. While some studies have found subtle difficulties in attention and memory following radiation treatment of ependymoma,[45] others have found intact verbal and visual learning.[46] Across studies, a number of potential risk factors for poor neurocognitive outcome have been proposed, including gender, hydrocephalus at diagnosis, endocrine deficiencies, surgical complications, receiving pre-cRT chemotherapy, and younger age at cRT.

Although it is well documented that childhood brain tumor survivors are at increased risk for poor quality of life,[47] few studies have examined quality of life outcomes in ependymoma survivors specifically, and predictors of poor quality of life in this population have not been well described. In general, studies investigating both neurocognitive outcomes and quality of life in children with ependymoma have been plagued by methodological limitations, including retrospective study design and small, heterogeneous samples.[48] ACNS0831 provides a unique opportunity to characterize the neurobehavioral functioning and quality of life of children post-diagnosis of ependymoma as a function of tumor and treatment factors and patient characteristics in prospective longitudinal design.

### 2.4 Gender and Race Differences

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

## 3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

### 3.1 Study Enrollment

#### 3.1.1 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 patient with a known or suspected neoplasm needs to be offered participation in APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study.*

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

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

3.1.2 IRB Approval

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

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

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

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

For information about the submission of IRB/REB approval documents and other regulatory documents as well as checking the status of study center registration packets, please see Appendix III.

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

**Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval**

**documentation to the CTSU Regulatory Office for initial, continuing or amendment review.** For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

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

3.1.4 Timing

Patients must be enrolled on study within 56 days of initial surgical resection. Surgical resection is defined as any attempt to resect tumor that results in the tissue diagnosis of ependymoma (including biopsy). Patients must be enrolled before treatment begins.

The date protocol therapy is projected to start must be no later than 21 calendar days after the date of study enrollment.

**Enrollment onto ALTE07C1 is strongly encouraged.**

3.1.5 Bilingual Services

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

3.1.6 Mandatory Submission of Imaging Studies for Central Review (see Section 17.0)

Pre-and post-operative brain and total spine MR with and without gadolinium must be submitted to the Quality Assurance Review Center (IROC RI (QARC)) to confirm eligibility.

Please note that there are other **required** Rapid Central Imaging Review time points for patients with a sub-total resection. For all imaging requirements with timing, please see Section 17.1 and Section 17.6.

3.1.7 Mandatory Submission of Tissue for Central Pathology Review (see Section 14.0)

**All patients must have tissue submitted for central pathology review after study enrollment**.

Patients with an infratentorial primary site must have pathology slides from the time of diagnosis submitted to the COG Biopathology Center within 10 days of study enrollment**.**

**Patients with a supratentorial primary site must have RAPID CENTRAL PATHOLOGY REVIEW,** in order to avoid discordant diagnoses and to verify diagnosis criterion for treatment stratification**. Pathology slides must be marked RAPID REVIEW and submitted by Federal Express Priority Overnight to the Biopathology Center within 5 days of study enrollment (see** Section 14.0 **for information regarding specimen submission). Results of rapid central review will be available within 1 week of the submission of pathology review materials.**

3.1.8 Assignment to Treatment Arms and Randomization

Patients will be randomized or non-randomly assigned to treatment arms based upon 1) the extent of resection, 2) tumor histology, and 3) tumor location.

NOTE: Treatment or randomization for supratentorial patients cannot be started until the central pathology review results are available.

**Randomization**

For patients eligible for randomization after initial surgery, randomization should occur as soon as possible after enrollment using the Callback function of the Member Site. Patients must be randomized **prior** to radiation. Patients who will receive proton therapy are eligible for this study. Definitions for extent of surgical resection can be found in Section 4.1.

**Supratentorial Patients**

Patients with **classic histology supratentorial disease** who have GTR1 after initial surgery will be non-randomly assigned to Observation only. Rapid central pathology review will be performed on all supratentorial tumors to confirm eligibility for observation only after enrollment. See Section 14.2.1 for discordant diagnosis.

Supratentorial patients with 1) GTR2 or 2) NTR, and with 3) anaplastic histology or 4) indeterminate grade histology will be Randomized.

**Infratentorial Patients**

Patients with an infratentorial primary tumor that have a total or near total resection ([GTR1 or GTR2 or NTR] definitions in Section 4.1) regardless of histology will be Randomized.

**STR (Incomplete Resection) Patients**

Patients with a sub-total resection (STR) (definition in Section 4.1) after initial surgery will be non-randomly assigned to Induction chemotherapy. Induction chemotherapy consists of 7 weeks (2 cycles) of chemotherapy. At the end of induction, patients must have rapid central imaging review to confirm response to therapy and determine the next steps.

**Patients with a Complete Response following Induction:**

*Supratentorial Classic Histology*: patients with a classic histology supratentorial tumor that have a CR following Induction chemotherapy will be non-randomly assigned to Observation.

*Infratentorial with Any Histology and Supratentorial Anaplastic Histology*: those who have a CR (see definition in Section 10.0) following Induction chemotherapy and have either an infratentorial primary or a supratentorial anaplastic primary tumor will be Randomized.

**Patients with Stable Disease, Partial Responses, Progressive Disease following Induction:**
Patients with stable disease (SD), partial response (PR), or locally progressive disease (LPD) (see definitions in Section 10.4) after Induction chemotherapy will undergo second surgery when possible. There is no limit to the number of surgical procedures performed after Induction chemotherapy and prior to cRT.

**Following Second Surgery**
Patients with an infratentorial primary or supratentorial anaplastic primary tumor who have a GTR1, GTR2, or NTR after second surgery will then be Randomized.

Patients with residual disease after second surgery will be non-randomly assigned to receive cRT followed by maintenance chemotherapy.

Patients with supratentorial classic primary tumor who have a GTR1 after second surgery will be assigned to Observation only.

Detailed information about the Treatment Plan including randomization at diagnosis and following induction chemotherapy and/or second surgery can be found in Section 4.0.

## 3.2 Patient Eligibility 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.**

INCLUSION CRITERIA

### 3.2.1 Age

Patients must be greater than 12 months of age and less than 21 years of age at the time of study enrollment.

### 3.2.2 Diagnosis

3.2.2.1 Patients must be newly diagnosed with histologically confirmed intracranial ependymoma. Patients with classic ependymoma (WHO II) or anaplastic ependymoma (WHO III) are eligible, as are various subtypes described as clear cell, papillary, cellular, or a combination of the above.

Note: Please see imaging and pathology requirements in Section 3.1.6 and Section 3.1.7.

3.2.4 Performance Level

There is no minimum performance level. Children with ependymoma may suffer neurologic sequelae as a result of their tumor or surgical measures taken to establish a diagnosis and resect the tumor. In the majority of cases there is neurologic recovery. Neurologic recovery is not likely to be impeded by protocol therapy.

EXCLUSION CRITERIA

3.2.5 Metastatic Disease

Patients with evidence of metastatic disease will be excluded. Any evidence of non-contiguous spread beyond the primary site as determined by pre- or post-operative MR imaging of brain, pre- or post-operative MR imaging of the spine, and post-operative CSF cytology obtained from the lumbar CSF space (the requirement for lumbar CSF examination may be waived if deemed to be medically contraindicated). CSF cytology from a ventriculostomy or permanent VP shunt that reveals the presence of tumor cells is indicative of metastatic disease.

3.2.6 Ineligible Diagnoses

Patients with a diagnosis of spinal cord ependymoma, myxopapillary ependymoma, subependymoma, ependymoblastoma, or mixed glioma are NOT eligible.

3.2.7 Prior Therapy

No prior treatment other than surgical intervention and corticosteroids. Patients are allowed to have had more than one attempt at resection prior to enrollment.

3.2.8 Pregnant female patients are not eligible for this study.

3.2.9 Post-menarchal females may not participate unless a pregnancy test with a negative result has been obtained.

3.2.10 Males and females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

3.2.11 Lactating females may not participate unless they have agreed not to breastfeed a child while on this study.

REGULATORY

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

3.2.13 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).

Once a patient has been determined to be eligible for protocol treatment, patients will be randomized or non-randomly assigned to treatment arms based upon the extent of resection, tumor histology, and tumor location.

Patients with Gross Total Resection Supratentorial Classic Ependymoma (GTR1) will be observed provided that rapid central pathology review (see Section 14.2.1) confirms the diagnosis of classic ependymoma and post-operative neuroimaging confirms that there is no evidence of disease. If the patient is found not to have classic ependymoma, they will be randomized and reconsented to the Randomized Treatment Arm and randomized.

The three treatment arms include:

1. Induction chemotherapy followed by surgery, cRT, maintenance chemotherapy, observation, or a combination depending on the response;
2. cRT followed by maintenance chemotherapy or observation;
3. Observation only

In cases when the extent of resection or histologic grade is indeterminate, patients will be randomized between radiation followed by maintenance chemotherapy or radiation followed by observation. These instances may include:

1. Surgeon cannot unequivocally report absence of microscopic disease;
2. Histologic grade is indeterminate;
3. Info necessary to determine extent of resection at time of operation is unavailable.

Induction chemotherapy consists of 2 cycles given over 7 weeks, and is outlined in Section 4.5. Guidelines for second surgery are discussed in Section 13.0. Radiation therapy will last 6-7 weeks depending on the dose. Radiation therapy will be directed at the primary site using an anatomically defined clinical target volume margin of 5 mm beyond the gross tumor volume (see Section 18.0 for cRT details), followed by maintenance chemotherapy or observation only. Patients receiving proton beam therapy are eligible. Post-radiation maintenance chemotherapy consists of four 21-day cycles (see Section 4.6 for details).

MR imaging is required for radiation treatment planning. Although the immediate post-operative MR evaluation may be used, it is preferable to obtain an MR within 3 weeks (or coincident with radiation therapy planning) and no greater than 4 weeks prior to the initiation of radiation therapy.

Rapid central review of imaging for response evaluation will be conducted following induction chemotherapy and second surgery (see Section 17.0 for details). MRIs should be obtained between Day 21 and 29 of Cycle B induction chemotherapy, and within 72 hours post-operatively. MRIs must be submitted to IROC RI (QARC) within 3 days for Rapid Central Review.

## 4.1 Surgery and Extent of Resection Guidelines

Guidelines to define the extent of resection at the time of initial and second surgery (if applicable) are critical to the performance of this trial. Patients are allowed to have had more than one attempt at resection prior to enrollment. Extent of resection may be classified for purposes of therapy and analysis as follows:

### 4.1.1 GTR1 (Gross Total Resection 1)

No residual tumor identified with the operating microscope and no evidence of disease on post-operative neuroimaging.

### 4.1.2 GTR2 (Gross Total Resection 2)

Microscopically visible residual tumor identified with the operating microscope and no evidence of disease on post-operative neuroimaging.

### 4.1.3 NTR (Near Total Resection)

Residual tumor evident on post-operative neuroimaging with thickness or nodularity measuring less than or equal to 5 mm in greatest dimension. Linear "streak" enhancement or signal intensity changes are not included in the measurement of residual tumor to determine near-total versus sub-total resection.

### 4.1.4 STR (Sub-Total Resection)

Residual tumor on post-operative imaging measuring greater than 5mm in nodularity or thickness. The definition of STR includes any surgical intervention that removes tissue that may be documented by pathology as tumor. A biopsy is an STR. More information is available in Section 4.2.3.

## 4.2 Treatment Plan by Extent of Resection, Histology, and Tumor Location at Time of Enrollment

### 4.2.1 Supratentorial Anaplastic Ependymoma (GTR1, GTR2, NTR), Anaplastic or Classic Infratentorial Ependymoma (GTR1, GTR2, NTR), and Supratentorial Classic Ependymoma (GTR2, NTR)

Patients will be randomized to receive either a) cRT and maintenance chemotherapy **OR** b) to receive cRT and observation.

### 4.2.2 Gross Total Resection Supratentorial Classic Ependymoma (GTR1)

Patients will be observed provided that rapid central pathology review (see Section 14.2.1) confirms the diagnosis of classic ependymoma and post-operative neuroimaging confirms that there is no evidence of disease. The operating neurosurgeon should explicitly state in the written operative report that no visible microscopic disease was apparent through the operating microscope.

Patients who are enrolled on this treatment arm and experience local recurrence will be taken off protocol therapy and receive therapy at the discretion of the treating physician.

4.2.3 Sub-Total Resection Any Histology or Location (STR)

All patients with a sub-total resection will receive two cycles of induction chemotherapy. At the completion of induction, the patient will undergo evaluation for chemotherapy response via rapid central imaging review (see Section 17.0). The evaluation will be used to determine the response to chemotherapy and the possibility of second surgery. There is no limit to the number of surgical procedures performed after induction chemotherapy and prior to radiation therapy. For patients who undergo second resection(s), the extent of resection and morbidity of surgery will be assessed, including confirmation of extent of resection by rapid central imaging review of post-operative MRIs (see Section 17.0).

Patients who develop metastatic disease (see definition in Section 10.4) at any time during protocol treatment will be taken off protocol therapy.

## 4.3 Randomization or Assignment for STR Patients Receiving Induction Chemotherapy

Induction Chemotherapy Response

Patients with supratentorial classic tumors who achieve a CR to induction chemotherapy will not undergo a second surgery and will be assigned to Observation.

Patients with other than supratentorial classic tumors who have a CR to induction chemotherapy will not undergo second surgery and will be randomized. Radiation should begin within 30 days after completion of induction chemotherapy (Day 28 of Cycle B) and maintenance chemotherapy should begin within 30 days of completion of radiation therapy.

Patients with SD/PR or local progression (see definition in Section 10.4) after induction chemotherapy should undergo second resection if deemed safely feasible by the institutional neurosurgeon. Second surgery should occur within 15 days after the completion of induction chemotherapy, (defined as Day 28 of Cycle B) and patients must have achieved count recovery post nadir. If a patient is unable to safely undergo second surgery or begin radiation due to inadequate count recovery, please notify the Study Chair.

Second Surgery

There might be situations in which a patient assessed after their initial surgery would not appear to be a candidate for second surgery due to tumor location or complications. However, the final decision about re-resection should be reserved until after chemotherapy has been completed. After the initial surgery and during the time period for which the chemotherapy has been planned, normal brain has a tendency to shift and reposition itself into a more natural configuration. Also, the appearance and extent of the residual tumor might become clearer, which could influence decisions about second surgery.

When, after thorough consideration, it has been determined by the primary oncology team that second surgery would not be in the best interest of the patient, the patient should proceed directly to cRT and maintenance chemotherapy after notifying the Study Chair. Conformal radiation therapy should begin within 30 days after the completion of induction (defined as Cycle B Day 28). Maintenance chemotherapy should begin within 30 days of completion of cRT.

Patients with supratentorial classic tumor who achieve GTR1 after second resection will be non-randomly assigned to Observation. Patients with an infratentorial primary tumor or a supratentorial anaplastic tumor who achieve a GTR/NTR after second resection will be randomized.

Patients with residual disease (STR) after second resection will be non-randomly assigned to receive radiation therapy followed by maintenance chemotherapy. Radiation should begin within 30 days of second surgery. If radiation therapy is delayed beyond 30 days, please notify the Study Chair. Maintenance chemotherapy should begin within 30 days of completion of radiation therapy.

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## 4.4 Concomitant Therapy Restrictions during Treatment

4.4.1
No other cancer chemotherapy or immunomodulating agents will be used.

4.4.2
Clinically significant drug interactions have been reported when using vincristine with strong cytochrome P450 isoform CYP3A4 inhibitors and inducers. Strong inhibitors of cytochrome CYP3A4 are known to alter vincristine metabolism, leading to increased vincristine neurotoxicity. Selected strong inhibitors or stimulators of cytochrome P450 3A4, include azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort. These drugs should be avoided with vincristine.

The clinical outcome and significance of CYP450 interactions with cyclophosphamide and etoposide are less clear. CYP450 3A4 stimulators or inhibitors should be avoided or used with great caution. Aprepitant also interacts with CYP3A4 and should be used with caution with etoposide or vincristine chemotherapy. Additional inducers or inhibitors of CYP450 enzymes can be found at http://medicine.iupui.edu/clinpharm/ddis.

4.4.3
Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care are to be used as necessary. Corticosteroids should not be used during chemotherapy administration as an antiemetic because of their effect on the blood-brain barrier.

See Section 7.0 for baseline studies to be obtained prior to starting Induction therapy or cRT. See Section 17.0 for imaging studies to be obtained following induction therapy and prior to cRT. Note the imaging studies should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT (post-op imaging can be used).

## 4.5 Induction Chemotherapy

Patients with sub-total resection any histology or location (STR) will receive induction chemotherapy. Induction chemotherapy should begin within 21 days following study enrollment. Induction chemotherapy consists of one cycle of Cycle A (vincristine, carboplatin, cyclophosphamide) and one cycle of Cycle B (vincristine, carboplatin, etoposide). The entire length of the induction chemotherapy phase is 7 weeks unless delay occurs due to myelosuppression or unanticipated toxicity.

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

4.5.1 Induction Cycle A (Weeks 1–3)

**Dose calculations should be based on actual BSA. There is no maximum dosing, except for vincristine which is capped at a maximum dose of 2 mg.**

To begin Induction Cycle A, patients must have ANC > 1000/μL and platelets > 100,000/μL.

**VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy.**
Days: 1 and 8
Dose: 1.5 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 0.05 mg/kg/dose (**max. dose is 2 mg**).

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine.

**CARBOplatin: IV over 15–60 minutes**
Day: 1
Dose: 375 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$, the dose is 12.5 mg/kg/dose.
Note: Infuse the diluted solution (to a concentration as low as 0.5 mg/mL). Avoid use of aluminum containing needles or administration sets.

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

**Cyclophosphamide: IV over 30–60 minutes**
Days: 1 and 2
Dose: 1000 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$, the dose is 33 mg/kg/dose.
Note: Administer cyclophosphamide after carboplatin administration. May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

**Mesna: IV (Short or Continuous Infusion*)**
Days: 1 and 2
Total IV Dose: 600 mg/m$^2$/day. For patients with BSA < 0.45 m$^2$, the dose is 20 mg/kg/day.

***IV short infusion:** For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily cyclophosphamide dose and is administered in 3 divided doses (200 mg/m$^2$/dose or 6.7 mg/kg/dose if BSA < 0.45 m$^2$) by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide).

Hour 4 and 8 mesna can be given orally if the patient is able to tolerate oral intake (without vomiting). The oral dose of mesna is **twice** the IV dose. Patients may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6. **For example:** if the cyclophosphamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

This total daily dose can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of the cyclophosphamide infusion.

**Myeloid Growth Factor: Subcutaneous (preferred) or IV**
Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1,500/µL after the expected nadir. Myeloid growth factor support need not be limited to filgrastim or biosimilar; pegfilgrastim is also permitted according to the institution's standard guidelines. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

The therapy delivery map (TDM) for Induction Cycle A is on the next page.

Begin Cycle B of Induction chemotherapy on Day 22 or when blood count parameters are met (whichever occurs later). Patient must be off myeloid growth factor for at least 24 hours before starting Induction Cycle B.

## 4.5.2 Induction Cycle A - Patients with STR after first surgery

| Induction Cycle A - Patients with STR after first surgery<br>Induction consists of two cycles (Cycle A and Cycle B).<br>Cycle A is given Weeks 1-3.<br>This cycle lasts 3 weeks (21 days). | _____<br>Patient name or initials<br><br>_____<br>DOB |
|---|---|

*Criteria to start Cycle A:* ANC > 1000/µL and platelets > 100,000/µL. Extensive details are in Section 4.0 (Treatment Overview) and Section 4.5.1. This cycle lasts 3 weeks (21 days) and this TDM is on **1** page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute[%] | 1.5 mg/m$^2$/dose<br>or<br>0.05 mg/kg/dose<br>for pts with BSA < 0.45 m$^2$ | 1 and 8 | [%]Or infusion via minibag as per institutional policy.<br><br>**Maximum dose is 2 mg.** | a. History, Physical Exam, Weight, Height<br>b. Neurologic Assessment<br>c. MR Brain with gadolinium<br>d. MR Spine with gadolinium<br>e. Electrolytes (Ca++, $PO_4$, Mg++, BUN)<br>f. Serum Creatinine or GFR or Creatinine Clearance<br>g. Liver function (ALT, AST, Bili)<br>h. Urinalysis<br>i. CBC (diff, platelets)<br>j. Audiogram or BAER<br><br>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE |
| CARBOplatin (CARBO ) | IV over 15-60 minutes | 375 mg/m$^2$/dose<br>or<br>12.5 mg/kg/dose<br>for pts with BSA < 0.45 m$^2$ | 1 | Administer **prior** to cyclophosphamide. | |
| Cyclophosphamide (CPM ) | IV over 30-60 minutes | 1000 mg/m$^2$/dose<br>or<br>33 mg/kg/dose<br>for pts with BSA < 0.45 m$^2$ | 1 and 2 | Administer **after** CARBOplatin administration. | |
| Mesna (MESNA) | IV (short or continuous infusion [CI]) | **See Section 4.5.1.** | 1 and 2 | Total IV dose: 600 mg/m$^2$/day or 20 mg/kg/day if BSA < 0.45 m$^2$<br><br>Administer **concurrently** with cyclophosphamide. | |
| Myeloid Growth Factor | SubQ (preferred) or IV | See Important Note | Daily*, beginning on Day 3 | * Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) on Day 3, until the ANC is > 1,500/µL after the expected nadir. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle. | |

**Ht____cm Wt___kg BSA____m$^2$**

| Date Due | Date Given | Day | VCR<br>____mg | CARBO<br>____mg | CPM<br>____mg | MESNA<br>___mg __mg __mg | Myeloid Growth Factor@<br>Growth Factor Used: _____<br>___mcg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below.** | | | | | | |
| | | 1 | ____mg | ____mg | ____mg | ___mg __mg __mg | | a, b, c&, e, f, g, h, i, j | |
| | | 2 | | | ___mg | ___mg __mg __mg | | | |
| | | 3 | | | | | ___mcg | | |
| | | 8 | ____mg | | | | | e$, f$, g$, i | |
| | | 15 | | | | | | e$, f$, g$, i | |
| | | 21 | | | | | | e$, f$, g$, i | Indicate date of last myeloid growth factor dose<br>_____ |
| | | 22 | Start next cycle (Cycle B, Section 4.5.3) on Day 22 or when blood count parameters are met (whichever occurs later). Patient must be off myeloid growth factor for at least 24 hrs before starting Cycle B. | | | | | | |

OBSERVATION NOTES:

@ Stop myeloid growth factor at least 24 hours prior to next chemotherapy cycle.

$ Repeat weekly if abnormal.

& If post-op cranial MRI was performed > 21 days before the first day of chemo, repeat cranial MRI with gadolinium to provide an appropriate baseline.

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.**

4.5.3 Induction Cycle B (Weeks 4–7 of Induction)

**Dose calculations should be based on actual BSA. There is no maximum dosing, except for vincristine, which is capped at a maximum dose of 2 mg.**

To begin Induction Cycle B, patients must have ANC > 1000/μL and platelets > 100,000/μL and not have had myeloid growth factor administered for at least one day (24 hours).

**VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy**
Days: 1 and 8
Dose: 1.5 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$, the dose is 0.05 mg/kg/dose. (**max. dose is 2 mg**).

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine.

**Etoposide: IV over 60–120 minutes***
Days: 1, 2, and 3
Dose: 100 mg/m$^2$/dose. Give immediately prior to carboplatin on Day 1. For patients with BSA < 0.45m$^2$, the dose is 3.3mg/kg.

Note: Infuse as diluted solution (concentration ≤ 0.4 mg/mL); *slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m$^2$/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or $D_5W$. Avoid use of large volumes of $D_5W$ due to potential development of hyponatremia.

**CARBOplatin: IV over 15 – 60 minutes**
Day: 1
Dose: 375 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$, the dose is 12.5 mg/kg/dose.
Note: Infuse the diluted solution (to a concentration as low as 0.5 mg/mL). Avoid use of aluminum containing needles or administration sets.

Patients who have compromised renal function should undergo a GFR. If the GFR is < 100 mL/min/1.73m$^2$ the carboplatin dose should be modified according to Section 5.0.

**Myeloid Growth Factor: Subcutaneous (preferred) or IV**
Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1,500/µL after the expected nadir. Myeloid growth factor support need not be limited to filgrastim or biosimilar; pegfilgrastim is also permitted according to the institution's standard guidelines. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

**See Section 5.0 for Dose Modifications based on Toxicities.**

After patients have completed the induction chemotherapy phase, MR of the brain should be performed between Day 21 and 29 of Cycle B to evaluate the feasibility of second surgery. **MRIs must be submitted for Rapid Central Review of response (see Section 17.0 for details).**

Patients with supratentorial/classic tumors who achieve a CR by induction chemotherapy **or** achieve a GTR1 at second surgery will be assigned to observation alone.

Patients who achieve SD/PR or have locally progressive disease (see definition in Section 10.4) after induction chemotherapy who are deemed potentially resectable will go on to second surgery.

Anaplastic supratentorial patients and infratentorial patients (any histology) who achieve a CR by induction chemotherapy or who achieve a complete resection (GTR/NTR) at second surgery will go on to be randomized between either: (a) cRT followed by maintenance chemotherapy **OR** (b) cRT followed by Observation.

Second surgery should be performed within 15 days after completing induction chemotherapy, which is defined as Day 28 of Cycle B. Conformal radiation therapy should begin within 30 days after completing induction chemotherapy or second surgery. The timelines for performance of second surgery and conformal radiation therapy are not rigid. There is no limit to the number of surgery procedures performed following induction chemotherapy. See Section 13.5 for more details.

Evidence of metastatic disease at any time during protocol therapy will remove the patient from protocol therapy.

For cRT details, see Section 18.0. For surgical guidelines, see Section 13.0. For assessments to be obtained during Observation only, see Section 7.4.

The therapy delivery map (TDM) for Induction Cycle B is on the next page.

## 4.5.4 Induction Cycle B - Patients with STR after first surgery

| Induction Cycle B - Patients with STR after first surgery<br>Induction consists of two cycles (Cycle A and Cycle B).<br>Cycle B is given Weeks 4-7.<br>This Cycle lasts 4 weeks (28 days). | _____<br>Patient name or initials<br>_____<br>DOB |
|---|---|

Criteria to start Cycle B: ANC > 1000/µL and platelets > 100,000/µL and no myeloid growth factor administered for at least the preceding day (24 hours), and adequate renal function. Extensive details are in Section 4.0 (Treatment Overview) and Section 4.5.3. This course lasts 4 weeks (28 days) and this TDM is on **1** page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute[&] | 1.5 mg/m$^2$/dose<br>or<br>0.05 mg/kg for pts with BSA < 0.45 m$^2$ | 1 and 8 | [&]Or infusion via minibag as per institutional policy<br><br>**Maximum dose is 2 mg**. | a. History, Physical Exam, Weight, Height<br>b. Neurologic Assessment<br>c. MR Brain with gadolinium<br>d. MR Spine with gadolinium<br>e. Electrolytes (Ca++, $PO_4$, Mg++, BUN)<br>f. Serum Creatinine or GFR or Creatinine Clearance<br>g. Liver function (ALT, AST, Bili)<br>h. Urinalysis<br>i. CBC (diff, platelets)<br>j. Audiogram or BAER<br><br>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE |
| Etoposide (ETOP ) | IV over 60-120 minutes+ | 100 mg/m$^2$/dose or 3.3 mg/kg for patients with BSA < 0.45m$^2$ | 1, 2, and 3 | +Slow rate of administration if hypotension occurs. Give Immediately prior to carboplatin on Day 1. | |
| CARBOplatin (CARBO ) | IV over 15-60 minutes | 375 mg/m$^2$/dose<br>or<br>12.5 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1 | See dose modifications for renal function in Section 5.1. | |
| Myeloid Growth Factor | SubQ (preferred) or IV | See Important Note | Daily*, beginning on Day 4 | * Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) on Day 3, until the ANC is > 1,500/µL after the expected nadir. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle. | |

**Ht____cm Wt____kg BSA____m$^2$**

| Date Due | Date Given | Day | VCR<br>____mg | CARBO<br>____mg | ETOP<br>____mg | Myeloid Growth Factor[#]<br>Growth Factor Used: _____<br>___ mcg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below.** | | | | | |
| | | 1 | ____mg | ____mg | ____mg | | a, b, e, f, g, h, i, j | |
| | | 2 | | | ____mg | | | |
| | | 3 | | | ____mg | | | |
| | | 4 | | | | ___ mcg | | |
| | | 8 | ____mg | | | | e$, f$, g$, i | |
| | | 15 | | | | | e$, f$, g$, i | |
| | | 21 | | | | | c%, d%, e$, f$, g$, i | |
| | | 28 | | | | | | Indicate date of last myeloid growth factor dose _____ |
| | | 29 | Upon completion of Induction Cycle B, patients will undergo response evaluation, and receive further protocol therapy as outlined in Section 4.5.3. Patients with metastatic disease following Cycle B are off protocol therapy. | | | | | |

OBSERVATION NOTES:

$ Repeat weekly if abnormal. % Neuroimaging should be obtained between Days 21-29.

# Stop myeloid growth factor at least 24 hours prior to next chemotherapy cycle.

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.**

## 4.6 Maintenance Chemotherapy

Maintenance chemotherapy is for patients randomized to receive maintenance chemotherapy and for STR patients with residual disease after second surgery (see Section 4.2).

Maintenance chemotherapy consists of four repeated 21-day cycles. The first three cycles will comprise vincristine, cisplatin, etoposide, and cyclophosphamide (see Section 4.6.1). The fourth cycle will comprise cisplatin, etoposide, and cyclophosphamide, without vincristine (see Section 4.6.3).

*Criteria to start each Maintenance cycle:* ANC > 1000/μL and platelets > 100,000/μL, and no myeloid growth factor administered for at least the preceding day (24 hours). An additional criterion to start Cycles 1 and 3 is adequate renal function Maintenance chemotherapy should begin within 30 days of completion of cRT.

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

### 4.6.1 Maintenance Chemotherapy Cycles 1 through 3

**Dose calculations should be based on actual BSA. There is no maximum dosing, except for vincristine which is capped at a maximum dose of 2 mg.**

**VinCRIStine: Administer IV push over 1 minute or infusion via minibag as per institutional policy.**
Days: 1, 8, and 15
Dose: 1.5 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 0.05 mg/kg (**max. dose is 2 mg**).

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine.

**Etoposide: IV over 60–120 minutes**
Days: 1, 2, and 3
Dose: 100 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 3.3 mg/kg.
Note: Administer immediately prior to CISplatin or cyclophosphamide. Infuse as diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m$^2$/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or $D_5W$. Avoid use of large volumes of $D_5W$ due to potential development of hyponatremia.

**CISplatin: IV over 1–8 hours**
Day: 1
Dose: 100 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 3.3 mg/kg/dose.
Note: Hydrate patients before and after CISplatin administration. See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for suggestions.

Special precautions: Avoid use of aluminum containing needles or administration sets, since aluminum interacts with CISplatin causing black precipitate formation and loss of potency. The infusion solution should include at least 0.2% sodium chloride. CISplatin solutions should not be refrigerated to avoid precipitation. Protect from light. 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®).

**Cyclophosphamide: IV over 30-60 minutes**
Days: 2 and 3
Dose: 1000 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 33 mg/kg/dose.
Note: Administer cyclophosphamide after CISplatin administration. May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

**Mesna: IV (short or continuous infusion*)**
Days: 2 and 3
Total IV Dose: 600 mg/m$^2$/day. For patients with BSA < 0.45 m$^2$ the dose is 20 mg/kg/day.
***IV short infusion:** For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily cyclophosphamide dose and is administered in 3 divided doses (200 mg/m$^2$/dose or 6.7 mg/kg/dose if BSA < 0.45 m$^2$) by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide. Hour 4 and 8 mesna can be given orally if the patient is able to tolerate oral intake (without vomiting).

The oral dose of mesna is **twice** the IV dose. Patients may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6. **For example:** if the cyclophosphamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

This total daily dose can also be administered as IV **continuous infusion**. The continuous infusion should be started 15–30 minutes before or at the same time as

cyclophosphamide and finished no sooner than 8 hours after the end of the cyclophosphamide infusion.

**Myeloid Growth Factor: Subcutaneous (preferred) or IV**
Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1,500/μL after the expected nadir. Myeloid growth factor support need not be limited to filgrastim or biosimilar; pegfilgrastim is also permitted according to the institution's standard guidelines. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

**See Section 5.0 for Dose Modifications based on Toxicities.**

Upon completion of one cycle, do not start the next cycle of Maintenance chemotherapy until 24 hours after the last dose of myeloid growth factor, and ANC > 1000/μL and platelets > 100,000/μL.

Following completion of the first 3 cycles of Maintenance Therapy (with vincristine) proceed with cycle 4 of Maintenance Therapy (without vincristine). Cycle 4 of Maintenance Therapy is detailed in Section 4.6.3. See Section 4.6.4 for the Therapy Delivery Map for Maintenance Cycle 4.

The therapy delivery map (TDM) for Maintenance Chemotherapy Cycles 1 through 3 is on the next page.

## 4.6.2 Maintenance Cycles 1–3

### Maintenance Cycles 1–3

Maintenance should begin within 30 days after completion of radiation therapy. **This course is for patients randomized to receive maintenance chemotherapy and for STR patients with residual disease after second surgery** (see Section 4.2). This course consists of one 21-day cycle repeated three times. This Course lasts 9 weeks (63 days). This therapy delivery map relates to Cycles 1, 2, and 3 of Maintenance. See Section 4.6.4 for the Therapy Delivery Map for Maintenance Cycle 4. Use a copy of this page once for each cycle. *(Please note cycle number below.)*

_____
Patient name or initials

_____
DOB

*Criteria to start each cycle:* ANC > 1000/µL and platelets > 100,000/µL, and no G-CSF administered for at least the preceding day (24 hours). Additional criteria to start Cycles 1 and 3: Adequate renal function. Details are in Section 4.0 (Treatment Overview). This course lasts 9 weeks (63 days) and this TDM is on **1** page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES |
|---|---|---|---|---|
| VinCRIStine (VCR) | IV push over 1 minute** | 1.5 mg/m$^2$/dose or 0.05 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1, 8 and 15 of Cycles 1-3 only | **Or infusion via minibag as per institutional policy.<br>Maximum dose is 2 mg. |
| Etoposide (ETOP) | IV over 60 -120 minutes+ | 100 mg/m$^2$/dose or 3.3 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1, 2 and 3 | +Slow rate of administration if hypotension occurs.<br>Administer immediately **prior to** CISplatin or cyclophosphamide administration. |
| CISplatin (CDDP) | IV over 1-8 hours (use institutional standards) | 100 mg/m$^2$/dose or 3.3 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1 | Hydrate patients before and after CISplatin administration. See CAGs for suggestions. |
| Cyclophosphamide (CPM) | IV over 1 hour | 1000 mg/m$^2$/dose or 33 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 2 and 3 | Administer **after** CISplatin administration. |
| Mesna (MESNA) | IV (Short or continuous [CI]) | **See Section 4.6.** | 2 and 3 | **Total IV dose: 600 mg/m$^2$/day or 20 mg/kg/day if BSA < 0.45 m$^2$**<br>Administer **concurrently with** CPM. |
| Myeloid Growth Factor | SubQ (preferred) or IV | See Important Notes | Daily, starting on Day 4 | Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) on Day 3, until the ANC is > 1,500/µL after the expected nadir. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle. |

**OBSERVATIONS**

a. History, Physical Exam, Weight, Height
b. Neurologic Assessment
c. MR Brain with gadolinium
d. MR Spine with gadolinium
e. Electrolytes (Ca++, $PO_4$, Mg++, BUN)
f. Serum Creatinine or GFR or Creatinine Clearance
g. Liver function (ALT, AST, Bili)
h. Urinalysis
i. CBC (diff, platelets)
j. Audiogram or BAER
k. Echocardiogram or Ejection Fraction

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

**Please enter Cycle # _____ Ht____cm Wt____kg BSA____m$^2$**

| Date Due | Date Given | Day | VCR ____mg | ETOP ____mg | CDDP ____mg | CPM _____mg | MESNA __mg __mg __mg | Myeloid Growth Factor* Growth Factor Used: _____ ___mcg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below.** | | | | | | | |
| | | 1 | ____mg | ____mg | ____mg | | | | a, b, c#, d#, e, f%, g, h, j, j, k# | |
| | | 2 | | ____mg | | ____mg | ____mg ____mg ____mg | | | |
| | | 3 | | ____mg | | ____mg | ____mg ____mg ____mg | | | |
| | | 4 | | | | | | ____mcg | | |
| | | 8 | ____mg | | | | | | a, e$, f$, g$, i | |
| | | 15 | ____mg | | | | | | a, e$, f$, g$, i | |
| | | 21 | | | | | | | a, e$, f$, g$, i | Indicate date of last myeloid growth factor dose ____ |
| | | 22 | Start next cycle of Maintenance on Day 22 or when cycle starting criteria are met (whichever occurs later). Patient must be off myeloid growth factor for at least 24 hrs before starting Cycles 2-4. | | | | | | | |

OBSERVATION NOTES:

* Stop myeloid growth factor at least 24 hours prior to next chemotherapy cycle.
# Obtain within 1 week prior to Cycle 1 only.
$ Repeat weekly if abnormal.
% Obtain prior to Cycle 1 and 3 only

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.**

4.6.3 Maintenance Chemotherapy Cycle 4

Note: Cycle 4 of Maintenance Therapy does NOT include vinCRIStine.

**Dose calculations should be based on actual BSA. There is no maximum dosing.**

**Etoposide: IV over 60–120 minutes**
Days: 1, 2, and 3
Dose: 100 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 3.3 mg/kg.
Note: Administer immediately prior to CISplatin or cyclophosphamide. Infuse as diluted solution (concentration ≤ 0.4 mg/mL); slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m$^2$/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or $D_5W$. Avoid use of large volumes of $D_5W$ due to potential development of hyponatremia.

**CISplatin: IV over 1–8 hours**
Day: 1
Dose: 100 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 3.3 mg/kg.
Note: Hydrate patients before and after CDDP administration. See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://www.cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for suggestions.

Special precautions: Avoid use of aluminum containing needles or administration sets, since aluminum interacts with cisplatin causing black precipitate formation and loss of potency. The infusion solution should include at least 0.2% sodium chloride. CISplatin solutions should not be refrigerated to avoid precipitation. Protect from light. 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®).

**Cyclophosphamide: IV over 30–60 minutes**
Days: 2 and 3
Dose: 1000 mg/m$^2$/dose. For patients with BSA < 0.45 m$^2$ the dose is 33 mg/kg/dose.
Note: Administer cyclophosphamide after CISplatin administration. May be administered as undiluted drug (20 mg/mL, reconstitute with 0.9% NaCl only to avoid hypotonic solution) or further diluted.

**Mesna: IV (short or continuous infusion*)**
Days: 2 and 3
Total IV Dose: 600 mg/m$^2$/day. For patients with BSA < 0.45 m$^2$ the dose is 20 mg/kg/day.
***IV short or continuous infusion:** For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 60% of the daily cyclophosphamide dose and is administered in 3 divided doses (200 mg/m$^2$/dose or 6.7 mg/kg/dose if BSA < 0.45 m$^2$) by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may

be administered 15 minutes before or at the same time as the cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide.

Hour 4 and 8 mesna can be given orally if the patient is able to tolerate oral intake (without vomiting). The oral dose of mesna is **twice** the IV dose. Patients may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6. **For example:** if the cyclophosphamide dose is 1,000 mg, then 200 mg of mesna will be given IV 15 minutes before or with the cyclophosphamide dose (Hour 0) and the **TWO** oral doses of 400 mg each will be given at Hours 2 and 6.

This total daily dose can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of the cyclophosphamide infusion.

**Myeloid Growth Factor: Subcutaneous (preferred) or IV**
Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) 24 hours after myelosuppressive chemotherapy, until the ANC is > 1,500/μL after the expected nadir. Myeloid growth factor support need not be limited to filgrastim or biosimilar; pegfilgrastim is also permitted according to the institution's standard guidelines. May be continued without regard to vinCRIStine. Discontinue at least 24 hours before the start of the next chemotherapy cycle.

**See Section 5.0 for Dose Modifications based on Toxicities.**

Following completion of the Cycle 4 of Maintenance Therapy, protocol therapy is complete. See Section 7.0 for required observations following end of therapy.

The therapy delivery map (TDM) for Maintenance Chemotherapy Cycle 4 is on the next page.

## 4.6.4 Maintenance Cycle 4

| Maintenance Cycle 4<br>**This course is for patients randomized to receive maintenance chemotherapy and for STR patients with residual disease after second surgery** (see Section 4.2). Cycle 4 of Maintenance Chemotherapy consists of one 21-day cycle.<br>This therapy delivery map relates to Cycle 4 of Maintenance. | _____<br>Patient name or initials<br>_____<br>DOB |
|---|---|

*Criteria to start this cycle:* ANC > 1000/µL and platelets > 100,000/µL with no G-CSF administered for at least the preceding day (24 hours). Details are in Section 4.0 (Treatment Overview) and Section 4.6.3. This cycle lasts 21 days and this TDM is on **1** page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| Etoposide (ETOP) | IV over 60–120 minutes+ | 100 mg/m$^2$/dose or 3.3 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1, 2 and 3 | +Slow rate of administration if hypotension occurs.<br><br>Administer immediately **prior to** cisplatin or cyclophosphamide administration. | a. History, Physical Exam, Weight, Height<br>b. Neurologic Assessment<br>c. MR Brain with gadolinium<br>d. MR Spine with gadolinium<br>e. Electrolytes (Ca++, $PO_4$, Mg++, BUN)<br>f. Liver function (ALT, AST, Bili)<br>g. Urinalysis<br>h. CBC (diff, platelets)<br>i. Audiogram or BAER<br>j. Serum Creatinine or GFR or Creatinine Clearance<br><br>OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE |
| CISplatin (CDDP) | IV over 1–8 hours (use institutional standards) | 100 mg/m$^2$/dose or 3.3 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 1 | Hydrate patients before and after CISPlatin administration. See CAGs for suggestions. | |
| Cyclophosphamide (CPM) | IV over 1 hour | 1000 mg/m$^2$/dose or 33 mg/kg/dose for pts with BSA < 0.45 m$^2$ | 2 and 3 | Administer **after** CISplatin administration. | |
| Mesna (MESNA) | IV (Short or continuous [CI]) | **See Section 4.6.** | 2 and 3 | Total IV dose: 600 mg/m$^2$/day or 20 mg/kg/day if BSA < 0.45 m$^2$<br>Administer **concurrently with** cyclophosphamide. | |
| Myeloid Growth Factor | SubQ (preferred) or IV | See Important Notes | Daily, starting on Day 4 | Start myeloid growth factor support (for example, G-CSF 5 mcg/kg/dose SubQ [preferred] or IV) on Day 3, until the ANC is > 1,500/µL after the expected nadir. Discontinue at least 24 hours before the start of the next chemotherapy cycle. | |

**Ht____cm Wt____kg BSA____m$^2$**

| Date Due | Date Given | Day | ETOP<br>____mg | CDDP<br>____mg | CPM<br>_____mg | MESNA<br>__mg __mg __mg | Myeloid Growth Factor Growth Factor Used: _____<br>_____mcg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below.** | | | | | | |
| | | 1 | ____mg | ____mg | | | | a, b, e, f, g, h, i, j$ | |
| | | 2 | ____mg | | ____mg | __mg __mg __mg | | | |
| | | 3 | ____mg | | ____mg | __mg __mg __mg | | | |
| | | 4 | | | | | ____mcg | | |
| | | 8 | | | | | | a, e$, f$, h, j$ | |
| | | 15 | | | | | | a, e$. f$, h, j$ | |
| | | 21 | | | | | | | Indicate date of last myeloid growth factor dose _____ |
| | | 22 | After Cycle 4 of Maintenance Chemotherapy, protocol therapy is complete. Refer to Section 7.0 for end of therapy required observations. | | | | | | |

OBSERVATION NOTES:
$ Repeat weekly if abnormal.

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.**

# 5.0 DOSE MODIFICATIONS FOR TOXICITIES

## 5.1 Dose Modifications during Induction Chemotherapy

### 5.1.1 Carboplatin

#### 5.1.1.1 Nephrotoxicity

If estimated creatinine clearance using the Schwartz formula drops below the normal range, 24-hour creatinine clearance or radionuclide GFR should be performed.

Carboplatin should be dose-modified as below for renal insufficiency:

| **GFR** (mL/min/1.73 $m^2$) | **Carboplatin Dose** |
|---|---|
| ≥ 70 | 375 mg/$m^2$ (12.5 mg/kg for < 0.45 $m^2$) |
| 50- 69 | 280 mg/$m^2$ (9.3 mg/kg for < 0.45 $m^2$) |
| 25-49 | 187 mg/$m^2$ (6.2 mg/kg for < 0.45 $m^2$) |
| ≤ 24 | none |

#### 5.1.1.2 Ototoxicity

Careful monitoring of children by expert audiologist and by serial audiometry throughout the treatment with carboplatin is recommended. Otoacoustic emissions (OAE) are the clinical methodology of choice for initial testing. If these are normal, patients do not need further evaluation, and should be coded as having no hearing loss. If they are abnormal, then brainstem evoked auditory responses (BAER) or pure tone audiometry should be used to more specifically describe the hearing loss. A decrease in auditory acuity at frequencies above 4000 Hz is expected and does not constitute a contraindication to further therapy. For Grades 0, 1, and 2 ototoxicity (CTCAE) no dose modification is recommended. For Grade 3 toxicity, a 50% reduction should be made in the carboplatin dosage. For Grade 4 ototoxicity, carboplatin can be continued at 50% dose reduction or at the discretion of treating physician and family.

#### 5.1.1.3 Allergic Reactions

Carboplatin allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose 50 mg), ranitidine 1 mg/kg IV (maximum dose 50 mg), and hydrocortisone 4 mg/kg IV (maximum dose 100 mg).

### 5.1.2 Etoposide

#### 5.1.2.1 Nephrotoxicity

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

| Measured CrCL | > 50 mL/min/1.73m$^2$ | 15-50 mL/min/1.73m$^2$ |
|---|---|---|
| Etoposide Dose | 100% of Dose | 75% of Dose |

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearances of < 15 mL/min and further dose reduction should be considered in these patients.

5.1.2.2 Hepatotoxicity

If the direct bilirubin is between 2 and 3 mg/dL, give 50% of the calculated dose of etoposide. If the direct bilirubin is > 3 mg/dL, hold the etoposide. Full dose may resume when the direct bilirubin has fallen to < 1.2 mg/dL.

5.1.2.3 Allergic Reactions

Etoposide allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose 50 mg), ranitidine 1 mg/kg IV (maximum dose 50 mg), and hydrocortisone 4 mg/kg IV (maximum dose 100 mg), and by slowing the rate of the infusion. For those reactions which are unable to be controlled with pre-medication and slowing of the rate of etoposide infusion, etoposide phosphate may be substituted in the same dose and at the same rate. Pre-medication for etoposide phosphate is recommended.

5.1.3 Vincristine

5.1.3.1 Vincristine Neurotoxicity

*Seizures*: Hold one (1) dose of vincristine, then reinstitute at 1 mg/m$^2$ or 0.03 mg/kg (for patients < 0.45 m$^2$) (1.5 mg maximum dose) while anticonvulsants are continued. If seizures do not recur, then escalate to full dosage. Rule out syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures. In patients with supratentorial tumors or with leptomeningeal disease, it may be impossible to distinguish tumor-related seizures from vincristine-related seizures. In such cases, careful evaluation of anticonvulsant levels and clinical status should be made prior to attributing seizures to vincristine and decreasing or holding vincristine doses.

*Severe neuropathic pain (Grade 3 or greater)*: Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), then escalate to full dose as tolerated. However, since vincristine is an important component of curative therapy, and the majority of neuropathies are ultimately reversible, treating physicians may choose to deliver full dose therapy. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies.

*Foot Drop, paresis*: Should be Grade 4 to consider holding or decreasing dose. These toxicities are largely reversible, though possibly over months to

years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion and provide ankle-foot orthoses (AFOs) and other forms of support. Drugs such as gabapentin may be of value.

*Vocal Cord Paralysis:* Hold dose(s). When symptoms subside, resume at 50% of previous calculated dose, then escalate to full dose as tolerated. See above for comment on CMT.

5.1.3.2 Jaw Pain

Treat with analgesics; do not modify vincristine dose unless determined to be in the best interest of the patient by the treating physician.

5.1.3.3 Hepatotoxicity

If direct bilirubin is greater than 6 mg/dL hold vincristine dose. If direct bilirubin is 3.1–6 mg/dL then follow guidelines below. For direct bilirubin less than 3.1 mg/dL administer vincristine at full dose.

| Direct Bilirubin Level (mg/dL) | Vincristine Dose Reduction |
|---|---|
| < 3.1 | Administer Full Dose (maximum dose 2 mg) |
| 3.1-5 | Administer at 50% of calculated dose (maximum dose 1 mg) |
| 5.1- 6 | Administer at 75% of calculated dose (maximum dose 0.5 mg) |
| > 6 | Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses. |

5.1.3.4 Constipation or Ileus

Constipation or ileus (≥ Grade 3) or typhlitis: Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

## 5.2 Dose Modifications during Maintenance Chemotherapy

### 5.2.1 Cisplatin

5.2.1.1 Hypomagnesemia

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

Prophylactic administration of magnesium (1–2 gm/L) in cisplatin hydration can be used to prevent low levels of magnesium.

5.2.1.2 Sensorineural Ototoxicity

Careful monitoring of children by expert audiologist and by serial audiometry throughout the treatment with Cisplatin is recommended. Audiometry prior to each maintenance cycle is recommended. Otoacoustic emissions (OAE) are the clinical methodology of choice for initial testing. If these are normal, patients do not need further evaluation, and should be coded as having no hearing loss. If they are abnormal, then brainstem evoked auditory responses (BAER) or pure tone audiometry should be used to more specifically describe the hearing loss. Adjust dose as below for unilateral or bilateral hearing loss. Use CTC 4.0 to grade ototoxicity. For Grade 1 ototoxicity (defined as threshold shift >20 dB at 8 kHz in at least one ear) reduce cisplatin by 25% of the total dose. For Grade 2 ototoxicity, defined as Threshold shift >20 dB at 4 kHz and above in at least one ear); reduce the dose by 50% of the total dose. For Grade 3 (threshold shift > 20 dB at 3 kHz or above in one ear; hearing loss sufficient to indicate therapeutic intervention) **or** Grade 4 ototoxicity (audiologic indication for cochlear implant and additional speech-language related services indicated) cisplatin should be deleted and not restarted.

5.2.1.3 Nephrotoxicity

If Cr Clearance/GFR is greater than 60 mL/min/1.73m$^2$ and has not dropped by more than 50% from original pre-chemotherapy baseline then give full dose Cisplatin. If Cr Clearance/GFR is 50–60 mL/min/1.73m$^2$ or has decreased by more than 50% of original pre-chemotherapy baseline, but is still ≥ 50 mL/min/1.73m$^2$, then give 75% dose of Cisplatin. If Cr Clearance/GFR is less than 50 mL/min/1.73m$^2$ then omit cisplatin.

5.2.2 Cyclophosphamide

5.2.2.1 Hematologic

If chemotherapy is due and the absolute neutrophil count is below 1000/µL or the platelet count is less than 100,000/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 > 1000 and the platelet count > 100,000, but the dose of cyclophosphamide should be reduced by 25% (i.e., each daily dose should be reduced by 25%).

If there is a delay more than 2 weeks and the patient has received a dose reduction in a previous cycle and 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 an additional 25% (i.e., each daily dose should be reduced by 50%). Subsequent cycles should be given at full dose as long as counts recover on time.

5.2.2.2 Hemorrhagic Cystitis

*Microscopic Hematuria*
For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), do not modify the cyclophosphamide dose. Add hydration and deliver mesna as a continuous infusion at 60% of the daily cyclophosphamide dose.

Hydration: administer 3000 mL/m²/day (125 mL/m²/hour) 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.

Mesna: Start with a total daily mesna dose that is equal to 60% of the daily cyclophosphamide dose administer in 3 divided doses by **short infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the cyclophosphamide dose; subsequent doses are given 4 and 8 hours after the start of cyclophosphamide. This total daily dose can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 8 hours after the end of the cyclophosphamide infusion. The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **TWO** bolus doses (originally at Hours 4 and 8) orally at 40% of the cyclophosphamide dose. The oral doses will be administered at Hours 2 and 6. Examples are available in the Chemotherapy Administration Guidelines.

For persistent microscopic hematuria ( > 2 abnormal urinalyses during a cycle of therapy), increase hydration to 3500–4000 mL/$m^2$/day and daily mesna dose to 100% of the cyclophosphamide dose at the schedule described above at the next cycle.

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

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during or following a cycle of therapy, do not modify cyclophosphamide dose. Use hydration and continuous infusion mesna at 100% of the cyclophosphamide dose.

For persistent gross hematuria after completion of a cycle of therapy, hold subsequent cyclophosphamide until the urine clears to less than gross hematuria. Reinstitute cyclophosphamide at full dose, with hydration and the mesna at 100% of the cyclophosphamide dose given as continuous infusion. For occurrence of a second episode of gross hematuria or persistence of microscopic hematuria on the continuous infusion regimen, continue the cyclophosphamide when the urine clears to less than gross

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

5.2.2.3 Nephrotoxicity
In patients with a measured creatinine clearance < 10 mL/min/1.73 $m^2$, decrease dose by 25% (give 75% of initial dose).

5.2.2.4 Hepatotoxicity
The overall pharmacokinetics of cyclophosphamide are not significantly altered in the presence of hepatic insufficiency. Although there is evidence to suggest that toxicity may be greater in hepatic insufficiency, recommendations for dosage adjustment in the presence of hepatic failure have not been established. Consider dose adjustments according to institutional guidelines.

5.2.3 Etoposide
See dose modifications during induction chemotherapy above (Section 5.1).

5.2.4 Vincristine
See dose modifications during induction chemotherapy above (Section 5.1).

## 6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the Commercial Agents Monographs (https://www.cogmembers.org/_files/disc/pharmacy/CommercialAgentsMonographs.pdf) and is provided under Standard Sections for Protocols at: https://cogmembers.org/site/pages/default.aspx?page=Prot_reference_materials.

## 7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated 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 Clinical, Laboratory and Disease Evaluations for STR (Incomplete Resection) Patients

Supratentorial patients with classic histology who achieve a CR following Induction or a GTR1 following Second Surgery will move to the Observation Arm of the study. (See Section 7.4 for required observations).

Supratentorial patients with anaplastic histology and all Infratentorial patients who achieve a CR following Induction or a GTR/NTR following Second Surgery will be randomized. (See Section 7.2 and Section 7.3 for required observations).

| STUDIES TO BE OBTAINED | Study Entry | Prior to Induction | During Induction | Prior to Second Surgery | Following Second Surgery | Prior to cRT | During cRT | Within 1 Week Prior to Maintenance | During Maintenance | Completion of Therapy [12] |
|---|---|---|---|---|---|---|---|---|---|---|
| History, Physical Exam, Weight and Height | X | X | Prior to each Cycle | X | | X | Every other week | X | Weekly | X |
| Neurologic Assessment | | X | Prior to each Cycle | X | X | X | Every other week | X | Prior to each Cycle | X |
| MR Brain with gadolinium | X [3] | X [5] | X[10] | | X [3] | X [7] | | X | | X |
| MR Spine with gadolinium | X [4] | | X[10] | | | | | X | | X |
| Lumbar CSF Cytology [1] | X | | | | | | | | | |
| Electrolytes (including Ca++, $PO_4$, Mg++, BUN) | | X | Prior to each Cycle [6] | | | | | X | Prior to each Cycle [6] | X |
| Serum Creatinine or GFR or Creatinine Clearance | | X | Prior to each Cycle [6] | | | | | X | X [11] | |
| Liver Function (ALT, AST, Total Bili) | | X | Prior to each Cycle [6] | | | | | X | Prior to each Cycle [6] | X |
| Urinalysis | | X | Prior to each Cycle | | | | | X | Prior to each Cycle | X |
| CBC (w/Differential and Platelets) | | X | Weekly | | | X | | X | Weekly | X |
| Audiogram or BAER | | X | Prior to each Cycle | | | X | | X | Prior to each Cycle | X |
| Echocardiogram or Ejection Fraction | | | | | | | | X | | |
| Required Pathology Specimens (see Section 14.0) | X | | | | X | | | | | |
| Ophthalmology Evaluation [9] | X | | | | | X | | | | X |
| Endocrine Evaluation [2] | | | | | | X | | | | X |
| Pregnancy Test [8] | X | | | | | | | | | |

**Studies obtained for the end of one time point can be used for the beginning of the next timepoint if timing requirements are met.**

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.

2. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix II) and LH/FSH and Estradiol/testosterone if child has delay puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
3. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
4. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with gadolinium.
5. If post-op cranial MRI was performed > 21 days before the first day of chemo, repeat cranial MRI with gadolinium to provide an appropriate baseline.
6. Repeat weekly if abnormal.
7. Preferably the scan should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT. (Post-op imaging can be used).
8. Obtain for females of childbearing potential.
9. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.
10. Obtain neuroimaging between Days 21-29 of Induction Cycle B.
11. Obtain prior to cycles 1 and 3 of Maintenance. Repeat weekly if abnormal.
12. For patients who complete therapy following RT, obtain 4 weeks after completion of therapy.

**This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.**

## 7.2 Required Clinical, Laboratory and Disease Evaluations for Patients Randomized to Radiation Therapy followed by Maintenance Chemotherapy

| STUDIES TO BE OBTAINED | Study Entry | Prior to cRT | During cRT | Within 1 Week Prior to Maintenance | During Maintenance | Four Weeks After Completion of Therapy[10] |
|---|---|---|---|---|---|---|
| History, Physical Exam, Weight and Height | X | X | Every other week | X | Weekly | X |
| Neurologic Assessment | | X | Every other week | X | Prior to each Cycle | X |
| MR Brain with gadolinium | X[3] | X[6] | | X | | X |
| MR Spine with gadolinium | X[4] | | | X | | X |
| Lumbar CSF Cytology [1] | X | | | | | |
| Electrolytes (including Ca++, $PO_4$, Mg++, BUN) | | | | X | Prior to each Cycle[5] | X |
| Serum Creatinine or GFR or Creatinine Clearance | | | | X | X[9] | |
| Liver Functions (ALT, AST, Total Bili) | | | | X | Prior to each Cycle[5] | X |
| Urinalysis | | | | X | Prior to each cycle | X |
| CBC (w/Differential and Platelets) | | X | | X | Weekly | X |
| Audiogram or BAER | | X | | X | Prior to each cycle | X |
| Echocardiogram or Ejection Fraction | | | | X | | |
| Required Pathology Specimens (see Section 14.0) | X | | | | | |
| Ophthalmology Evaluation[8] | X | X | | | | X |
| Endocrine Evaluation[2] | | X | | | | X |
| Pregnancy Test [7] | X | | | | | |

**Studies obtained for the end of one time point can be used for the beginning of the next timepoint if timing requirements are met.**

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix II) and LH/FSH and Estradiol/testosterone if child has delay puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
3. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
4. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with contrast.
5. Obtain prior to each cycle; repeat weekly if abnormal.
6. Preferably the scan should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT. (Post-op imaging can be used).
7. Obtain for females of childbearing potential.
8. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.
9. Obtain prior to cycles 1 and 3 of Maintenance. Repeat weekly if abnormal.
10. Obtain all requirements 4 weeks after completion of therapy.

### 7.3 Required Clinical, Laboratory and Disease Evaluations for Patients Randomized to Receive Radiation Therapy followed by Observation

| STUDIES TO BE OBTAINED | Study Entry | Prior to cRT | During cRT | 4 Weeks After Completion of Therapy |
|---|---|---|---|---|
| History, Physical Exam , Weight and Height | X | X | Every other week | X |
| Neurologic Assessment | | X | Every other week | X |
| MR Brain with gadolinium | X[3] | X[5] | | X |
| MR Spine with gadolinium | X[4] | | | X |
| Lumbar CSF Cytology [1] | X | | | |
| CBC (w/Differential and Platelets) | | X | | X |
| Audiogram or BAER | | X | | X |
| Required Pathology Specimens (see Section 14.0) | X | | | |
| Ophthalmology Evaluation[7] | X | X | | X |
| Endocrine Evaluation[2] | | X | | X |
| Pregnancy Test [6] | X | | | |

**Studies obtained for the end of one time point can be used for the beginning of the next timepoint if timing requirements are met.**

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix II) and LH/FSH and Estradiol/testosterone if child has delay puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
3. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
4. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with contrast.
5. Preferably the scan should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT. (Post-op imaging can be used).
6. Obtain for females of childbearing potential.
7. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

### 7.4 Required Observations For Supratentorial Classic Ependymoma GTR1 Patients (Observation)

| Observation (Time measured from date of enrollment) | Study Entry | 4 Months | 8 Months | 12 Months | 16 Months | 20 Months | 24 Months | 28 Months | 32 Months | 36 Months | 42 Months | 48 Months | 54 Months | 60 Months Then Annually |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History and Physical | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height, Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Neurologic Assessment | X | | | X | | | X | | | X | | X | | X |
| MR Brain with gadolinium | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MR Spine[1] (with gadolinium) | X | | | | | | | | | | | | | |
| CSF Cytology [2] | X | | | | | | | | | | | | | |
| Audiogram or BAER | X | | | X[4] | | | X[4] | | | X[4] | | X[4] | | X[4] |
| Ophthalmology Evaluation | X | | | X[4] | | | X[4] | | | X[4] | | X[4] | | X[4] |
| Endocrine Evaluation [3] | X | | | X[4] | | | X[4] | | | X[4] | | X[4] | | X[4] |
| Required Pathology Specimens (see Section 14.0) | X | | | | | | | | | | | | | |

1. Repeat if new symptoms develop or if patient has local recurrence.
2. Obtain unless lumber puncture is contraindicated and deemed medically unsafe. Must be negative at baseline, otherwise patients is excluded.
3. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (see Appendix II) and LH/FSH and Estradiol/testosterone if child has delayed puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
4. Repeat only if clinically indicated or abnormal at baseline.

## 7.5 Optional Studies

The following specimens and evaluations are optional depending on whether or not the patient has signed an informed consent for them. If patient consents, send tumor tissue and peripheral blood according to collection and shipping instructions in Section 15.0.

### 7.5.1 Biology Specimens

With Amendment 3, the tissue samples will be utilized as is detailed in Section 2.2 and Section 9.4.

| Study | Sample | When |
|---|---|---|
| Gene expression microarray | Snap frozen tumor tissue | At time of diagnosis and second surgery |
| Genomic hybridization (GCH) array | Snap frozen or paraffin embedded tumor tissue | At diagnosis |
| | Peripheral Blood (5 cc in a green top tube [sodium heparin]) | Prior to treatment and at time of second surgery |
| | Peripheral Blood (5 cc in a yellow top tube [ACD]) | Prior to treatment and at time of second surgery |
| | Peripheral Blood (5 cc of blood in a purple top tube [EDTA]) | Prior to treatment and at time of second surgery |
| Telomere length | Snap frozen tumor tissue | At diagnosis |
| Telomerase activity, (all consenting patients) | Snap frozen tumor tissue | At time of second surgery |
| hTert expression, and hTERC | Paraffin block | At time of resection(s) |
| gammaH2AX | Paraffin block | At time of resection(s) |

### 7.5.2 Neuropsychologic Evaluations

Patients who consent to participate on ALTE07C1 will be assessed at three times points, in accordance with the COG Standard Neuropsychological Battery: 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 (Wechsler Abbreviated IQ) and specific areas of neuropsychological functioning (i.e., Visual-motor processing speed (Wechsler Processing Speed Index)), Working memory (Wechsler Working Memory Index), Auditory-verbal (list learning, CVLT and narrative memory CMS tasks) and Visual (dot location and faces from CMS learning and memory), emotional-behavioral functioning (BASC-2 internalizing and externalizing composite scores), functional adaptive skills (ABAS-II General Adaptive Composite, a global measure of adaptive (practical, conceptual, social) daily living skills), and quality of life (PedsQL Physical and Psychosocial Summary Scores). Total testing time should be approximately 1 hour at each assessment point.

## 7.6 Follow-up

**Required Observations Following Protocol Therapy for all patients other than Observation Arm**

| **Observations** (Dated from Completion of Therapy) | **4 Months** | **8 Months** | **12 Months** | **16 Months** | **20 Months** | **24 Months** | **28 Months** | **32 Months** | **36 Months** | **42 Months** | **48 Months** | **54 Months** | **60 Months Then Annually** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History, Physical Exam (incl. Ht, Wt, VS) | X | X | X | X | X | X | X | X | X | X | X | X | X |
| MR Brain with gadolinium | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Neurologic Assessment | X | | X | | | X | | | X | | X | | X |
| MR Spine[1] with gadolinium | | | X | | | X | | | | | | | |
| Audiogram or BAER | | | X | | | X | | | X | | X | | X |
| Ophthalmology Evaluation | | | X | | | X | | | X | | X | | X |
| Endocrine Evaluation[2] | | | X | | | X | | | X | | X | | X |

1. Perform at the indicated time points and repeat if new symptoms develop.
2. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone annually. Tanner Stage and LH/FSH and Estradiol/testosterone at baseline if child has delayed puberty or precocious puberty before age 8 in girls or 9 in boys and then at end of therapy/annually beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) at end of therapy/annually - begin screening at age 11 or with signs of precocious puberty.

See COG Late Effects Guidelines for recommended post treatment follow-up http://www.survivorshipguidelines.org

# 8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

## 8.1 Criteria for Removal from Protocol Therapy

a) Development of distant progressive disease at any point during study
b) Local disease progression at any time during the study **EXCEPT** patients with sub-total resection (STR) who experience local disease progression prior to maintenance chemotherapy. These patients will NOT be removed from protocol therapy (see definition in Section 10.4).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Completion of planned therapy.
e) Physician determines it is in patient's best interest.
f) Development of a second malignancy.
g) Treating physician chooses to proceed with treatment according to the institutional review rather than the results from rapid central review.
h) Supratentorial patients who do not have an ependymoma on rapid central pathology review.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below).

## 8.2 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) Tenth anniversary of the date the patient was enrolled on this study.

# 9.0 STATISTICAL CONSIDERATIONS

## 9.1 Study Design

After initial surgery, all patients with a total or near total resection (GTR1/GTR2/NTR), except those with classic supratentorial disease and GTR1, will be randomized to radiation therapy followed by maintenance chemotherapy, or radiation therapy followed by observation. Patients with classic supratentorial disease and GTR1 will be on observation only. All patients with incomplete resection (STR) after initial surgery will receive induction chemotherapy.

At the end of induction chemotherapy, those achieving a CR after induction chemotherapy, except those with classic supratentorial disease, will be randomized to radiation therapy followed by maintenance chemotherapy or radiation therapy followed by observation. Patients with SD/PR or local progression after induction chemotherapy will undergo second surgery when possible; patients with GTR/NTR after second surgery, except those with classic supratentorial disease and GTR1, will then be randomized to radiation therapy followed by maintenance chemotherapy or radiation therapy followed by observation. Patients with classic supratentorial disease who achieve either CR after induction chemotherapy or GTR1 after second surgery will be non-randomly assigned to observation

only. Patients with residual disease after second surgery, or with SD/PR or local progression after induction chemotherapy but not amenable for second surgery, will be non-randomly assigned to receive radiation therapy followed by maintenance chemotherapy.

The primary aim of the study is to evaluate whether the addition of maintenance chemotherapy (VCEC) given after conformal radiation will have an impact on event free survival (EFS) and overall survival (OS) in newly diagnosed patients with intracranial ependymoma. Randomization between VCEC and observation arm will be stratified by 2 groups below based on when they become eligible for randomization: 1) patients with GTR/NTR after initial surgery; 2) patients with incomplete resection after initial surgery and then CR after induction chemotherapy, or patients with GTR/NTR after second surgery.

Secondary aims include estimating EFS and OS for: (1) incompletely resected patients who are non-randomly assigned to receive post radiation maintenance chemotherapy because of failure to achieving a CR after induction chemotherapy or incomplete resection at second surgery; (2) patients with supratentorial classic disease who achieve either GTR1 after surgery (initial or second) or CR after induction chemotherapy and therefore are assigned to observation only.

## 9.2 Patient Accrual and Expected Duration of Trial

Per Amendment #1D and based on CTEP recommendations, the study design was converted from a maximum-time design to a maximum-information design. More specifically, barring early stopping, the primary analysis will be done when 85 events (as defined under EFS below) have been observed. Maximum number of eligible and evaluable patients to be accrued and randomized for the primary objective remains 320, as originally planned. If 85 events have not yet been observed by the time 320 patients have been randomized for the primary objective, accrual will be considered complete and we will follow patients until 85 events have been observed before initiating the primary analysis of the trial data. In the unlikely event that 85 events are not observed 3 years after the last patient enrolls on the study, we will nevertheless conduct the primary analysis on pragmatic grounds.

ACNS0121, the predecessor study to ACNS0831, enrolled at least 90 patients per year, which was the projected accrual rate for this study at the time of its initial design. However the observed accrual rate to date on the current trial has been slower than that of ACNS0121 and thus the expected accrual rate has been reduced to 60 patients per year as per Amendment #1D. With an estimated 70% randomization rate, to achieve 320 randomized patients, the target maximum accrual for the entire trial is 460 patients and the accrual duration is estimated to be approximately 8 years. The maximum accrual for the study is extended from the expected number of 460 to a maximum of 500 to accommodate ineligible enrollments (up to 8%) and slight fluctuation in the rate of randomization. Note however that since the primary analysis will be done at the time 85 events have been observed, in the randomized cohort, accrual to the study may be terminated prior to enrolling 500 patients. Furthermore given that the study design incudes interim analyses for efficacy as well as futility, early stopping is certainly possible. Estimated accrual and study duration under various scenarios are detailed in the next section under ‘Monitoring for Outcomes’.

## 9.3 Statistical Analysis Methods

Endpoints

- Event-free survival (EFS), defined as time to the first occurrence of any of the following events: disease progression, disease recurrence, second malignant neoplasm, or death from any cause. For this endpoint, local disease progression in patients with sub-totally resected disease prior to maintenance will not be classified as disease progression in the primary analyses, although they may be so classified for some secondary analyses.
- Overall survival (OS), defined as time to death from any cause.

Power Considerations

In the previous study, ACNS0121, we observed about 80% complete resection rate (GTR/NTR) following initial surgery. After excluding patients with supratentorial classic disease who were completely resected (GTR1) and would go on observation only, which was expected to be about 5% of the total eligible enrollments, we estimated that we would have approximately 75% of enrolled patients eligible for randomization after initial surgery. Among the 20% of patients with incomplete resection after initial surgery, we assumed a 10% CR rate after induction chemotherapy which was similar to what was observed on ACNS0121. Among the patients who achieved < CR after induction chemotherapy, we assumed that 50% would go through 2$^{nd}$ surgery and 40% would have complete resection after 2$^{nd}$ surgery. Therefore the percentage of patients who became CR after chemotherapy or had complete resection after second surgery was estimated to be 20%*10%+20%*90%*50%*40%=6% of total eligible enrollments. It was assumed that ~5% among these 6% would be patients with supratentorial classic disease with CR or GTR1 who would go on observation only; which resulted in approximately 6% of total enrollments being eligible for randomization through this path. Combining with the 75% patients eligible for randomization after the initial surgery, altogether we had projected that about 80% of the enrollment cohort would be eligible for randomization. Since the study activation, however, only around 70% of the enrolled patients have been eligible for randomization. This is partially due to the fact that 10% of enrollments to date (twice as many as projected based on ACNS0121) have been patients with supratentorial classic disease that were completely resected (GTR1) making them eligible for observation only arm. Another contributing factor for lower than expected rate of randomization has been patient refusal or early termination of treatment prior to randomization. Therefore, per Amendment #1A, we are revising the projected rate of randomization for this study to be 70%.

At the time of the initial development of this protocol, the outcome data on ACNS0121 was not yet available because the study was still under DSMC monitoring. An earlier ependymoma protocol CCG 9942 had enrolled 84 patients; where patients without residual tumor were treated with irradiation only and patients with residual tumor received pre-irradiation chemotherapy. The overall 2 year EFS on CCG 9942 was about 70%; the group of 43 patients who had irradiation alone (because of no residual tumor) and the group of 21 patients who achieved some response (CR/PR) after pre-irradiation chemotherapy had slightly higher 2 year EFS at about 75%. Therefore, for the post radiation observation arm we had assumed 2 year EFS of 75% (4-year EFS 66%; long term EFS 60%) under a cure model with an exponential failure rate for the patients who fail. These assumptions appear to be reasonable based on the later released data from ACNS0121. Per the 2014 ISPNO abstract of ACNS0121, 5-year EFS estimates for 281 patients treated with immediate post-

operative CRT was 67.3%±4.5% for patients with near-total or macroscopic gross-total (GTR2) resection (stratum 3, treatment 3); was 69.5%±3.8% for those with WHO grade III, supratentorial or any grade, infratentorial after GTR1 (stratum 4, treatment 3). When combined with the 25 additional patients who achieved CR after induction chemotherapy or GTR after second look surgery, the 5-year EFS estimate for the entire cohort was slightly lower at around 67%. Additional failures beyond 5 years were also observed supporting the slightly declining outcome assumption for the long term. With a maximum of 160 patients per arm accrued over 8 years and with up to 2 years of additional follow up after the last patient enrollment, we will have about 93% power for detecting a higher EFS in the post-radiation VCEC arm when it has 2 year EFS of 87% (4-year EFS 81%; long term EFS 76%). The test considered is a 1-sided log rank test with type I error of 0.05. A loss to follow-up of 10% by the end of year 5 under an exponential model is included for each arm; the assumed loss to follow-up is approximately 2% every year for the first 5 years.

If on each randomized arm 10% of the patients are non-compliant and switch to the other arm, in the intent-to-treat analysis where we include patients in their assigned arm rather than the treated arm the power is reduced to about 80%. The intent-to-treat analysis suffers because the observed difference between the 2 arms becomes smaller; with 10% switch-over the 2-year EFS for the post-radiation observation arm becomes 76% instead of 75%, while the 2-year EFS on post-radiation VCEC arm reduces to 86% instead of 87%. In this case intent-to-treat analysis maintains the comparability of the 2 groups of patients by randomization but has lower power than the as-treated analysis. Similarly, the power for intent-to-treat analysis is approximately 75% if 20% of the treatment arm patients switch to control treatment while none of the control arm patients are non-compliant; the power is approximately 82% if 20% of the control arm patients switch to the treatment arm and none of the treatment arm patients are non-compliant.

Monitoring for Toxic Death

There were no toxic deaths observed on ACNS0121 (eligible n=356). The study committee will review any occurrence of toxic death observed on this study for safety evaluations and report the results to the DSMC in DSMC report as well as in the study progress report. Based on the findings, the study committee may propose appropriate actions if necessary such as study modification or suspension; at any time DSMC may make their own safety assessments and recommendations. DSMC reports and study progress reports will be prepared every 6 months for the first 2 years of the study, and later upon DSMC approval will be generated once every year if the study goes smoothly during the first 2 years.

Monitoring for Randomization Rate and Randomization Compliance

The percentage of patients that are randomized will be reported at each progress report and will be monitored approximately once every year after the opening of the study. Note however that the composition of the patient cohort enrolled on this study is unpredictable which has already been observed as of Amendment #1D in the notably larger than expected 'observation only' patient cohort: 23 out of 226 eligible enrollments (10.2%) at the time of Amendment #1D for ACNS0831 vs. only 11 in 355 (3.1%) eligible patients on ACNS0121. Thus, as of Amendment #1D, we will monitor the randomization rate among patients who were eligible for randomization and are enrolled after the activation of Amendment #1D. We consider a randomization rate of 90% or higher among patients who are eligible to be randomized to be acceptable. We will use a 1-sided 95% exact CI to assess the adequacy of the randomization rate once at least 40 patients have been randomized. If the 95% UB estimate of the randomization rate is lower than 90% we will detail the reasons for the

lower than expected randomization rate and seek the DSMC's input regarding what actions may need to be taken.

We will also examine the rate of non-compliance for randomization (i.e., patients receiving treatment of the opposite arm, not the assigned arm) on each arm and report these rates to the DSMC as part of the regularly scheduled DSMC reports. We consider a compliance rate of 90% or higher among randomized patients to be acceptable. We will use a 1-sided 95% exact CI to assess the adequacy of the compliance rate once at least 40 patients have been randomized. If the 95% UB estimate of the compliance rate is lower than 90% we will detail the reasons for the lower than expected compliance rate and seek the DSMC's input regarding what actions may need to be taken.

If the randomization percentage is inadequate or the non-compliance rate is unacceptably high, DSMC may consider study suspension or modification, taking into account factors such as the observed issue, its magnitude, potential reasons and the number of patients remaining to be enrolled, etc.

Monitoring for Outcomes

Interim monitoring on the randomization comparison will be performed and will be based on 1-sided log rank tests. Monitoring will be performed once a year coinciding with the annual DSMC reports, and monitoring boundaries will be calculated based on the observed number of events via Lan-Demet's method with spending function $\alpha t^2$. The expected maximum number of interim analyses to be conducted post Amendment #1D is 6.

Since the study was converted from a time-based design to an information based design as part of Amendment #1D, and some of the type 1 error (i.e., 0.0023) was spent on interim analyses prior to this conversion, 0.0023 will be subtracted from the original overall type 1 error rate (0.05) and the rejection boundaries for interim analyses post Amendment #1D will be calculated based on alpha=0.0477 in order not to cause an inflation in the study-wide type 1 error. Note that this small reduction in alpha results in virtually no change in the overall power of the study (0.930 vs. 0.925).

Given the information based design that has been implemented as per Amendment #1D, the assumptions made about accrual as well as EFS distributions and the above described interim analyses for early stopping for efficacy, if the alternative hypothesis is true, the expected duration of the trial is approximately 6.5-7 years after initiating enrollment. In other words if the RT+chemotherapy arm is superior to the RT-only arm in the randomized cohort at the level that was hypothesized in the study design (i.e., HR≈0.5), then we expect that we will stop accrual to the study following one of the interim analyses. We estimate that on average this will happen approximately 6.5-7 years after initiating enrollment based on an estimated 53 events. If on the other hand the null hypothesis is true and there is no appreciable difference in the two arms in terms of efficacy, we expect to observe 85 events shortly after the accrual is complete, at about 8 years. This estimate does not include the additional interim monitoring for futility described below which may allow us to stop enrollment earlier under the null hypothesis. While various forms of non-compliance do not affect the estimate of trial duration under the null hypothesis, under the alternative hypothesis the overall effect of non-compliance is to prolong the study by up to 6 months, on average.

A futility monitoring will be performed at the same time as the efficacy interim analyses and will be based on the conditional probability of detecting the EFS difference between

the 2 randomized arms at the end of the study given the current observed data. Failure pattern for future patients and current patients who are still at risk will be simulated under the alternative hypothesis. In the simulations, if the conditional probability of detecting the difference between the 2 arms given the current observed data falls below 10%, the study will be referred to the DSMC for study modification or suspension.

We will also perform interim informal monitoring on the outcome for patients with supratentorial classic disease that were on observation only following a complete resection or CR to induction chemotherapy. ACNS0121 data on such patients have become available as of Amendment #1D. Eleven eligible patients were enrolled on ACNS0121 in the observation arm out of a total of 355 eligible enrollments. Per 2014 ISPNO abstract, there were 5 events among the 11 patients with 5-year EFS of 61.4% (±14.4%). Importantly however the 5-year OS rate is 100% in these patients. We will estimate EFS for observation-only patients on our study and compare that to the estimates from ACNS0121. We will use the most up to date data on ACNS0121 for these comparisons until the data for the primary manuscript of that study are frozen, after which we will use those frozen data for our comparisons. Informal monitoring will be based on whether the 95% confidence intervals for the 1-year and 3-year EFS estimates based on a KM approach on our study include the corresponding estimates from ACNS0121. This informal monitoring rule will serve as a guideline for continued monitoring of outcome on this group of patients, and is not to be interpreted literally as a formal rule for terminating or modifying treatment for this group of patients. The informal monitoring on observation only patients will be performed at the same time as the monitoring on the primary study comparison on the randomized patients. Monitoring results will be presented to the DSMC along with the OS outcome.

Informal monitoring will also be performed for the subset of patients who are non-randomly assigned to receive maintenance chemotherapy due to achieving less than CR after induction chemotherapy or due to incomplete resection after second surgery, by comparing the outcome of such patients to that of similar patients from ACNS0121 who were treated without post-radiation maintenance chemotherapy. We will use the most up to date data on ACNS0121 for these comparisons until the data for the primary manuscript of that study are frozen, after which we will use those frozen data for our comparisons. Monitoring will be based on a 1-sided log rank test and the observed p-value will be reported without a benchmark since no effect size has been specified for this comparison and the control cohort is from a previous trial. This monitoring is informal in nature and serves as basis for continued assessment for outcome in this group, since such comparison is not the primary study question. This informal monitoring will be performed at the same time as the monitoring on the primary study comparison on the randomized patients. Monitoring results will be presented to the DSMC.

Analysis Plans for Primary Objective

We will use Kaplan-Meier curves to estimate the observed EFS and OS for the two randomization arms (post-radiation Maintenance arm and post-radiation Observation only arm). Log rank tests will be used to compare the observed EFS and OS between the two randomization arms. Stratified log rank test will also be performed to examine the treatment difference with consideration and adjustment for the randomization groups. If outcome data on ACNS0121 or this study suggest a difference or a different pattern in outcome between the 2 randomization strata, then we will supplement the primary analyses with log-rank tests performed separately in each stratum in order not to confound the overall conclusions of the study with respect to the effect of maintenance therapy.

Furthermore, if significant non-proportionality is apparent in the survival curves (e.g., crossing of the curves) we may also use parametric or cure model approaches to supplement the primary analyses based on the log-rank test. For the comparative survival analysis on randomized patients, the EFS and OS will be calculated from the time of randomization.

The primary analysis will be based on intent-to-treat. In the event that the non-compliance rate is relatively high (>5% in either arm), we will also perform an as-treated analysis to examine potential changes in the overall trial conclusions from the primary intent-to-treat analysis.

Analysis Plans for Exploratory Clinical Objectives

Kaplan-Meier curves will also be used to estimate the EFS and OS for the subset of patients who were non-randomly assigned to receive maintenance chemotherapy after incomplete resection; this group includes those who remain less than CR after induction chemotherapy and those do not achieve complete resection with second surgery. Exploratory log rank test will be performed to compare the outcome in this group of patients to similar patients treated on ACNS0121 without post-radiation chemotherapy to assess the effect of post-radiation maintenance chemotherapy in such patients. Similar log rank test will be performed to see if this group of incompletely resected patients who were assigned to receive maintenance chemotherapy has lower EFS/OS than the patients who are randomized to maintenance chemotherapy because of complete resection or CR after induction chemotherapy.

EFS and OS will also be estimated using Kaplan-Meier curves for the subset of patients with supratentorial classic disease that achieve complete resection or CR to induction chemotherapy and are assigned to observation only.

Analysis Plan for Neurocognitive and QOL Outcomes

Barring early stopping, this study expects to randomize 320 patients (160 per arm) between radiation only and radiation followed by maintenance chemotherapy. As of the March 31, 2016 data freeze, of the 214 patients randomized, 69 patients (32%) were co-enrolled on the ALTE07C1 study, of these 69, 33 were treated with RT and 36 were treated with RT+maintenance chemotherapy. Dropout rate is a bit more difficult to estimate at this time since most patients are still within the assessment window. However given the relatively low participation rate observed to date, the neurocognitive/QOL objectives were moved from secondary to exploratory. For these exploratory analyses, our intent is to describe each outcome measures via descriptive summary statistics and plots. Descriptive statistics will be used to summarize the neurocognitive and QOL outcome measures at each time point and for the different patient subsets. Given the limitations in the number of participants and the large number of outcomes to be evaluated, the expectation from these data is that they will provide pilot information to estimate potential effect sizes as well as variability that can be used to inform future trials.

For the exploratory objective of comparing neurobehavioral outcome collected through ALTE07C1 for patients treated with proton beam radiation therapy compared to children treated with conventional radiation delivery techniques, similar descriptive approaches will be used as described above.

9.4 **Correlative Biology Studies**

The correlative biology studies listed in the secondary objectives are described in Section 15.0. The associated statistical analyses to be performed are detailed below.

As of Amendment 3, 479 patients have been enrolled on this study and 451 patients are eligible. Among the eligible patients, 390/451 (86.5%) have paraffin embedded tissue from their primary tumor at the BPC with the following breakdown:

| Subjects with Paraffin Embedded Tissue | N | % of total |
|---|---|---|
| ARM | | |
| Unassigned | 13 | 65% |
| Maintenance | 61 | 88% |
| Observation | 32 | 86% |
| Randomization | 284 | 87% |
| All | 390 | |

There are also 146 subjects who have frozen tissue available.

The methodology which will be used to define methylation based subgroups is described in Section 15. It is expected that a majority of subjects will be classified in one of the 4 subtypes below using the methylation approach: ST-RELA, ST-YAP1, PFA and PFB. It is not possible to determine the percentage of patients for which this classification will fail due to assay or tissue quality problems but based on experience from previous cohorts (e.g., medulloblastoma samples from ACNS0331 and ACNS0332) the failure rate is expected to be low (~5% of patients with adequate tissue). These subtypes will then be incorporated into Cox Regression analyses (or similar models if significant non-proportionality exists) along with treatment variables in an effort to determine degree and nature of associations with clinical outcome as measured by EFS and OS. If notable variability exists in outcome based on tumor location, these analyses may be performed separately for posterior fossa (PF) and supratentorial (ST) tumors which would then reduce the number of variables in the model as well (e.g., 2 subtypes rather than 4, etc.). The proposed analyses will be performed separately for the randomized cohort, the observation cohort and the cohort assigned to maintenance in order to better account for the treatment effect and the design of the study.

The outcome data for ACNS0831 remains under DSMC monitoring; however, the statistical design stipulates that the final analysis will be done when 85 EFS events are observed in the randomized cohort. Based on the data reported in ACNS0121 (the previous COG Ependymoma study), the rate of EFS events in the observation cohort is expected to be similar to the RT-only arm of the randomized cohort; whereas the outcome in the cohort non-randomly assigned to maintenance is expected to be worse compared to the RT-only arm in the randomized cohort. The design assumptions in the randomized RT–only vs. RT + Maintenance arms specify 2-year EFS of 75% vs. 87%, respectively. With 85 events in the randomized comparison, the proposed Cox models should be able to incorporate the 4 Ependymoma subtypes in addition to treatment as part of the analysis. The 4 subtypes

are location specific (2 for supratentorial and 2 for posterior fossa tumors) and the current information suggests that ~40% of the randomized subjects have supratentorial tumors and 60% have posterior fossa tumors. If the event distribution does not allow for a single model for the entire randomized cohort, location-specific models are also incorporated into the analysis plan for these exploratory biology objectives. Since the observation and maintenance cohorts are much smaller in sample size, these will be analyzed descriptively as separate cohorts.

Similar analyses will be performed for IHC based analyses for H3 K27 status for identifying PFA vs. PFB tumors and these will be contrasted against methylation based analyses. H3 K27M status will also be correlated with outcome. Similarly the detection rate of copy number variants for 1q gain and CDKN2A as assessed by DNA methylation profiling vs. interphase fluorescence in situ hybridization (iFISH) will be compared by cross tabulation methods and the association of these variants (1q gain in PF and CDKN2A loss in ST ependymomas) with EFS and OS will be evaluated using similar methods as described above which will incorporate treatment variables. We will also perform similar analyses to summarize frequencies of specific genetic alterations that include RELA fusions, specifically C11orf95-RELA fusions; YAP1 fusions and H3 K27M mutation.

As further exploratory analyses, we will study associations of the biomarkers listed above with WHO grade, tumor location, extent of resection, age and other demographic variables and incorporate these additional variables in outcome analyses for EFS and OS along with treatment, as feasible and appropriate.

## 9.5 Gender and Minority Accrual Estimates

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

| Accrual Targets | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 31 | 40 | 71 |
| Not Hispanic or Latino | 179 | 250 | 429 |
| **Ethnic Category: Total of all subjects** | 210 | 290 | 500 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 1 | 0 | 1 |
| Asian | 13 | 15 | 28 |
| Black or African American | 19 | 35 | 54 |
| Native Hawaiian or other Pacific Islander | 2 | 1 | 3 |
| White | 175 | 239 | 414 |
| **Racial Category: Total of all subjects** | 210 | 290 | 500 |

This distribution was derived from study ACNS0121.

# 10.0 EVALUATION CRITERIA

## 10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 5.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v5.0' is understood to represent the most current version of CTCAE v5.0 as referenced on the CTEP website (i.e., v5.02 and all subsequent iterations prior to version 6.0).

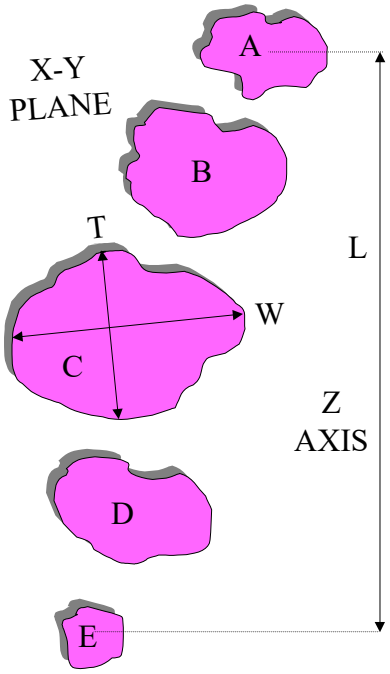
## 10.2 Methodology to Determine Tumor Measurement

In order to completely document the assessment of response, the measurements of the longest tumor dimension, and its perpendicular, of 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 the longest tumor dimension, and it's perpendicular. Either T1 or T2 weighted images are used - 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. This longest measurement of the tumor is referred to as the width (W).

2. The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in the selected plane.




**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

3. The cystic or necrotic components of a tumor are <u>not</u> considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be "measurable".

Options:

- if the cyst/necrosis is eccentric, the W and T 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

4. 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.
5. Overall Response Assessment
   The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, and new lesions in the preceding columns.

| Target Lesions | Non-target Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | **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.

## 10.3 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.

## 10.4 Response Criteria for Target Lesions

1. Response criteria are assessed in 2 dimensions – the product of W x T.
2. To assess response/progression, the ratio is calculated:

$$\frac{W \times T \text{ (current scan)}}{W \times T \text{ (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence.
4. Response Criteria for target lesions:

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

**Partial response (PR):** ≥ 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.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease.

Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure.

Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

### 10.5 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.

## 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 11.1 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.

### 11.2 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.***

11.2.1 Secondary Malignancy

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

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

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**11.2.2 Second Malignancy**

A ***second malignancy*** is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

11.3 **Reporting of Adverse Events for Commercial Agents – via CTEP AERS abbreviated pathway**

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 front of this protocol immediately following the Study Committee roster.

- 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 CTEP Active Version of 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

### 11.4 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 4 and higher non-hematologic Adverse Events (any attribution).

As of Amendment #1D, routine reporting will include Grade 3 Central Nervous System Necrosis (retrospective and prospective) for 2 years after study enrollment. Imaging and reports must be submitted for all patients with reported Grade 3 or above CNS System Necrosis for 2 years after study enrollment.

## 12.0 RECORDS AND REPORTING

See the Case Report Forms posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

### 12.1 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. CDUS reporting is not a responsibility of institutions participating in this trial.

## 13.0 NEUROSURGICAL GUIDELINES

### 13.1 General

When feasible, an attempt will be made to perform a gross total resection; if not feasible, an attempt will be made to remove as much tumor as possible without jeopardizing the patient. Biopsy alone, with no attempt at resection, may be associated with statistically worse survival and local progression during chemotherapy and should not be done. No patient will be eligible for this study without a pathologic diagnosis and histological confirmation.

### 13.2 Imaging Confirmation of Extent of Resection

All patients will have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI with and without contrast. Post-operative imaging of the brain should be done within 72 hours of surgery and prior to the onset of edema or gliosis which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time or is difficult to interpret, the scan should be repeated 10 or more days after surgery.

### 13.3 Peri-operative Corticosteroids

13.3.1
Some patients with large tumors may require initiation of corticosteroid therapy pre-operatively to reduce associated cerebral edema or improve neurologic function.

13.3.2
Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of dexamethasone, in divided doses, every 4-6 hours.

13.3.3
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 (7 days).

### 13.4 Initial Surgery

13.4.1
The guidelines for surgery are provided with the recognition that many patients on this study will have had their first operation prior to referral to the oncology service. Control of significant hydrocephalus in the perioperative period may be achieved with placement of either a ventriculostomy or ventriculoperitoneal shunt at the discretion of the neurosurgeon. Patients are allowed to have had more than one attempt at resection prior to enrollment.

13.4.2
For infratentorial tumors, suboccipital craniotomy or craniectomy should be performed using standard neurosurgical procedures. Midline tumors are best approached by a midline incision extending to the upper cervical region. When appropriate, the posterior arch of C-1 should be removed as well so that the tonsils and brainstem can be decompressed. A wide dural opening will permit exposure of the cerebellar vermis, tonsils, medulla, both cerebellar hemispheres, and the upper cervical region. Careful search for extension of disease in the arachnoid and leptomeninges should be made. Biopsies of these sites should be performed if disease extension is suspected. Evidence of brainstem invasion should be

sought and noted in the operative report if present. Replacement of overlying bone and posterior vertebral body elements should be reported. The use of Surgicel (Johnson & Johnson, Somerville, NJ) and other hemostatic products should be reported. The site of origin should be sought and described in the operative report.

13.4.3
Tumor should be removed and hemostasis achieved using standard techniques. The surgeon should try to remove as much of the tumor as is safely possible, without comprising function. If resection cannot be complete, surgeons should estimate in their reports the percentage of tumor removed.

13.4.4
As much tissue as possible should be submitted intact to the pathologists for review. At the time of **diagnosis and at the second surgery** (if applicable), specimens outlined in Section 14.0 of the protocol must be sent to the Biopathology Center (BPC). Unsafe tumor resection should not be undertaken for the purposes of tissue banking; however, removed tumor tissue should not be discarded.

13.4.5
Techniques for bone and dura closure will be left to the discretion of the neurosurgeon. Post-operatively, patients should be monitored for hematoma formation and hydrocephalus. A decision concerning placement of a permanent VP shunt should be made within two weeks of tumor removal.

## 13.5 Second Operation

13.5.1
**The definition of second surgery in this study is surgery performed after the administration of Induction chemotherapy and prior to radiation therapy.** The purpose of the second operation is to safely remove as much tumor as possible that persists after induction chemotherapy. If it is determined pre-operatively that residual tumor cannot be removed in its entirety, serious consideration should be made to resect the tumor to a minimum level of disease. Second surgery should be performed within 14 days after completing Induction Cycle B chemotherapy (Day 21). Conformal radiation therapy may then be given within 30 days after completing chemotherapy or second surgery. The timelines for the performance of second surgery and conformal radiation therapy are not rigid.

13.5.2
There is no limit to the number of surgery procedures performed prior to enrollment or following chemotherapy. We expect to see cases where "second" surgery is performed and post-operatively the institutional team determines that additional surgery is feasible or necessary prior to radiation therapy.

13.5.3
Guidelines for this operation are similar to those for the first operation; however, control of increased intracranial pressure and ventriculomegaly should not be concerns at this time. An approach most suitable to the child should be taken. The direction of approach can be either similar to the first operation or different from it depending on the site of residual disease and the judgment of the surgeon.

13.6 **Extent of Resection Definition and Treatment**
See Section 4.1.

## 14.0 NEUROPATHOLOGY GUIDELINES AND CENTRAL PATHOLOGY REVIEW SPECIMEN REQUIREMENTS

### 14.1 Histological Grading

14.1.1 Classic Ependymoma – WHO II
Classic ependymoma (EP) will be the classic lesion in which perivascular pseudorosettes are a requisite feature. Less cell-dense, more fibrillary regions may be present. Necrosis may be common. Unless very focal, and unaccompanied by regions of higher cellularity and mitotic activity, vascular endothelial proliferation is not permitted in this category.

14.1.2 Anaplastic Ependymoma (AEP) – WHO III
Anaplastic ependymoma will include only tumors with clearly defined ependymal differentiation, in the form of perivascular pseudorosettes. The defining features of "anaplasia" will be: 1) widespread regions of high cell density, 2) cytological atypia, and 3) microvascular proliferation. The hypercellularity may be diffuse or multifocal, the latter in the form of circumscribed regions that abut those of lower cell density. Atypia may be expressed as cells with increased nuclear pleomorphism and coarse chromatin. Vascular proliferation, of the glomeruloid variety, should be found within or just outside the hypercellular regions. The cellular anaplastic regions may be mitotically more active than those of lesser cellularity, although mitotic activity has not been quantified, nor has any threshold mitotic index been determined to direct the lesion into the AEP category. Grading may be difficult, because of variation in cell density and mitotic activity across the tumor. For this reason, we require vascular proliferation for this category, except in the few cases where overt atypia and abundant mitotic activity are clearly present.

### 14.2 Central Pathology Review Required for All Patients

The classification and grading of the tumors will be performed according to the WHO criteria.[49] A modification of these has been applied to a series of ependymoma with significant differences in outcome in patients with classic (WHO grade II) ependymoma and anaplastic (WHO grade III) ependymoma. The submission of pathology material shall be made directly from the participating institutions. Review pathologists may utilize unstained sections for a variety of supplementary tests, e.g., Ki-67. The remaining slides shall be kept as back-up material, or shall be used to perform additional staining as needed.

If pathologic interpretation relating to a patient being considered for ACNS0831 is considered difficult, it is possible to consult on the pathology with the central review pathologist, Dr. David Ellison at St. Jude Children's Research Hospital, ahead of enrollment and the submission of materials for central pathology review according to protocol. However, this request for a second clinical opinion is arranged in the usual way, from pathologist to pathologist, and not through the Biopathology Center. If the patient is subsequently enrolled on ACNS0831, the submission of pathology materials to the Biopathology Center must be followed; the consultation does not count as the central

pathology review and does not remove the need to submit specimens to the Biopathology Center.

Required Materials for Central Pathology Review (Rapid or Standard Central Review):

1) 1 x H&E stained slide and 1 x unstained spare from **ALL** available paraffin blocks
2) Representative paraffin embedded tissue block. If block is not available, submit 10 unstained slides from the most representative block.
3) Institutional pathology reports
4) Operative report(s)
5) COG Specimen Transmittal Form to accompany each shipment: Please use current form from https://www.cogmembers.org/site/prot/generic.aspx.

Please label all pathology review materials with patient's COG Patient ID Number and the Surgical Path ID (SPID Number) and block number from the corresponding pathology report.

It is the responsibility of the Principal Investigator enrolling a patient on this trial to request from the submitting pathologist that s/he send the appropriate set of forms, local pathology report and all required specimens to the Biopathology Center. The PI must enroll the patient onto the trial concurrently with this submission, so that a diagnosis can be entered on-line when rapid pathology review is undertaken for those patients with supratentorial ependymoma (see Section 14.2.1).

Please see below for information on whether to send a case for Rapid or Standard Central Review. Cases sent for Rapid Central Review must be marked for RAPID REVIEW and shipped FedEx Priority Overnight within 5 days of enrollment using the COG FedEx account (https://www.cogmembers.org/_files/reference/FEDEXmemo.pdf). Cases for Standard Central Review are shipped by regular mail or using your institution's courier account within 10 days of enrollment to:

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

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

14.2.1 Rapid Central Pathology Review for Patients with Supratentorial Primary Tumors

Only those patients with a supratentorial primary tumor location will require rapid central pathology review at study entry. Cases must be marked for rapid review and sent within 5 days of enrollment by Federal Express Priority Overnight to the Biopathology Center. Results of rapid central review will generally be available within 5 working days of the receipt of pathology review materials.

All supratentorial STR patients regardless of histology will receive induction chemotherapy. Only supratentorial patients who have Classic Histology confirmed

by central review and GTR1 will be assigned to observation; all other GTR 1/2 and NTR supratentorial patients will be randomized between a) (cRT) and maintenance chemotherapy **OR** b) (cRT) and Observation including:

- Classic Histology by central review with GTR2, NTR; OR
- Anaplastic Histology by central review with GTR1, GTR2, NTR; OR
- Rapid central pathology review cannot be performed for any reason; OR
- Tumor histologic grade is indeterminate by central review

Second Opinion for Discordant Diagnoses
In the event that a diagnosis other than ependymoma is returned at pathology review, the principal central review pathologist will liaise with the trial PI and registering center's pathologist about the diagnostic considerations, and the back-up central review pathologist will be consulted as appropriate.

GTR 1 Patients
Patients with supratentorial tumor location, extent of resection GTR1 and with a diagnosis of classic ependymoma (WHO grade II) by rapid central review will be assigned to Observation only.

In the event that a discordant grade is returned at pathology review, i.e., classic instead of anaplastic/indeterminate or vice versa, the principal central review pathologist will liaise with the trial PI and registering center's pathologist about diagnostic considerations, and the back-up central review pathologist will be consulted as appropriate. If the final assessment is classic ependymoma, the patient will be observed; if the final assessment is anaplastic ependymoma or indeterminate histology, the patient will be randomized. If the treating physician chooses to proceed with treatment according to the institutional review rather than the final central review, the patient will be removed from protocol therapy (see Section 8.1).

14.2.2 Standard Central Review of Pathological Data (Initial and Second Resection)
Within 10 days of enrollment, for patients with infratentorial primary tumor locations, institutions must submit materials for Standard Central Review. For all patients undergoing second surgery, institutions must submit materials for Standard Central Review within two weeks of second surgery.

## 15.0 OPTIONAL BIOLOGY STUDIES

**Participation in optional biology studies is strongly encouraged. In addition, institutions are encouraged to enroll and submit specimens for** APEC14B1, *Project:EveryChild A Registry, Eligibility Screening, Biology and Outcome Study.*

### 15.1 Biology Specimen Requirements

Process tumor specimens from first and second surgeries according to the guidelines below. Send snap frozen tissue and matched control blood specimens to the Biopathology Center in Columbus, Ohio. Portions of the tissue will be used for the correlative biology studies listed in Section 15.2.

15.1.1 Required Materials

At the time of **diagnosis and second surgery,** tumor tissue must be sent to the Biopathology Center for Biology Studies:

1) **Frozen Tumor Tissue**: As many 100 mg pieces of tissue as possible should be frozen in foil in liquid nitrogen within 10 minutes of removal. Frozen tissue should be sent on dry ice to the BPC. A minimum tumor tissue > 0.5 $cm^2$ is preferred.
   - If frozen tumor is not available, formalin-fixed block with >80% tumor should be sent although this will compromise the studies being performed. (Paraffin blocks will be retained at the BPC unless return is requested.)
   - If frozen tumor is not available **and** the institution cannot release blocks; three to ten 50 µm scrolls should be sent and 10 unstained slides. (Please indicate percent tumor represented.)
2) **Peripheral Blood**: 5 cc of peripheral blood in a green top tube (sodium heparin), 5 cc of peripheral blood in a yellow top tube (ACD) 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. For second surgeries, please send blood at this time also.
3) **COG Specimen Transmittal Form** must accompany each shipment. Please use current form available at https://www.cogmembers.org/site/prot/generic.aspx

Please label blood and frozen tissue with the patient's COG Patient ID Number, collection date and specimen type. Label block or slides with the COG Patient ID number, Surgical Pathology ID and block number. Include the corresponding pathology report with each shipment of tissue.

15.1.2 Specimen Shipment

The BPC will provide a dual chamber specimen procurement kit upon request. Kits are ordered via the BPC Kit Management system accessed via the following link: https://ricapps.nationwidechildrens.org/KitManagement/. The dual chambered kit allows for the shipment of room temperature and frozen specimens in the same container. Dry ice may be placed in either compartment of the kit, but should not be put in both. For packing and shipping instructions please see **Shipping Specimens in a Dual Chambered Kit** at https://www.cogmembers.org/_files/reference/labs/ShippingSpecimensDual.pdf.

Biology specimens may be shipped to the BPC using a FedEx shipping label provided by the BPC. Access the Kit Management application to print a shipping label. Please note that the BPC does not pay for shipments of blocks or slides when they are sent separately. Ship to:

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

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

### 15.2 Special Studies Performed on Samples

**All specimens will be banked and processed at the COG Biopathology Center (BPC) and distributed from there as well.**

Special studies will be performed on tumor tissue specimens collected from first and second surgeries and from the peripheral blood samples obtained prior to initiation of therapy and from any second surgeries.

Samples of the snap frozen tissue and samples of the matched control blood specimens will be used for the molecular genetic studies, by Dr. David Ellison and Dr. Nicholas Foreman and others as described below. The tissue will be collected centrally and distributed based on priority of the biologic correlative studies (see Section 15.3 below for priority list of studies).

### 15.3 Priority List of Special Biology Studies

The experimental approach is designed to make optimal use of tissue submitted to the COG Biopathology Center. In order to optimally interpret the trial's clinical data, molecular biomarkers in three categories will be assessed:

Study #1: Molecular groups as defined by DNA methylation profiling and immunohistochemistry.

- RELA (ST-RELA)
- YAP1 (ST-YAP1)
- PFA
- PFB

Study #2: Copy number variants

- 1q gain in posterior fossa ependymomas
- CDKN2A loss (homozygous deletion) in supratentorial ependymomas

Study #3: Specific genetic alterations

- RELA fusions, specifically C11orf95-RELA fusions
- YAP1 fusions
- H3 K27M mutation

### 15.4 Sample Processing at the BPC

Peripheral blood mononuclear cells (PBMCs) will be studied via flow cytometry. Blood will be processed to remove red blood cells (ficol or lyse), and the resulting PBMC will be viably frozen using freezing media.

15.5 **Methodology**

Molecular groups will be determined by DNA methylation profiling using DNA extracted from FFPE tissue and Illumina EPIC (850K) arrays. Immunohistochemistry for H3 K27-me3 will also be used to identify PFA and PFB tumors.[33] The copy number variants 1q gain and CDKN2A loss can be assessed as part of the analysis of data from DNA methylation profiling arrays and will also be evaluated by interphase fluorescence in situ hybridization (iFISH).[36] iFISH with break-apart probes to RELA and YAP1 loci on 11q13 and 11q22, respectively, can be used to detect gene rearrangements and is a surrogate marker of RELA and YAP1 gene fusions in supratentorial ependymomas.[31] H3 K27M mutation can be detected by immunohistochemistry with a mutation-specific antibody that has found significant utility in diagnostic laboratories for identifying diffuse midline gliomas.[32]

Immunohistochemistry and interphase fluorescence in situ hybridization (iFISH)

Clinical standard operating procedures, as used in the Anatomic and Molecular Pathology sections of the St. Jude Pathology department, will be used for immunohistochemistry and iFISH. The following antibodies and probes will be used:

*Immunohistochemistry:*

- RevMab Biosciences anti-histone H3 K27M (clone – RM192)
- Cell Signaling anti-histone H3 K27-trimethylation

*iFISH*:

Break-apart probes are used in the evaluation of the C11orf95, RELA, and YAP1 loci. Copy number at the EXO1 (1q) and CDKN2A loci is assessed with reference to a control probe on the other chromosome arm.

| | |
|---|---|
| CTD-3241G19 | 1p (control) |
| RP11-610O24 | 1q (EXO1) |
| | |
| CH17-384P01 | *CDKN2A* |
| RP11-235C23 | 9q (control) |
| | |
| CH17-215P06 | *C11orf95* ba-c |
| CH17-67K13 | *C11orf95* ba-c |
| CH17-388O01 | *C11orf95* ba-t |
| | |
| CH17-14J18 | *RELA* ba-c |
| RP11-642F7 | *RELA* ba-c |
| CH17-211O12 | *RELA* ba-t |
| | |
| CH17-380G02 | *YAP1* BA-c |
| RP11-11N20 | *YAP1* BA-c |
| RP11-1082I13 | *YAP1* BA-t |

DNA methylation profiling for determination of molecular group and assessment of copy number variation

Genomic DNA extracted from available FFPE tissue samples using a QIAamp DNA FFPE Tissue Kit (Qiagen) will be used to generate DNA methylation data on Illumina Infinium MethylationEPIC BeadChip arrays according to the manufacturer's instructions. DNA samples will be checked for quality using the Infinium HD FFPE QC Assay Protocol, followed by bisulfite conversion using EZ-96 DNA Methylation™ Kit (Zymo Research Corp). The purified converted DNA will then be restored, following the Infinium HD FFPE Restore Protocol, to a state amplifiable by the Infinium HD FFPE methylation whole genome amplification protocol. After whole genome amplification, endpoint fragmentation and cleanup, the DNA samples will be hybridized onto the BeadChips, followed by washing, single-base extension and staining. Finally, the BeadChips will be scanned by the iScan System in the setting of Methylation NXT.

All computational analyses will be performed in R. Raw signal intensities will be obtained from IDAT-files using the minfi Bioconductor package. Each sample will be normalized by performing a background correction (shifting of the 5% percentile of negative control probe intensities to 0) and a dye-bias correction (scaling of the mean of normalization control probe intensities to 10,000) for both color channels. Beta-values will be calculated from the retransformed intensities using an offset of 100 (as recommended by Illumina). Before unsupervised clustering analysis the following filtering criteria will be applied: removal of probes targeting the X and Y chromosomes (n=11,551), removal of probes containing a single-nucleotide polymorphism (dbSNP132 Common) within five base pairs of and including the targeted CpG-site (n=7,998), and probes not mapping uniquely to the human reference genome (hg19) allowing for one mismatch (n=3,965).

### 15.6 Future Studies with Remaining Banked Biospecimens

Prior to the use of any remaining banked samples following the correlative studies described in Section 15.3, a protocol amendment or separate biology proposal will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

## 16.0 NEUROPSYCHOLOGICAL FUNCTION STUDY

Enrollment onto the neuropsychological function study ALTE07C1 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.

Because of the high risk of neurodevelopmental problems in young children treated for ependymoma, assessment of functional and neuropsychological status will be completed to obtain information about tumor and treatment related morbidity. The premise of this study is that newer radiation planning and delivery techniques are capable of reducing neuropsychological sequelae for all children, including the very young. While it has historically been difficult to obtain neuropsychometric data in a cooperative group study, these data are nonetheless critical to the success of this treatment approach and its acceptance by patients, parents and the neuro-oncology community.

## 17.0 NEUROIMAGING 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 Rapid Central Review

All patients will have Central Review, however, **Rapid Central Review** will be performed at 2 time points **ONLY FOR PATIENTS WHO HAVE SUB-TOTAL RESECTION** after initial surgery: 1) After induction chemotherapy to determine response and 2) After second surgery to determine extent of resection. MRI scans must be submitted for rapid Central Review within 3 days. Results will be available on the RDE system within 1 week after IROC RI (QARC) has received a reviewable copy of the scans. See Section 17.6 regarding submission guidelines for central review.

- Studies to be submitted for rapid central review with radiology and operative reports:
  - Pre-op and post-op brain MRI (If not previously submitted)
  - Pre-op or post-op spine MRI with radiology (If not previously submitted)
  - Brain MRI at the end of Induction
  - Brain MRI after second surgery

MRI studies must be submitted for rapid Central Review in Dicom format on a CD or electronically. Film copies will not be accepted.

In instances in which the Central Review differs from that of the institution, a second central radiology reviewer will examine the films and will function as an adjudicator in order to facilitate appropriate stratification. If such discrepancies cannot be immediately resolved, a web-based or phone conference will be organized by IROC RI (QARC) to expedite resolution of any discrepancies in interpretation of the imaging data.

### 17.2 Neuroimaging

The neuroimaging (MR) examination is the basis for determining the extent of resection and/or induction chemotherapy response, and subsequent therapy. The determination of residual disease is based on abnormal anatomy. Ependymoma has a mixed pattern of enhancement and requires evaluation with all available imaging sequences including enhanced and non-enhanced, T1 – weighted, T2 – weighted, Fluid Attenuated Inversion Recovery (FLAIR) techniques capable of water suppression to define residual tumor, as well as diffusion MR, where available.

### 17.3 MR Brain With and Without Contrast

To document the degree of residual tumor, pre and post-operative MR imaging of the brain with and without contrast (gadolinium) must be performed. Post-operative imaging of the brain should be done within 72 hours of surgery and prior to the onset of edema or gliosis which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time, or the scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.

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 (depending on tumor)

Precontrast:

1. Axial 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 diffusion tensor, 30 directions, 2.5-5 mm skip 0 (1 NEX, matrix 96 x 96, FOV = 24, B = 1000)

Post contrast:

1. Coronal T1: 4mm skip 0.4
2. T1-weighted gradient echo volume sequence (SPGR or equivalent)
3. Axial Perfusion (see optional sequences,

Notes:

1. DO NOT INTERLEAVE T1 weighted sequences
2. Flow compensation should not be used / not on all T1 enhanced sequences
3. Fat Saturation not necessary

### 17.4 Tumor Measurements

The dimensions of the tumor will be recorded for the L-R, A-P and S-I dimensions. Measurements of combined solid tumor and cyst will be obtained in its maximum dimension as well as through 2 perpendicular planes.

### 17.5 MR Spine Imaging

Pre-operative or post-operative MRI must be performed within 10 days prior to surgery or 10 or more days after surgery. It is preferable to have a Spine MRI with and without gadolinium, however, we recognize that many sites only perform post-operative spine MRI with gadolinium. This is acceptable if it is of good quality and no hemorrhage is present. The MRI of the spine should include the entire spine and must be performed in at least two planes. If there is significant motion artifact and/or hemorrhage, then the scan is not evaluable and should be repeated.

At a minimum, MRI of the entire spine should be obtained in the sagittal plane with both post gadolinium T1-weighted imaging and T2-weighted images, to assess for the presence of drop metastases. If present, the largest dimension of the largest metastasis will be measured.

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

For primary tumors of the spinal cord, add:

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

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 artifacts)
- 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 artefacts from physiologic motion (cardiac, respiratory) or from CSF pulsation.
2. T2 weighted sequences (sagittal or axial) are not needed. They are optional.

### 17.6 Central Review

Central review will be performed to confirm eligibility, response and relapse by the study neuroradiologists. As of Amendment #1D, imaging during follow-up (retrospective and prospective) will be submitted for all patients who received radiation therapy.

Please see Section 17.1 for guidelines regarding Rapid Central Review for patients who have sub-total resection. The following scans should be submitted for central review for all patients in addition to the operative report:

Head MR: Axial T1-weighted images without contrast; axial T1-weighted images with contrast; T2-weighted images; FLAIR images, coronal and sagittal post gadolinium T1-weighted images. Post contrast T1-weighted images should preferably be 4 mm thick slices with no skip

Spine MR: pre or post-operative sagittal post-contrast T1-weighted and T2-weighted images at a minimum.

The size of the tumor and metastases will be recorded to assess response.

The following scans and reports must be submitted with the operative report(s):

| | Scan | Brain | Spine |
|---|---|---|---|
| 1) | Preoperative (initial) | X | X (pre or post-op) |
| 2) | Postoperative | X | X (pre or post-op) |
| 3) | Post Induction Chemotherapy (Cycle B Days 21-29) | X | X |
| 4) | Post Second Surgery (If applicable) | X | - |
| 5) | Post RT (4 weeks post RT) | X | - |
| 6) | End of Maintenance Chemotherapy | X | X |
| 7) | Relapse | X | X |

Note: As of Amendment #1D, patients with reported Grade 3 or above CNS system necrosis within 2 years of study enrollment must submit imaging and reports for central review within 2 weeks of completion. Patients who experience toxicity must continue to have imaging submitted up to 2 years after study enrollment. See Section 11.4.

The study committee requests submission of pre and post-operative imaging from any and all surgeries performed to resect tumor in addition to those noted above. This includes patients who have more than one surgery prior to enrollment or more than one surgery after induction chemotherapy. Please also include any repeat Brain MRs done prior to starting treatment.

### 17.7 Address Information

Copies of the required studies for central review should be forwarded to:

IROC Rhode Island
Building B, Suite 201
640 George Washington Highway
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

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 http://irocri.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.

## 18.0 RADIATION THERAPY GUIDELINES

**Radiation Therapy (RT) can only be delivered at approved RT facilities (COG administrative policy 3.9).**

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**

The indications and sequencing of radiation therapy for this protocol will be based on extent of resection and tumor grade and location. Patients enrolled on this protocol after subtotal resection will receive induction chemotherapy for seven weeks followed by second surgery and radiation therapy. Patients enrolled after gross-total or near-total resection will receive immediate post-operative radiation therapy unless they have microscopic gross-total resection (GTR1) and supratentorial, classic ependymoma. Maintenance chemotherapy after radiation therapy will be mandated for certain patients and randomized for others. This study specifies a 5mm clinical target volume margin and mandates the use of CT-MR registration to define the target volumes. 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.

18.0.2 **Treatment Planning Specifics**

The guidelines for this study were developed based on the performance of COG investigators when executing the guidelines for ACNS0121 and the experience from St. Jude Children's Research Hospital prospectively monitoring the side effects of conformal radiation therapy in young children with ependymoma. The prescribed dose for ependymoma has evolved to a standard of 59.4 Gy when using a clinical target volume margin of 1cm for all children except those under the age of 18 months treated with gross-total resection. There are ample data demonstrating that these prescribed doses and target volumes are reasonable and safe. The data suggest that further volume reductions are warranted because of the correlation between radiation dose, treatment volume and a variety of functional outcomes. In this study, the clinical target volume has been reduced to 0.5 cm with the expectation that the dose will be lower to normal tissues and side effects will be reduced. To achieve the protocol specified dose of 59.4 Gy and respect normal tissue tolerances, with emphasis on dose to the spinal cord, brainstem and optic chiasm, prior protocols have emphasized a two phase approach. The two phase approach included 54 Gy administered during the first phase followed by a second phase reduction in the treatment volume to exclude spinal cord, brainstem or optic chiasm, when indicated. Because of the association of the brainstem and the target volume in patients with infratentorial ependymoma, prior studies using photons have not specified brainstem dose-volume constraints and few unexpected adverse events have been observed in these patients. Children with ependymoma tend to be young and vulnerable from the events leading to diagnosis and neurosurgery. We continue to place an emphasis on reducing dose to normal tissues and have designed a new algorithm to follow that specifies a volume-based change in treatment after 54 Gy. The goal is to achieve a minimum dose level of 54 Gy to the planning target volume before further reducing dose to spinal cord, brainstem and optic chiasm, when indicated.[50,51] We will continue to limit the total dose to 54 Gy for children under the age of 18 months at the start of irradiation provided that they have undergone gross-total resection. Additional limitations in radiation dose and volume will be applied for patients treated using proton therapy.

18.0.3 **Credentialing Requirements**

Radiation therapy will be administered using protons or photons. Allowable photon methods include 3D-conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). Proton therapy may be delivered using passively scattered proton or scanning beams provided that the specific beam line has been approved for use in clinical trials by IROC Houston (RPC). 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 irradiate the IMRT Head and Neck Phantom available from IROC Houston (RPC). See http://rpc.mdanderson.org for information regarding the phantom irradiation and other credentialing requirements. All centers participating in this protocol must complete the IROC RI (QARC) CT/MR image fusion benchmark, which is available from the IROC RI QA Center (http://iroc.qarc.org/ ).

18.0.4 **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 http://iroc.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.

18.0.5 **Guidelines and Requirements for the Use of Proton Beam Therapy**

Investigators using proton beam therapy will be required to comply with the guidelines for the use of protons in National Cancer Institute sponsored cooperative group trials. These guidelines are available at http://www.irocri.qarc.org and http://rpc.mdanderson.org. The guidelines specify the following for the participating institution: both scattered and scanned proton beams may be used provided that the specific beam line has been approved by IROC Houston; the IAEA TRS 398 protocol shall be used for beam calibration; dose reporting will be in Cobalt Gy Equivalent (1 CGE = 1 proton Gy * 1.1). Radiation doses shall be prescribed using protocol specified definitions for gross (GTV) and clinical (CTV) target volumes. For set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis as appropriate. The proton institution is required to participate in on-site and remote review according to COG guidelines.[52-54]

18.0.6 **Rationale for Limiting Radiation Dose and Volume to the Brainstem Using Proton Therapy**

Local failure is predominant mode of failure in children treated with post-operative radiation therapy for ependymoma. Beginning with the POG-9132 study (1991-1994) the primary site dose was escalated to 69.6 Gy using a hyper-fractionated approach (1.2 Gy BID) and later to 59.4 Gy (1.8 Gy daily) consistent with the treatment of other aggressive or high-grade brain tumors. Based on the reported experience at St. Jude,[20] which included a high-rate of gross-total resection (>80%), the cumulative incidence of local failure was approximately 16.3% (9.6-23.0, 95% CI) when measured at 5-7 years.

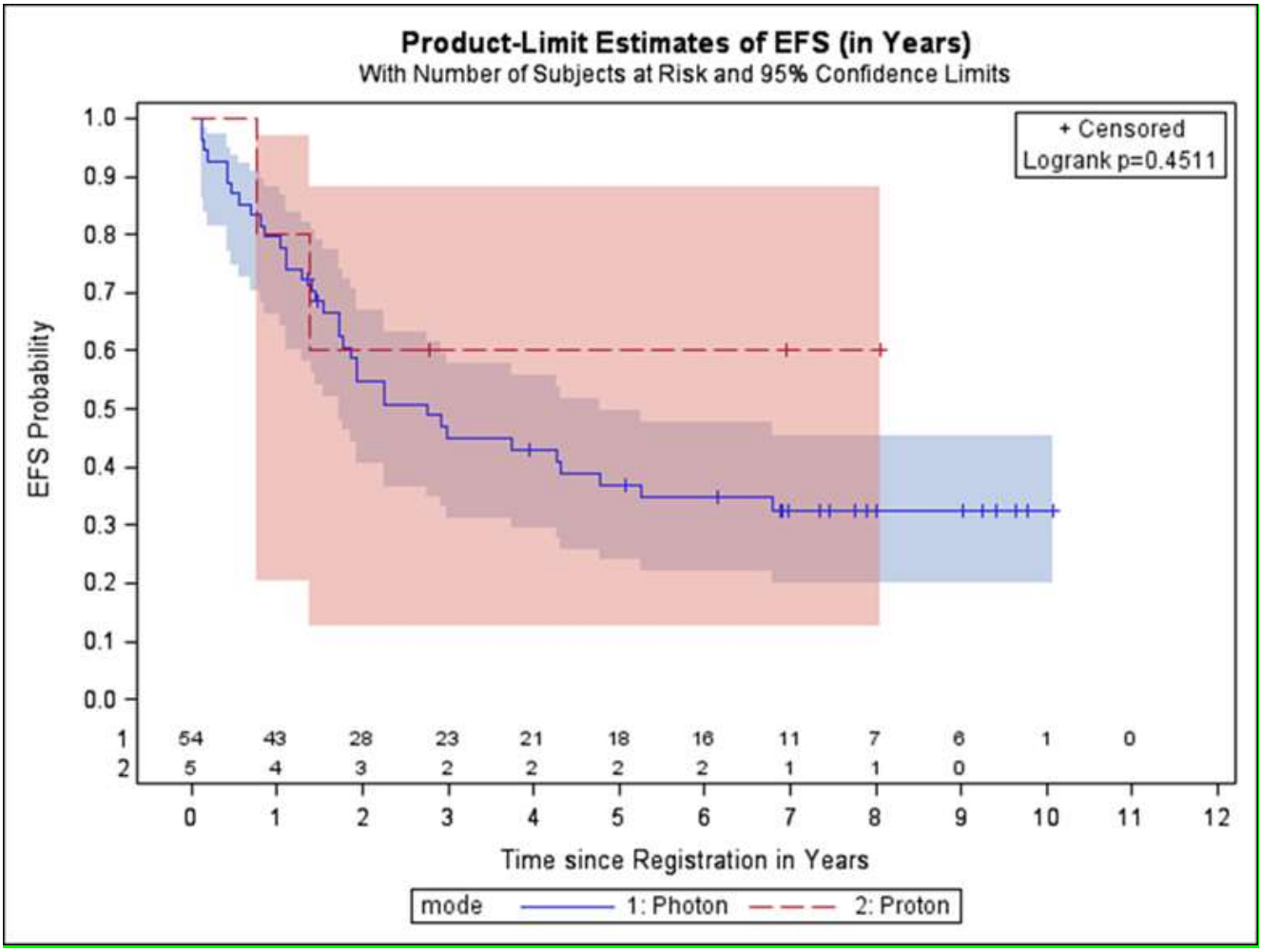
The following table (Table 18.0) provides information about photon and proton therapy trials for children with ependymoma. The number of children treated using 54 Gy is small in any of the north American series; however, for the European series ([55,56] – presented at ESTRO 2015) better rates of tumor control are observed in patients treated with the higher dose regimens.

**Table 18.0**

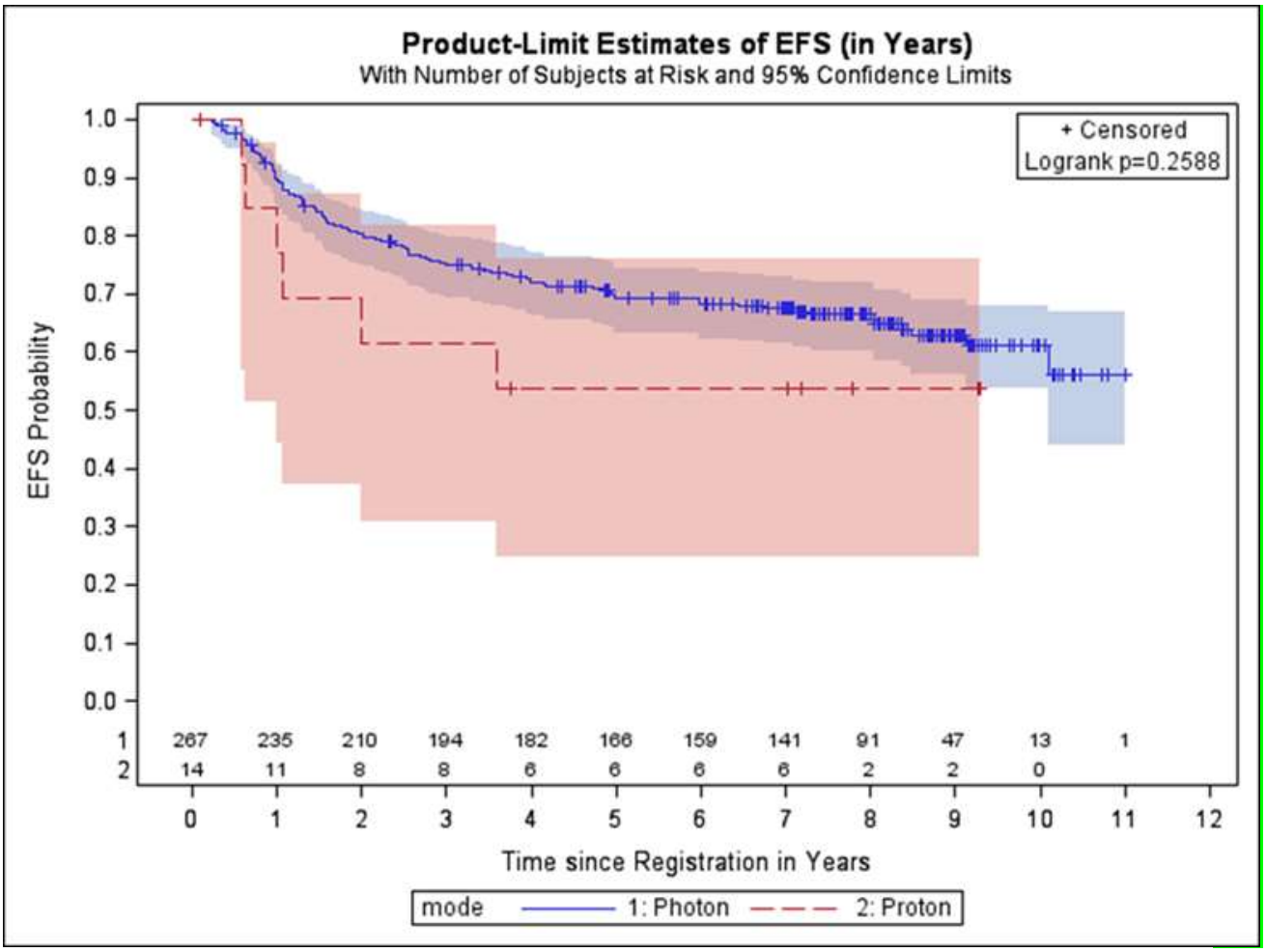
| Source | Treatment Dates | Age Restriction | Target Volume | CTV Margin | Dose Regimens cGy/CcGE | Total Irradiated | Location Ratio (IT/ST) | Modality |
|---|---|---|---|---|---|---|---|---|
| **US Cooperative Group Studies** | | | | | | | | |
| **POG-9132[57]** | **1991-1994** | **>36mo** | **Pre-op** | **2.0cm** | **69.6/1.2 BID** | **31** | **31/0** | **Photon** |
| **CCG-9942 [15]** | **1995-1999** | **>36mo** | **Pre-op** | **1.5cm** | **59.4/1.8 55.8/1.8*** | **84** | **49/35** | **Photon** |
| **ACNS0121** | **2003-2007** | **>12mo** | **Post-op** | **1.0cm** | **59.4/1.8 54.0/1.8**** | **378** | **258/96†** | **Photon-Proton** |
| **ACNS0831** | **2010-Present** | **>12mo** | **Post-op** | **0.5cm** | **59.4/1.8 54.0/1.8**** | **>300** | **Not yet known** | **Photon-Proton** |
| **Single or Multi-Institution Studies** | | | | | | | | |
| **St. Jude [20]** | **1997-2003** | **>12mo** | **Post-op** | **1.0cm** | **59.4/1.8 54.0/1.8**** | **153** | **122/31** | **Photon** |
| **PSI [58]** | **2004-2013** | **>12mo** | **Post-op** | **1.0-0.5cm** | **59.4/1.8** | **50** | **36/14** | **Proton-PBS only** |
| **French Cohort [55]** | **2000-2013** | **>36mo** | **No details** | **No details** | **59.4/1.8 54.0/1.8** | **177** | **136/41** | **Photon-Proton** |
| **Italian Cohort[56]** | **2003-** | **>36mo** | **No details** | **No details** | **59.4/1.8 67.8/1.8-2.0***** | **160** | **110/50** | **Photon** |

Legend:
IT = infratentorial, ST = supratentorial, †-2 patients had trans-tentorial tumors
*Patients with GTR and infratentorial tumors, or residual tumor (infratentorial or supratentorial) received 59.4 cGy. Patients with GTR and supratentorial tumors received 55.8 cGy.
** - Patients less than 18 months of age at resection and GTR1 (gross total resection with no visible residual tumor identified at surgery or on post-operative imaging) or GTR2 (microscopically visible residual tumor identified at surgery an no evidence of disease on post-operative imaging) received 54 Gy.

The following graph compares the ACNS0121 Stratum 2 (sub-total resection/ chemotherapy/second surgery when feasible/radiation therapy) proton and photon patients. There were two local failures amongst 5 patients.




The following graph compares the ACNS0121 Stratum 3+4 (near- or gross-total resection/radiation therapy) proton and photon patients. There were 4 distant and 2 local failures amongst 13 patients.




Summary of ACNS0121 proton review – there are too many different groups and clinical factors to suggest that a deviation in radiation dose of less than 10% has any impact on outcome.

Among patients with infratentorial tumors who received either 54 GyE (n=4) or 59.4 GyE (n=8) proton therapy on ACNS0121, one of 4 patients who received 54GyE experienced distant progression; 6 of 8 patients who received 59.4 cGyE experienced progression (3 local and 3 distant).

The investigators further narrowed the subgroup of patients receiving 54 GyE or 59.4 GyE proton therapy on ACNS0121 to include only those patients with infratentorial tumors with a gross/near total resection (strata 3 and 4) (total n=8). One of 3 patients who received 54 cGyE experienced progression (distant) and 4 of 5 patients who received 59.4 cGyE experienced progression (1 local and 3 distant).

The RT guidelines for the ACNS0831 protocol (activated 3/29/2010) were developed based on the guidelines used in the ACNS0121 protocol. The ACNS0121 protocol guidelines were widely accepted. There are notable differences between the ACNS0121 and ACNS0831 RT guidelines. In ACNS0831 the investigators reduced the clinical target volume margin from 1.0 cm to 0.5 cm, there was a mandated target volume reduction after

5400 cGy, quantitative normal tissue constraints were included, and the guidelines for proton therapy were more specific.

Review of the patients that have been treated thus far on ACNS0831 reveals that there is some evidence that investigators are reluctant to treat patients with infratentorial tumors using doses in excess of 54 Gy on this study even though the initial target volume margins are smaller (CTV1=0.5cm and PTV1=0.3cm) than for the prior study (CTV=1.0cm and PTV=0.5cm) and there is a mandated volume reduction for treatment from 54 Gy to 59.4 Gy and investigators are allowed to prioritize normal tissue dose constraints over target volume (PTV2) coverage. Without considering the rate of enrollment, investigator reluctance to use doses > 54 Gy does not appear to have reached a level that affects current protocol performance, compromises disease control, or risks poor functional outcomes. The modification of the guidelines previously proposed was meant to strengthen, clarify, and increase acceptance of existing guidelines. The intent was not to compromise treatment of the initial target volume to a minimum of 54 Gy. The goal was to allow for supplemental ("boost") irradiation of at highest risk for local tumor recurrence to 59.4 Gy prioritizing a more stringent brainstem dose constraint and highlighting that investigators could limit the CTV expansion into the brainstem.

The Study Committee has amended the protocol with Amendment #1D to reflect this shift in practice which will help provide uniformity going forward and a way to look at the data on the patients already treated to provide helpful data in future COG studies to answer the questions posed about toxicity and tumor control.

### 18.1 Indications for Radiation Therapy

Patients enrolled on this protocol after subtotal resection will receive induction chemotherapy for seven weeks followed by second surgery and radiation therapy (except for supratentorial classic patients with GTR1 after second surgery, who will not be irradiated).

Patients enrolled after gross-total or near-total resection will receive immediate post-operative radiation therapy unless they have microscopic gross-total resection (GTR1).

Patients enrolled after microscopic gross-total resection (GTR1) and supratentorial, classic ependymoma will not be irradiated.

### 18.2 Timing

18.2.1 All patients who will require irradiation should be seen in consultation by a radiation oncologist at the time of study enrollment. The purpose of the consultation is to participate in staging and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning.

18.2.2 There are no contraindications to radiation therapy. Patients taking phenytoin should be weaned and/or switched to a different anticonvulsant as soon as feasible.

### 18.3 Emergency Irradiation

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol and urgent irradiation is not envisioned under any circumstance.

## 18.4 Equipment and Methods of Delivery and Verification

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

18.4.1 Treatment planning

CT (volumetric) based planning is required to optimize dose to the PTV while protecting normal tissues. Organs at risk within the irradiated volume should be contoured including those required. A DVH is necessary to determine target coverage and evaluate dose to normal tissues. CT section thickness should be ≤ 5mm although 2–3mm is preferred.

18.4.2 In-room verification of spatial positioning

18.4.2.1 Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

18.4.2.2 Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging. A printout or screen capture of representative axial images showing the isocenter and the correct alignment in relationship to the patients' position will be considered documentation of positioning. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

## 18.5 Target Volumes

18.5.1 General comments

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62, and 78 (https://icru.org/) define prescription methods and nomenclature that will be utilized for this study. Although the MRI obtained immediately prior to radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after surgical resection. Most patients with ependymoma require a combination of pre- and post-operative MR sequences to delineate the extent of disease. MR pre- and post-gadolinium contrast T1, T2, and FLAIR sequences should be reviewed. The sequence that best defines the extent of residual disease and post-operative tumor bed should be registered to the treatment planning CT and used to determine the GTV. The GTV, CTV and PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

The target volume definitions for this protocol are similar to those used in the ACNS0121 study with notable exceptions: the clinical target volume margin is

5mm and there is a mandatory target volume reduction after 54 Gy. On the ACNS0121 study the clinical target volume margin was 10 mm and there was not a target volume reduction. The most practical way to comply with this protocol would be to follow the steps outlined below and consider the information contained in the more formal definitions of the target volumes.

Practical Targeting Guidelines for GTV1, CTV1, and PTV1

- Obtain a treatment planning CT using a 2–3 mm image section thickness. Contrast is not required.
- Register the pre-operative MR sequences that best demonstrate the full extent of disease. Most often this would be the T2 or FLAIR MR sequences. In some cases, the post-contrast T1-weighted MR sequences will be useful.
- Contour the pre-operative tumor (GTV_PREOP) on the registered MR data to satisfy the protocol requirement to delineate this volume.
- Register the post-operative or more recently acquired (when available) pre-irradiation T1-weighted MR image data to the treatment planning CT. Register other imaging data sets as required to delineate post-operative residual disease and the tumor bed.
- Contour GTV1 which is defined the post-operative residual disease and the edge of the (often collapsed) post-operative tumor bed. The edge of any structure in contact with the pre-operative tumor (GTV_PREOP) should be included as part of GTV1.
- Expand GTV1 geometrically by 5mm to create CTV1. The physician should modify CTV1 at non-neural and neural interfaces where invasion is unlikely. This would include the inner-table of the skull, base of skull and tentorium for non-neural structures. For neural structures this would include brainstem, uninvaded ventricle wall, and borders associated with mass effect.
- Expand the final form of CTV1 geometrically by 3 or 5 mm to create PTV1 (Section 18.5.8).

Practical Targeting Guidelines for GTV2, CTV2, and PTV2

- GTV2 may be the same as GTV1 or modified from GTV1 depending on the clinical scenario as defined in Section 18.5.5.
- There is no CTV2.
- Expand GTV2 geometrically by 3 or 5 mm to create PTV2 (see Section 18.5.9).

### 18.5.2 Photon definitions for GTV, CTV, and PTV

- Gross tumor volume (GTV) is based on the post-operative MR examination and includes gross residual tumor and the tumor bed at the primary site. In defining the GTV, the investigator should consider the initial pre-operative imaging examination that defined the extent of tumor and the tissues involved anatomically. The GTV in most cases will be a contracted or collapsed tumor bed. Tissue defects resulting from surgical approaches will not be included as part of the GTV when not previously involved by tumor. Investigators should register the pre-operative MR imaging sequence that demonstrated tumor and contour the structure to be identified as **GTV_preop** to assist in the delineation and evaluation of the GTV**.**

- Clinical target volume (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, falx, and tentorium where applicable or extends up to but not beyond neuroanatomic structures through which tumor extension or invasion is certain not to have occurred); the CTV margin will be 5mm for all patients. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires treatment planning MR and/or diagnostic MR imaging data with image section thickness ≤ 5mm. **In the setting where the target volumes interface with the brainstem, the expansion of the CTV into the brainstem should be limited to 3mm.**

- Planning target volume (PTV) includes a margin which is added to the CTV in 3-dimensions to create the PTV. It is geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 3 or 5mm. The use of a PTV margin of 3mm requires written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging. For this study, IGRT is defined as 2- or 3-dimensional digital imaging positioning. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient. The PTV margin chosen by the treating investigator requires treatment planning MR and/or diagnostic MR imaging data with imaging section thickness ≤ the chosen PTV margin.

18.5.3 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 18.6.3.

18.5.4 Gross Tumor Volume 1 (GTV1)

GTV1 will include the post-operative resection margin of tissues initially involved with disease and the entirety of residual tumor defined on post-operative MR with consideration given to the pre-operative imaging evaluation. In the setting of gross-total resection, the post-contrast T1-weighted MR sequence is generally the most useful. In the setting of non-enhancing residual disease, T2-weighted imaging may be required. GTV1 will take into account changes in brain anatomy resulting from tumor resection or CSF shunting.

- GTV1 is the volume of tissue containing the highest concentration of tumor cells.
- GTV1 includes the post-operative tumor bed which is the edge of the resection cavity.
- GTV1 includes residual disease defined by post-operative neuroimaging.
- The surgical corridor should not be included in the delineation of the GTV unless suspected to contain tumor.
- When there is discrepancy between imaging studies or intra-operative findings, the larger volume will define GTV1.

18.5.5 Gross Tumor Volume 2 (GTV2)

The purpose of GTV2 is to administer radiation dose to the volume of tissue containing the highest concentration of tumor cells and allow the investigator to limit dose to the spinal cord, brainstem and optic chiasm after the initial phase of treatment to 54 Gy. There are several options to define GTV2: GTV2 may be the same as GTV1 when the composite plan dose distributions to the optic chiasm and spinal cord do not exceed the recommendations in Section 18.8. When the recommended spinal cord dose distribution might be exceeded, GTV2 should be equal to GTV1 minus the any portion of GTV1 caudal to the intracranial aspect of the foramen magnum. When the recommended optic chiasm dose distribution might be exceeded, GTV2 should be equal to GTV1 minus the optic chiasm with a planning organ at risk (PRV) margin equal to the margin chosen for PTV1. When both the spinal cord and optic chiasm dose distributions might be exceeded, both of the outlined procedures should be followed.

- Option 1: GTV2 = GTV1
- Option 2: GTV2 = GTV1 minus the GTV1 volume caudal to the foramen magnum
- Option 3: GTV2 = GTV1 minus (optic chiasm + PRV margin chosen for PTV1)
- Option 4: GTV2 = combined procedure used for options 2 and 3

18.5.6 Clinical Target Volume 1 (CTV1)

- CTV1 is defined as the volume of tissue containing subclinical microscopic disease
- CTV1 for this protocol is the GTV1 with an anatomically confined margin of 0.5cm
- CTV1 should be tailored at tissue interfaces where invasion/infiltration is not likely
- CTV1 extent in brainstem should be limited to 3mm

CTV1 may be manually moved inward to the inner table of the bony calvarium

18.5.7 Clinical Target Volume 2 (CTV2)

- CTV2 = There is no CTV2

18.5.8 Planning Target Volume 1 (PTV1)

The PTV-1 will include the CTV-1 plus a geometric margin of 3 or 5mm in all dimensions. The PTV may extend beyond bone margins and the skin surface. There are two options for PTV1 depending on the institutional method for daily

localization, verification and interventions performed to reduce the set-up uncertainty.

- Option 1: PTV1 = 3mm (requires daily digital imaging and intervention or equivalent, 18.5.2)
- Option 2: PTV1 = 5mm (no special requirements)

18.5.9 Planning Target Volume 2 (PTV2)

- The PTV2 will include GTV2 with an additional margin equal to the margin used to create PTV1. PTV2 may extend beyond bone margins and the skin surface.
- Option 1: PTV2 = 3mm (requires daily digital imaging and intervention or equivalent, 18.5.2)
- Option 2: PTV2 = 5mm (no special requirements)
- **There is no PTV2 for children under the age of 18 months at the start of irradiation if their extent of resection has been characterized as gross-total resection.**

## 18.6 Target Dose

18.6.1 Dose Definition

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

18.6.2 Prescribed dose and fractionation

- Planning Target Volume 1 (PTV1): The total dose to the PTV1 prescription isodose surface will be 5400 cGy administered in 30 fractions of 180 cGy. The patient should be treated with one fraction per day. All fields should be treated each day in photon treatments. Simultaneous integrated boost is not allowed.

- Planning Target Volume 2 (PTV2): The total boost dose to the PTV2 prescription isodose surface will be 540 cGy administered in 3 fractions of 180 cGy. The cumulative dose will be 5940 cGy. The patient should be treated with one fraction per day. All fields should be treated each day in photon treatments. Simultaneous integrated boost is not allowed. **Children under the age of 18 months at the start of irradiation will not receive boost treatment after 54 Gy provided their extent of resection has been characterized as gross-total resection.**

**Table 18.6.2 Prescribed Doses and Fractionation**

| Nominal Dose by Site | Target Volume | Dose/fraction | *Number of Fractions* |
|---|---|---|---|
| Primary Site 5400 cGy | PTV1 | 180 cGy | *30* |
| *Primary Site Boost 540 cGy†* | *PTV2* | *180 cGy* | *3* |

† Primary site boost treatment will not be administered to children under the age of 18 months at the start of irradiation if their extent of resection has been characterized as gross-total resection.

18.6.3 Dose uniformity

For photons, at least 95% of the protocol-specified dose should encompass 100% of the PTV1/PTV2 and no more than 10% of PTV1 or PTV2 should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

For protons, at least 95% of the protocol-specified dose should encompass 100% of the PTV1/PTV2 and no more than 10% of PTV1 or PTV2 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 or 5 mm according to Section 18.5.8 or Section 18.5.9. 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 Margin† = CTV + Range Uncertainty + Set-up Margin + Internal Margin

- CTV = the distal aspect of the CTV
- Range Uncertainty = 1.5% of the water-equivalent range of the CTV at max depth
  - ≥ 1 mm
- 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
  - ≥ 1 mm

†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 4 mm.

When pencil beam scanning techniques are used with scenario based optimization (also known as robust optimization), the plan may be optimized for 100% of the CTV to receive 95% of the protocol-specified dose. The protocol-defined PTV should be reviewed to confirm sufficient coverage.

18.6.4 Tissue heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. For questions about heterogeneity corrections or approved algorithms, please contact IROC RI (QARC) (http://iroc.qarc.org/).

18.6.5 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

## 18.7 Treatment Technique

18.7.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissues.

18.7.2 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 Section 18.6.3. 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.

18.7.3 Field Shaping

Field shaping for photons will be done with either customized cerrobend blocking or multileaf collimation. For passive scattering or uniform scanning proton techniques, field shaping will be done with either brass apertures or proton-specific multileaf collimation.

18.7.4 Simulation including patient positioning and immobilization

18.7.4.1 Patient positioning

Reproducible setups are critical and the use of immobilization devices is strongly encouraged. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

18.7.4.2 Immobilization devices

Standard immobilization devices for the torso, extremities or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

18.7.5 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

18.7.6 Motion Management and Margins to Account for Target Volume Changes During Treatment

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the IM component of the PTV and is meant to account for potential motion or changes in the CTV. The planning organ at risk volume (PRV) includes the corresponding organ at risk (OAR) volume surrounded by a margin to compensate for motion or physiologic change in the OAR. If adequate clinical data do not exist to define the IM component of the PTV or the PRV margin, the following suggestions are provided:

- A margin matching the PTV margin may be added to any OAR to form the PRV.
- Brain tumors susceptible to cyst expansion should be monitored closely.
- Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele or steroid use should be monitored carefully and with repeat imaging when indicated.

18.7.7 Treatment Planning Procedures

Table 18.7.7

| |
|---|
| Treatment Planning CT<br>Section thickness: ≤ 3mm<br>Volume: thoracic inlet-top of head<br>↓<br>Register MR Imaging<br>Pre-op (post-Gd T1WI or T2WI)<br>Post-op (post-Gd T1W1)<br>↓<br>Required Contours<br>GTV_preop<br>GTV1, CTV1, PTV1 (Section 18.4)<br>GTV2, CTV2=PTV2 (Section 18.4)<br>Normal Tissue Contours (Section 18.8)<br>↓<br>Radiation Treatment Planning<br>Target Volume Coverage (Section 18.5)<br>Normal Tissue Dose Recommendations (Section 18.7)<br>↓<br>Data Submission to IROC RI (QARC)<br>Due Day 3 and End of Treatment (Section 18.9)<br>Electronic and Hard Copy Data (Section 18.9) |

18.8 **Organs at Risk**

The organs at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines.

18.8.1 Cochleae

- D50% ≤ 3500 cGy – Goal (single cochlea)
- D50% ≤ 2000 cGy – Preferred (single cochlea)
- Comment – There is no dose limit for the cochleae.
- Structure definition - Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

18.8.2 Optic Globes

- D50% ≤ 1000 cGy and D10% ≤ 3500 cGy – Goal
- D50% ≤ 2000 cGy and D10% ≤ 5400 cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the anterior chamber of the eye and minimize dose to the entire eye without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition - Each eye should be separately contoured on the treatment planning CT or MR as a circular structure from the most superior to inferior aspect.

18.8.3 Optic Nerves and Chiasm

- D50% ≤ 5400 cGy and D10% ≤ 5600 cGy – Goal
- D50% ≤ 5600 cGy and D10% ≤ 5800 cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition – The optic nerve may be contoured on CT or MR. The contour should appear on at least two successive CT or MR images.

18.8.4 Spinal Cord

- D50% ≤ 2600 cGy and D10% ≤ 5700 cGy – Goal
- D50% ≤ 5000 cGy and D10% ≤ 5900 cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage during treatment of PTV1. If any portion of the spinal cord receives the prescription dose during the treatment of PTV1, it is preferable to allow that portion of the spinal cord to receive 5400 cGy during the first 30 fractions of treatment.
- Investigator discretion may be used during the initial phase of treatment (0–5400 cGy) for exceptional cases to minimize the dose to the upper cervical spinal cord and reduce target volume coverage after 5040 or 5220 cGy.
- During treatment of PTV2, the entire spinal cord volume should receive no more than 70% or 126 cGy per fraction during each of the last three treatments to achieve the recommended maximum dose constraints provided in this section.
- Structure Definition - For the purposes of this study, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For purposes of comparison and

consistency with dose volume data, the spinal cord should be contoured on a number of images to be determined by the image section thickness (CT section thickness, n=number of images; 2mm, n=30; 2.5 mm, n=24; 3 mm, n=20). Using these guidelines, only the superior-most 6cm of anatomic spinal cord is contoured.

18.8.5 Brainstem – Photon Therapy

- D50% ≤ 6100 cGy and D10% ≤ 6300 cGy – Goal
- D50% ≤ 6200 cGy and D10% ≤ 6400 cGy – Maximum
- Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure Definition - The brainstem may be contoured on the treatment planning CT or MR and will include the midbrain, pons and medulla. The cranial extent will be inferior to the IIIrd ventricle and optic tracts. The caudal extent will end at the foramen Magnum.

18.8.6 Brainstem – Proton Therapy

- D50% ≤ 5240CcGE and D0.1cc ≤ 5660CcGE – Goal
- D50% ≤ 5400CcGE and D0.1cc ≤ 5800CcGE – Maximum
- Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage during treatment of PTV1. In the event that the recommended maximum dose constraints provided in this section would be exceeded as a result of treatment of PTV2, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure Definition - The brainstem may be contoured on the treatment planning CT or MR and will include the midbrain, pons and medulla. The cranial extent will be inferior to the IIIrd ventricle and optic tracts. The caudal extent will end at the foramen Magnum.

## 18.9 Dose Calculations and Reporting

18.9.1 Prescribed Dose

The prescribed dose for each target volume and/or phase of treatment shall be submitted using the RT-1 Dosimetry Summary Form or Proton Reporting Form. If IMRT or proton therapy is used, the monitor units generated by the IMRT/ proton therapy planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total dose delivered shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record.

18.9.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The appropriate dose-volume histograms should be submitted. If IMRT is used for the primary tumor, 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. A DVH for "Body" shall also be submitted to enable calculation of the required volumes in Table 18.9b. "Body" is defined as the outer contour of the patient on the treatment planning CT data set.

Table 18.9a Required DVH data regardless of primary treatment site

| Required DVH |
|---|
| Optic Chiasm |
| Brainstem |
| Spinal Cord |
| Right Cochlea |
| Left Cochlea |
| Body |
| Unspecified Tissue |

Treated Volume (mL), Irradiated Volume (mL) and Conformity Index (CI)
The treated volume (TV) is the tissue volume that receives therapeutic dose. For the purpose of this protocol this would include the prescribed total dose of 59.4 Gy and 95% of the prescribed dose or 56.4 Gy. This information may be used by the investigators, along with the absolute volume of the PTV, to calculate the conformity indexes (CI) $CI_{100\%}$ and $CI_{95\%}$, respectively. The irradiated volume (IV) is the tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance. The descriptive statistics for these and other tissue volumes maybe used for correlation with unusual side effects or to develop practical guidelines for future high-grade brain tumor protocols.

Table 18.9b Required Volumetric Information

| Required Volumes (ml) |
|---|
| TV95%=V56.4 Gy |
| TV100%=V59.4 Gy |
| IV35=V35 Gy |
| IV45=V45 Gy |
| IV54=V54 Gy |
| PTV |
| CTV |
| GTV |
| Entire Brain |
| Unspecified Tissue |

## 18.10 Quality Assurance Documentation

**Institutions are required to submit the treatment plan as DICOM RT.**
Digital data must include treatment planning CT, structures, plan, and dose files. Submission may be by sFTP or CD. Submission by sFTP is encouraged to ensure prompt review. Instructions for data submission by sFTP or CD are on the IROC RI (QARC) web site at http://iroc.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 or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

**Within three days of the start of radiation therapy, detailed treatment data shall be submitted for on treatment review.**

**Please submit the following for the Primary Site Target Volume:**

**External beam Treatment Planning System**

- 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 18.8. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- MRI studies that have been fused with the planning CT should be submitted along with the digital RT data. The corresponding spatial registration files should also be submitted, if available.

**Supportive Data**

- All diagnostic imaging and reports used to plan the target volume. This includes CT or MRI PRIOR to attempted surgical resection of the primary tumor. Digital format is preferred.
- 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.
- If a PTV margin of 3 mm is used, written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging. See Section 18.5.2

**Forms**

- RT-1/IMRT Dosimetry Summary Form; or
- Proton Reporting Form (whichever is 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 and reference points
- Documentation listed above showing any modifications from original submission.

Data not included with the digital submission should be forwarded to:

IROC Rhode Island
Building B, Suite 201
640 George Washington Highway
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Email: DataSubmission@qarc.org

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

COG Protocol Dosimetrist
IROC Rhode Island
Phone: (401) 753-7600
Email: physics@qarc.org

## 18.11 Definitions of Deviations in Protocol Performance

| | **DEVIATION** | |
|---|---|---|
| | **Minor** | **Major** |
| **Prescription Dose (0-5400 cGy/CcGE)** | | |
| | Difference in prescribed or computed dose is 6-10% of protocol specified dose | Difference in prescribed or computed dose is > 10% of protocol specified dose |
| **Dose Uniformity (0-5400 cGy/CcGE)** | | |
| | >10% PTV received > 110% of the prescription dose<br>*or*<br>95% isodose covers < 100% of CTV | 90% isodose covers < 100% of CTV |
| **Volume (0-5400 cGy/CcGE)** | | |
| | CTV1 or PTV1 margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV1) or without written justification (PTV1) | GTV1 does not encompass MR-visible residual tumor |
| **Organs at Risk** | | |
| | Will be assessed at time of data review | Will be assessed at time of data review |

## 18.12 Patterns of Failure Evaluation

The patterns of failure for patients with localized ependymoma may be described as local, distant or a combination of local and distant and are based primarily on imaging evaluation of the neuraxis. Local failure is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant failure is defined as the appearance of tumor at sites other than known prior sites of disease. Distant failure most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis

represents distant failure. Combined local and distant failure is defined when evaluation of the entire neuraxis reveals local and distant failure. The present study involves treatment of the primary site only and the prescription dose will be confined to a limited volume encompassing the tumor and/or tumor bed. It is possible that the volume that receives the prescription dose will not subtend the entire area at risk and that the rate of failure for patients treated using the guidelines of this protocol will be higher than that observed for patients treated with conformal radiation therapy using the same prescription dose and a larger CTV margin (ACNS0121 or historical data). If the treatment volume did not include the entire area at risk one would expect an increase in the rate of failure and a change in the pattern of failure with local failure as a component of failure occurring at a higher than expected rate. The monitoring of EFS will assess the rate of failure. Determining the patterns of failure will require an assessment of tumor recurrence with respect to targeting and dosimetry. Failure may be described as in-field, marginal or out-of-field when focal irradiation techniques are used. Out-of-field failure is recurrence that occurs entirely outside of the CTV and is synonymous with distant failure. In-field failure is recurrence that originated entirely within the volume that was targeted to receive the prescription dose (CTV). Marginal failure is recurrence originating on the margin of the volume targeted to receive the prescription dose (CTV) and may be described in terms of location or the dose received.

There is no universally accepted analytical method to assess pattern of failure and to determine whether failure is in-field, marginal or out-of-field. For this study, the pattern of failure will be assessed qualitatively and quantitatively by registering MR data obtained at the time of failure to the dosimetry from the original treatment plan.[21] Failures will be determined qualitatively to be "in-field" when the recurrence appears to have originated from within and remains confined to the CTV, "marginal" when a portion of the recurrence is within the CTV but the majority of the recurrence is outside of the CTV, "distant" when the recurrence does not involve the CTV. Recurrences will be quantitatively categorized as in-field, marginal, or out-of-field based on the proportion of the recurrence that received at least 95% of the prescription dose.[59] This requires contouring of the recurrence and computation of the dose-volume histogram. Marginal failure occurs when between 20 and 80% of the recurrence volume receives more than 95% of the prescription dose, thus, in-field failure occurs when more than 80% of the recurrence volume receives more than 95% of the prescription dose and out-of-field failure occurs when less than 20% of the volume received more than 95% of the prescription dose. Any method has significant limitations, however, since the point of origin for tumor recurrence cannot be ascertained with absolute certainty and does not explicitly determine marginal failure. Because of this finding, we are not certain of the best method to define the patterns of failure at this time.

## APPENDIX I: YOUTH INFORMATION SHEETS

### INFORMATION SHEET REGARDING RESEARCH STUDY- ACNS0831
### (for children from 7 through 12 years of age)

**A Study of Treating Newly Diagnosed Ependymoma without X-Ray Treatment**

1. We have been talking with you about your brain tumor which is called ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you were just diagnosed with ependymoma. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to get rid of ependymoma than the normal treatment.

   The normal treatment is an operation to take out as much of the tumor as possible. Then, after the operation children also get x-ray treatment to kill any cancer cells that may still be in the brain. But, this x-ray treatment can cause bad health problems. Study doctors want to see if not giving x-ray treatment will help keep children from having bad health problems in the future from the x-ray treatment without having the tumor grow back.

3. Children who are part of this study had a tumor that was completely taken out by an operation. The tumor is also a kind that doctors think will probably not grow back. Because of these things, study doctors do not want to give you any treatments but they want to watch you closely. You will have tests and exams to check for any signs that the tumor may be coming back. This "careful watching" is sometimes done for children who are not part of this study. If your tumor does come back, study doctors will talk to you about other treatments at that time.

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 you will not have any bad health problems from the x-ray treatment when you are older. But, we do not 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 risk to you from this study is that your tumor may come back because you are not getting the x-ray treatment. If this happens, you would need other treatment to try to get rid of the tumor. Other things may happen to you that we do not 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. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

7. We would like your "okay" to collect some extra blood. We will take the extra blood when other normal blood tests are done, so there will be no extra needle sticks. We would also like your "okay" to collect any tumor tissue that is left over from any operations you have while you are part of this study. We want to see if there are ways to tell how the cancer will react to treatment. You can still take part in this study even if you do not allow us to collect the extra blood or tumor tissue for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0831**
**(for teens from 13 through 17 years of age)**

**A Study of Treating Newly Diagnosed Ependymoma without X-Ray Treatment**

1. We have been talking with you about your brain tumor which is called ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have a newly diagnosed ependymoma tumor. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to get rid of ependymoma than the standard treatment.

   The standard treatment is surgery to remove as much of the tumor as possible. Then, after the operation children and teens also get radiation therapy (the use of high-energy x-rays) to kill any cancer cells that may still be in the brain. However, the radiation therapy can cause bad health problems (also called side effects) that show up when you are older. Study doctors want to see if not giving radiation therapy will help keep children and teens from having side effects from the radiation therapy without having the tumor grow back.

3. Children and teens who are part of this study have had their tumor completely removed. The tumor is also a kind that doctors think is unlikely to grow back. Because of these things, study doctors do not want to give you any treatments but they want to watch you closely. You will have tests and exams regularly to check for any signs that the tumor may be coming back. This "careful watching" is sometimes done for children and teens who are not part of this study. If your tumor does come back, study doctors will talk to you about other treatments at that time.

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 you will avoid side effects from radiation therapy, but we do not 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 your cancer may come back because you will not be receiving radiation therapy. If the tumor does come back, you would need other treatment to try to get rid of the tumor. There is also a risk that surgery may not be possible or that the tumor will come back and spread throughout the brain and spine. Other things may happen to you that we do not 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. We are asking your permission to collect extra blood. We will take these samples when other standard blood tests are done, so there will be no extra needle sticks. We are also asking your permission to collect any tumor tissue that is left over from any surgeries you have while you are part of this study. We would like to use the blood and tumor tissue to do tests to see if there are ways to tell how the cancer will respond to treatment. If there is any tumor tissue left over from these tests, we would like to save it for other research tests in the future. You can still be treated on this study even if you do not allow us to collect the extra blood and tumor tissue or save the leftover tumor tissue for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY- ACNS0831**
**(for children from 7 through 12 years of age)**

**A Study of Adding Anti-Cancer Drugs to Treatment for Newly Diagnosed Ependymoma**

1. We have been talking with you about your brain tumor which is called ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you had an operation and the doctor was able to take out all but a very small bit of the tumor. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to get rid of ependymoma than the normal treatment.

   The normal treatment is an operation to take out as much of the tumor as possible. Then, after the operation children also get x-ray treatment to kill any cancer cells that may still be in the brain. Study doctors want to try a new treatment that gives anti-cancer drugs after the x-ray treatment. Study doctors hope this new treatment will work better than the normal treatment to kill cancer cells that are still in the brain.

3. All children who are part of this study will get x-ray treatments. One group of children in this study will then get anti-cancer medicines after the x-ray treatment. One group of children will not. The group you will be in will be decided by chance, like flipping a coin for "heads" or "tails". If you are in the group that gets the anti-cancer medicines, you will be treated with the medicines for about 12 weeks. If you are in the other group, you will not have any more treatment during the rest of this study. You will be watched carefully and have regular tests done.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." If you get the new treatment, we hope that a benefit to you of being part of this study is that you get a treatment that works better than the normal treatment to get rid of the tumor. But, we do not 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". If you get the new treatment, the risk to you from this study is that you may have bad health problems from the anti-cancer drugs. If this happens you may need treatment for the problems. If you are in the group that gets the normal treatment, the risk to you is that you may not get a treatment that is better at getting rid of the tumor. Other things may happen to you that we do not 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. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

7. We are asking your "okay" to collect some extra blood. We will take the extra blood when other regular blood tests are done, so there will be no extra needle sticks. We are also asking your "okay" to collect any tumor tissue that is left over from any operations you have while you are part of this study. We want to see if there are ways to tell how the cancer will react to treatment. You can still take part in this study even if you do not allow us to collect the extra blood or tumor tissue for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0831**
**(for teens from 13 through 17 years of age)**

**A Study of Adding Chemotherapy to Treatment for Newly Diagnosed Ependymoma**

1. We have been talking with you about your brain tumor which is called an ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you had surgery and doctors were able to remove all but a very small amount of the ependymoma tumor. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment to get rid of ependymoma will work better than the standard treatment.

   The standard treatment is surgery to take out as much of the tumor as possible. After surgery, radiation therapy (treatment with high-energy X-rays) is used to kill any cells that are still in the brain. Study doctors want to see if giving chemotherapy (anti-cancer drugs) after radiation therapy will work better to get rid of the cancer or keep it from growing.

3. All children and teens who are part of this study will be treated with radiation therapy. You will get radiation therapy 5 days a week for about 6 weeks. Half of the children and teens will also be treated with chemotherapy. The process to decide who gets chemotherapy is called "randomization". It is a lot like flipping a coin for "heads" or "tails", except it is done by computer. If you are in the group that will be treated with chemotherapy, you will be treated with several drugs for about 12 weeks. If you are in the group that does not get chemotherapy, you will not have any more treatment while you are on this study. You will be watched carefully and have regular tests done.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." If you receive chemotherapy, we hope that a benefit to you of being part of this study is getting a treatment that works better to get rid of your tumor than the standard treatment. But, we do not 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." If you receive chemotherapy, the risks to you from this study are bad effects, called "side effects" from the drugs. These side effects include fewer red blood cells, white blood cells, and platelets in your blood, which can make it easier to get an infection, make you feel tired, and cause you to bruise and bleed more easily. If you have side effects, you may need treatment for them. If you are in the group that gets the standard treatment, the risk to you is that you may not get a treatment that is better at getting rid of the tumor. Other things may happen to you that we do not 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 you have.

7. We are asking your permission to collect extra blood. We will take these samples when other standard blood tests are done, so there will be no extra needle sticks. We are also asking your permission to collect any tumor tissue that is left over from any surgeries you have while you are part of this study. We would like to use the blood and tumor tissue to do tests to see if there are

ways to tell how the cancer will respond to treatment. If there is any tumor tissue left over from these tests, we would like to save it for other research tests in the future. You can still be treated on this study even if you do not allow us to collect the extra blood and tumor tissue or save the leftover tumor tissue for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY- ACNS0831**
**(for children from 7 through 12 years of age)**

**A Study of Adding Anti-Cancer Medicines and Second Surgery to Treatment for Newly Diagnosed Ependymoma**

1. We have been talking with you about your brain tumor that is called an ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you had an operation and the doctor was able to take out most of the tumor but not all of it. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if a new treatment will work better to get rid of ependymoma than the normal treatment for this disease.

   The normal treatment for this kind of tumor is an operation to take out as much of the tumor as possible. After the operation children also get x-ray treatment to kill any cells that are still in the brain. Study doctors want to see if giving anti-cancer medicines after the operation can help kill any tumor that is still in the brain. Study doctors also hope that giving anti-cancer medicines will make it easier for doctors to take out the rest of the tumor in another operation.

3. All children who are part of this study will be treated with anti-cancer medicines. Then, study doctors will do scans to see how well the anti-cancer medicines worked to kill the tumor. What happens next depends on what the scans show and the kind of cells that are in the tumor. You may be watched carefully, have a second operation, or get x-ray treatments. You may also have more anti-cancer medicines after the x-ray treatments. The process to decide who gets anti-cancer medicines after x-ray treatments is called "randomization". It is a lot like flipping a coin for "heads" or "tails", except it is done by computer. Your doctor will tell you what treatments you will have while you are on this study.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." If you get the anti-cancer medicines, we hope that a benefit to you of being part of this study is that you get a treatment that works better to get rid of the tumor than the normal treatment. But, we do not 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". A risk to you from this study is bad health problems from the anti-cancer medicines. If this happens you may need treatment for the problems. There is also the risk that the tumor may grow while you are taking the anti-cancer medicines. If this happens, there is a risk that another operation may not be possible. There is also a risk that the tumor may spread into other areas of your brain or spine. Other things may happen to you that we do not 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. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions you have.

7. We are asking your "okay" to collect some extra blood. We will take the extra blood when other regular blood tests are done, so there would be no extra needle sticks. We are also asking your "okay" to collect any tumor tissue that is left over from any operations you have while you are part of this study. We want to see if there are ways to tell how the cancer will react to treatment. You can still take part in this study even if you do not allow us to collect the extra blood and tumor tissue for research.

**INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS0831**
**(for teens from 13 through 17 years of age)**

**A Study of Adding Chemotherapy and Second Surgery to Treatment for Newly Diagnosed Ependymoma**

1. We have been talking with you about your brain tumor which is called ependymoma. Ependymoma is a type of cancer that grows in the brain. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you had surgery and the doctor was able to remove most of the tumor but not all of it. A research study is when doctors work together to try out new ways to help people who are sick. This study will see if new treatments will work better to get rid of ependymoma than the standard treatment for this disease.

   The standard treatment for this kind of tumor is an operation to take out as much of the tumor as possible. After the operation children and teens also get radiation therapy (the use of high-energy x-rays) to kill any tumor cells that are still in the brain. Study doctors want to see if giving chemotherapy (anti-cancer drugs) can help shrink any leftover tumor so that a second operation can remove most if not all of the tumor before treatment with radiation therapy is done. Study doctors also want to see if giving chemotherapy after radiation therapy will help get rid of the tumor for as long as possible.

3. All children and teens who are part of this study will be treated first with chemotherapy. This chemotherapy lasts 7 weeks and includes several drugs. Then, study doctors will do scans to see how well the chemotherapy worked to kill the tumor. What happens next depends on what the scans show and the kind of cells that are in the tumor. You may be watched carefully, have a second operation, or have radiation therapy. Also, if you have radiation therapy, you may or may not have more chemotherapy after it. (The process to decide who gets chemotherapy after radiation therapy is called "randomization". It is a lot like flipping a coin for "heads" or "tails", except it is done by computer.)

   If you have radiation therapy, it will be given 5 days a week for about 6 weeks. If you have the second chemotherapy, it will last for 12 weeks and includes four drugs. If you have a second operation and the doctors are able to take out all of the tumor and you do not have one certain kind of tumor, you will go on to have either radiation therapy and more chemotherapy, or radiation therapy only. For some children and teens who have a certain type of tumor that the doctors are able to remove completely, there will be no more treatment. Your doctor will tell you what treatments you will have while you are on this study.

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 the new treatments work better to get rid of the tumor than the standard treatment. However, we do not 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." A risk to you from this study is having side effects from the chemotherapy. These side effects include fewer red blood cells, white blood cells, and platelets in your blood, which can make it easier to get an infection, make you feel tired, and cause you to bruise and bleed more easily. If you have side effects, you may need treatment for them. There is also the risk that the

tumor may grow while you are on the first part of chemotherapy. If this happens, there is a risk that another operation may not be possible, or that the tumor may spread into other areas of your brain or spine. Other things may happen to you that we do not 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 you have.

7. We are asking your permission to collect extra blood. We will take these samples when other regular blood tests are done, so there will be no extra needle sticks. We are also asking your permission to collect any tumor tissue that is left over from any surgeries you have while you are part of this study. We would like to use the blood and tumor tissue to do tests to see if there are ways to tell how the cancer will respond to treatment. If there is any tumor tissue left over from these tests, we would like to save it for other research tests in the future. You can still be treated on this study even if you do not allow us to collect the extra blood and tumor tissue or save the leftover tumor tissue for research.

## APPENDIX II: TANNER STAGING CRITERIA

Classification of Sex Maturity Stages in Girls
(Adapted from: Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in girls. Arch Diseases in Childhood 44:291, 1969)

| SMR Stage | Pubic Hair | Breasts (Females) |
|---|---|---|
| 1 | Preadolescent with vellus over the pubic area no more profuse than on the abdomen. | Preadolescent, with coloration of the papilla only. |
| 2 | Sparse growth of long, slightly pigmented downy hair which is straight or only slightly curled, and appearing usually at the base of the penis or along the labia. | Breast bud stage: breast and papilla are elevated above the chest in a small mound, without enlargement of the areolar diameter. |
| 3 | Pubic hair is darker, courser and more curly, and the hair is spreading sparsely over the pubic area. | Further elevation and enlargement of the breast and areola but no separation of the contours. |
| 4 | Further spread of the pubic hair, still considerably less than in the adult, and no extension of hair bilaterally up to the middle of the thigh. | The areola and papilla project from the breast to form a secondary mound. |
| 5 | Adult in amount and type of hair. | Adult state: projection of the papilla only, due to recession of the areola to the general contour of the breast. |

Classification of Sex Maturity Stages in Boys
(Adapted from: Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Diseases in Childhood 45:13, 1970)

| SMR Stage | Pubic Hair | Genitalia (Males) |
|---|---|---|
| 1 | Preadolescent with vellus over the pubic area no more profuse than on the abdomen. | Preadolescent: Testes, scrotum, and penis are of about the same size and proportion as in early childhood. |
| 2 | Sparse growth of long, slightly pigmented downy hair which is straight or only slightly curled, and appearing usually at the base of the penis or along the labia. | Beginning enlargement of the scrotum and testes; reddening of the scrotum, and changes in its texture. |
| 3 | Pubic hair is darker, courser and more curly, and the hair is spreading sparsely over the pubic area. | Penile enlargement (mm) with increase in length and further growth of the scrotum and testes (mm). |
| 4 | Further spread of the pubic hair, still considerably less than in the adult, and no extension of hair bilaterally up to the middle of the thigh. | Further increase in penile size; growth in breadth and development of the glans. Further enlargement of the testes and scrotum and continued darkening of the scrotal skin. |
| 5 | Adult in amount and type of hair. | Adult genitalia in size and shape. |

## APPENDIX III: CTEP AND CTSU REGISTRATION PROCEDURES

### CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

| Documentation Required | IVR | NPIVR | AP | A |
|---|---|---|---|---|
| FDA Form 1572 | ✔ | ✔ | | |
| Financial Disclosure Form | ✔ | ✔ | ✔ | |
| NCI Biosketch (education, training, employment, license, and certification) | ✔ | ✔ | ✔ | |
| HSP/GCP training | ✔ | ✔ | ✔ | |
| Agent Shipment Form (if applicable) | ✔ | | | |
| CV (optional) | ✔ | ✔ | ✔ | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

## CTSU REGISTRATION PROCEDURES

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

**Downloading Site Registration Documents:**

Site registration forms may be downloaded from the ACNS0831 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
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the COG link to expand, then select trial protocol #ACNS0831
  Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

**Requirements For ACNS0831 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted )
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.

**Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab
→Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

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

**Checking Your Site's Registration Status:**

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username

and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

## APPENDIX IV: 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.***

### Carboplatin

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

### Cisplatin:

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

**Cyclophosphamide:**

| **Drugs that may interact with cyclophosphamide*** |
|---|
| • Allopurinol<br>• Chloramphenicol<br>• Cyclosporine<br>• Digoxin<br>• Etanercept<br>• Hydrochlorothiazide<br>• Indomethacin<br>• Nevirapine<br>• Pentostatin<br>• Warfarin |

| **Food and supplements that may interact with cyclophosphamide**** |
|---|
| • St. John's Wort<br>• 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.*

**Etoposide**

| **Drugs that may interact with etoposide*** |
|---|
| • Antibiotics<br>• Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin<br>• Antidepressants and antipsychotics<br>• Aripiprazole, clozapine, nefazodone<br>• Antifungals<br>• Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole<br>• Arthritis medications<br>• Leflunomide, tofacitinib<br>• Anti-rejection medications<br>• Cyclosporine, tacrolimus<br>• Antiretrovirals and antivirals<br>• Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir<br>• Anti-seizure medications<br>• Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone<br>• Heart medications<br>• Amiodarone, dronedenarone, verapamil<br>• Some chemotherapy (be sure to talk to your doctor about this)<br>• Many other drugs, including the following:<br>• Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan |

| **Food and supplements that may interact with etoposide**** |
|---|
| • Echinacea<br>• Glucosamine<br>• St. John's Wort<br>• Grapefruit, grapefruit juice, Seville oranges, star fruit |

**Sometimes these drugs are used with etoposide 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.*

**Vincristine:**

| **Drugs that may interact with vincristine*** |
|---|
| • Antibiotics<br>• Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin<br>• Antidepressants and antipsychotics<br>• Aripiprazole, nefazodone, trazodone<br>• Antifungals<br>• Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole<br>• Arthritis medications<br>• Leflunomide, tocilizumab, tofacitinib<br>• Anti-rejection medications<br>• Cyclosporine, tacrolimus<br>• Antiretrovirals and antivirals<br>• Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tenofovir, tipranavir<br>• Anti-seizure medications<br>• Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone<br>• Heart medications<br>• Amiodarone, digoxin, dronedenarone, propranolol, verapamil<br>• Some chemotherapy (be sure to talk to your doctor about this)<br>• Many other drugs, including the following:<br>• Aprepitant, deferasirox, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, warfarin |

| **Food and supplements that may interact with vincristine**** |
|---|
| • Echinacea<br>• St. John's Wort<br>• 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.*

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