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CHILDREN'S ONCOLOGY GROUP

ACNS1221

A Phase II Study For The Treatment Of Non-Metastatic Nodular Desmoplastic Medulloblastoma In Children Less Than 4 Years Of Age

A Groupwide Phase II Study

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[redacted]

AGENT NSC# AND IND#'s

AGENT	NSC#	IND#
Carboplatin	241240	Exempt
Cyclophosphamide	026271	Exempt
Etoposide	141540	Exempt
Filgrastim (G-CSF)	614629	Exempt
Leucovorin	003590	Exempt
Mesna	113891	Exempt
Methotrexate	000740	Exempt
Vincristine	067574	Exempt

SEE SECTION 14.0 FOR SPECIMEN SHIPPING ADDRESSES

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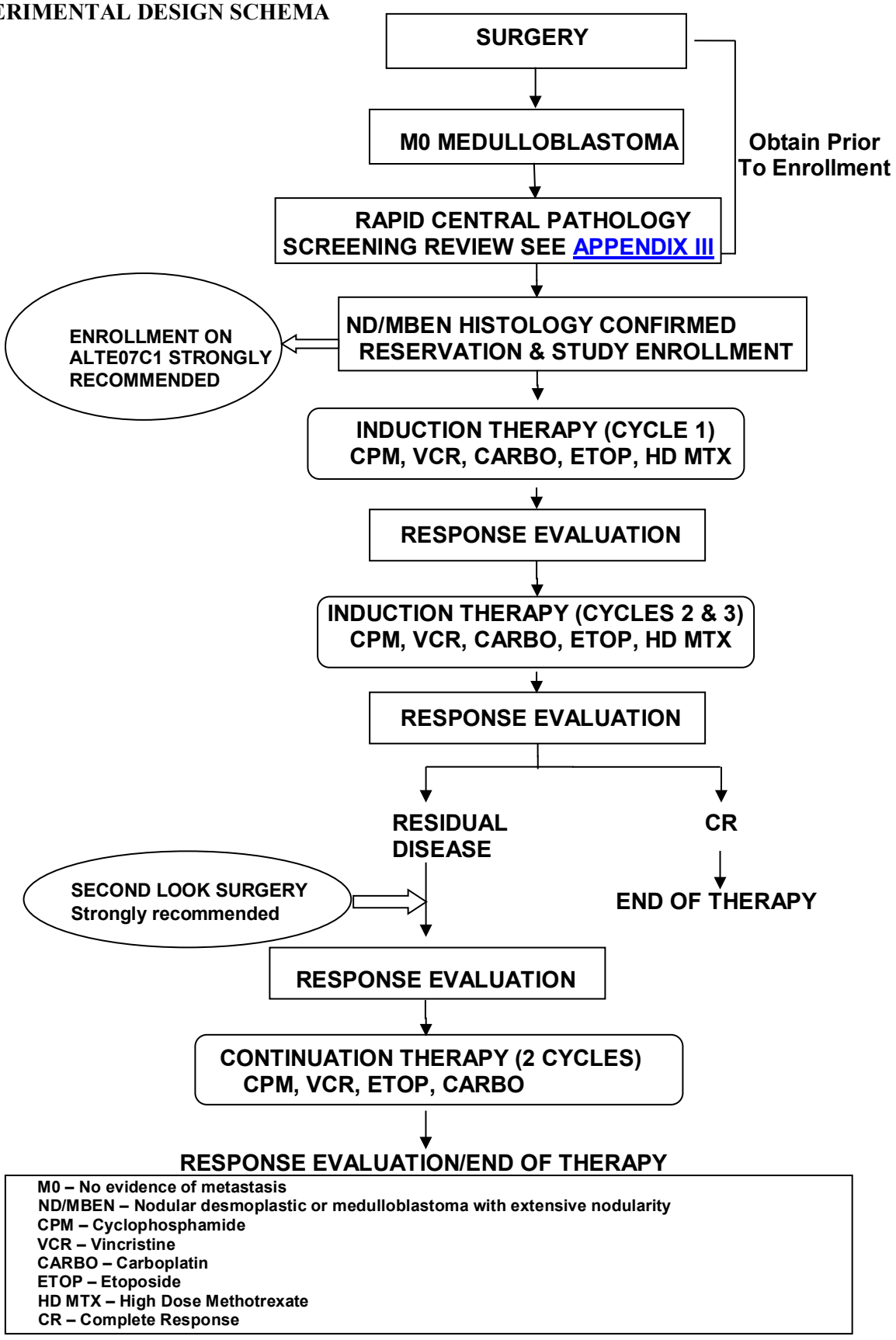
ABSTRACT

The ACNS1221 study is a single arm multi institutional trial for newly diagnosed young children (0-<4 years of age at study enrollment) with nodular desmoplastic or medulloblastoma with extensive nodularity (M0 ND/MBEN medulloblastoma). The primary objective is estimating the PFS distribution associated with treatment as per HITSKK 2000 protocol without intraventricular methotrexate. Eligibility for this protocol will be based on central rapid screening pathology review. While the primary objective is estimating the PFS distribution associated with the proposed treatment for the purpose of determining the sample size the design utilizes a binomial endpoint to look for evidence that the 2-year PFS rate is less than 90%. The 90% threshold is both desirable for this patient population and is relatively comparable to that achieved with HIT SKK 2000 regimen.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

Estimate of the PFS distribution for patients 0-<4 years of age with M0 desmoplastic medulloblastoma (nodular desmoplastic or medulloblastoma with extensive nodularity) treated with the modified HIT SKK regimen (excluding the use of intraventricular methotrexate).

We hypothesize that the PFS distribution associated with treatment as per HIT SKK 2000 protocol without intraventricular methotrexate in newly diagnosed young children (0-<4 years of age at diagnosis) with M0 ND/MBEN medulloblastoma will be comparable to the outcome observed on HIT SKK 2000 protocol with intraventricular methotrexate. Note however that this trial is an independent assessment of the efficacy associated with the proposed therapeutic approach and any comparisons of outcome between this study and HIT SKK 2000 can only be made in a descriptive fashion.

1.2 Correlative Science Objectives

1.2.1

Evaluate the feasibility of a rapid central pathology screening review for treatment allocation according to histology and assess agreement between institutional and central pathology review diagnoses as well as among central pathology review diagnoses.

1.2.2

Prospectively evaluate the molecular profile of ND/MBEN medulloblastoma in young children.

1.2.3

Monitor and describe the neurocognitive and adaptive functioning of young children with ND/MBEN medulloblastoma treated on this protocol using the ALTE07C1 protocol.

2.0 BACKGROUND

2.1 Medulloblastoma Trials of Infancy and Early Childhood

Medulloblastoma (MB) in infancy and early childhood (<5 years) are relatively rare and constitute a significant therapeutic challenge because of the greater vulnerability of the developing brain to treatment related toxicity specifically to cranial radiation. Craniospinal radiation, which is a major component of the standard treatment of medulloblastoma, is usually avoided or delayed in this age group. More recently, limiting RT to focal radiation has been attempted and the final results of these approaches are pending. However, overall, the outcome of medulloblastoma in infancy and early childhood is traditionally poorer than in older children.

The past 3 decades of clinical trials in infant brain tumors have explored the use of chemotherapy to delay the use of extended field of radiation in order to preserve neurocognitive function. Early infant study protocols were initially applied to all CNS tumor types in this age group. Over time, separate treatment strategies have emerged for histologically-determined sub-groups, such as ependymomas, rhabdoid tumors, choroid plexus tumors and medulloblastoma. The most recent era of trials have demonstrated improved survival rates and provided early evidence of reduced neuro-toxicity, compared to historical data. These clinical trials have also brought to light new prognostic factors that can be used to risk stratify brain tumors in early childhood. Among these, the nodular/desmoplastic histological subtype is prognostic only in the infant medulloblastoma cohort unlike the extent of resection and the metastatic status which have been shown to be associated with outcome in both infants and older children with medulloblastoma.[1-3]

The favorable outcome of the ND/MBEN subgroup was initially reported by the German group (HIT SKK 92) and was later confirmed in retrospective analyses of most of the contemporary infant trials.[1,2,4,5] However, all these studies have analyzed histology as a prognostic factor in a retrospective manner. Therefore, the logical next step is to incorporate the histologic subtype into the clinical risk stratification at the time of diagnosis and to tailor treatment according to the known prognostic factors (histology, extent of resection and metastatic status).

The trial will focus on non-metastatic (M0) medulloblastoma with nodular desmoplastic/extensive nodularity (ND/MBEN). The aim is to achieve similar excellent outcome with reduced treatment related neurotoxicity.

2.2 The Nodular Desmoplastic (ND)/Medulloblastoma with extensive nodularity (MBEN) histological subtype in infants

Previous series indicate that the nodular/desmoplastic histology is more common in the infant group. Reported rates vary widely among studies, ranging from 29% to 75%. The rate reported in the metaanalysis conducted by Rutkowski et al.[5] was 41%. The 9934 protocol had the highest percentage of desmoplastic patients based on central pathology review compared to all other published series. In the CCG-9921 protocol, the frequency of desmoplastic histology[4] amongst centrally reviewed tumors was 22 of the 76 patients (29%). Table 1 provides a summary of reported frequencies in several large infant trials.

Table 1: Summary of Reported Frequencies of Desmoplastic Medulloblastoma

Trial	Desmoplastic N (%)	Non Desmoplastic N
SFOP[1]	25 (33%)	50
HIT SKK 92[5]	20 (46%)	23
HIT SKK 2000[6]	19 (42%)	26
Head Start III (ASCO 2011)	28 (30%)	64 (70%)
CCG-9921[4]	22 (29%)	54
P9934[7]	39 (75%)	13
CCG-99703 (Cohen, personal communication)	13 (56%)	10
Meta-analysis[5]	108 (41%)	
France	33 (45%)	41
Germany	29 (40%)	43
USA	10 (32%)	21
UK	17 (61%)	11
Italy	19 (36%)	36

HIT SKK, HeadStart I, II; CCG 9921 and 9934 are the only trials providing frequency for Non metastatic Medulloblastoma

Part of the explanation in the varying rates of desmoplasia may be related to selection bias among the various infant medulloblastoma series such as different ages for inclusion, different eras of diagnostic tools and awareness of the diagnosis, as well as absence of the requirement for specifying desmoplastic medulloblastoma diagnosis in the protocol. However, there is also evidence that lack of consensus on the definition of desmoplastic medulloblastoma is also contributing to this discrepancy. Therefore, it appears essential in the context of a protocol that is intending to treat according to histologic subtype to incorporate a rapid central pathology screening review process rather than relying on institutional diagnosis. This study will include pre-screening and rapid central pathology screening review to confirm eligibility. In addition, the study will use vitrual microscopy (VIPER) online automated pathology review system at the COG Biopathology Center (BPC) for the rapid screening central review. This automated system will notify the pathologists and track the rapid central review. Representative H&E and reticulin slides will be scanned at the BPC into an ACNS1221 digital tissue review database for use by the review pathologists.

Currently 3 COG CNS studies (ACNS0831 for Ependymoma; ACNS0333 for the ATRT and ACNS0334 for the High Risk Medulloblastoma in infants) have a rapid central pathology screening review process in place to confirm the tumor histology after enrolling on the study. Although the timing of the rapid central pathology reviews is not an objective of the studies, for ACNS0831 and ACNS0334 approximately 80% of the reviews were completed within the indicated time frame of 12 days on ACNS0831 (5 days for tissue submission after study enrollment and 1 week for review) and 19 days on ACNS0334 (3 working days for tissue submission after study enrollment and 2 weeks for review). In most

cases, the delays were due to inadequate tissue submission from the institution. Although the timing of the rapid review for ACNS0333 is identical to ACNS0334, the percent is lower possibly due to the fact frozen tissue is required.

2.3 Treatment of ND Medulloblastoma/MBEN and Outcome

Table 2 Summary of EFS data for infant M0 medulloblastoma

M0Mb	ND/MBEN		Non Desmoplastic		
	N	5 y EFS	N	5y EFS	p
HIT SKK 2000	19 (42%)	95%	23	30%	< 0.01
HS I, II	9 (43 %)	67%	12	42%	=0.34
CCG 9921	18 (37%)	72%	31	16%	< 0.0001
P9934 $	39(53%)	58%*	13	23%*	0.008
99703	13 (56%)	85 % **	10	60%**	NS
*4y EFS ** 3y EFS $ based on 52 patients with central pathology review					

The German group was the first to report the favorable outcome associated with nodular desmoplastic histology in infants using a conventional chemotherapy approach with high dose methotrexate and repeated intraventricular injections of methotrexate (HIT SKK 92). In their initial report[3], the 3 year PFS for patients with desmoplastic and classic medulloblastoma were 85%±8 and 34%±10, respectively. They further confirmed their findings in the subsequent protocol HIT SKK 2000, which was using the same chemotherapy backbone with the addition of 2 cycles of conventional chemotherapy following complete response to therapy. The 5 year EFS for patients with localized ND/MBEN and classic medulloblastoma were 95%±5 and 30% ±11, respectively.[6]

In the meta-analysis conducted by Rutkowski et al., data from Germany, France, UK, Italy and Headstart I and II protocols were pooled.[5] The 8 year EFS and OS for patients with desmoplastic histology were 55% and 76%, respectively. The prognostic value of desmoplasia has also been retrospectively reviewed in several recent North American infant trials. In the CCG-9921 protocol, infants with desmoplastic medulloblastoma[4] showed an excellent outcome using conventional therapy, without radiation and without high dose methotrexate. Out of 18 M0 patients with desmoplastic medulloblastoma treated with this regimen, only 4 required radiation. The 5 year EFS for this group was 72%±11 (5 year OS of 83%±9), which is comparable to the results of the HIT SKK 92 protocol that used both HD MTX and intraventricular methotrexate (82%±9).

Similarly preliminary results from the Head Start III protocol using an intensive high dose methotrexate based induction followed by a consolidation with high dose chemotherapy and autologous stem cell rescue confirmed the high survival rate of patients with a nodular/desmoplastic histology with a 3 year EFS of 89%±6.[2]

The P9934 protocol included infants aged 8 months to < 3 years with non metastatic medulloblastoma, with and without residual disease. This protocol used conventional

chemotherapy (oral etoposide, cyclophosphamide, cisplatin and vincristine) and early radiation to the tumor bed.[7] Children with nodular desmoplastic histology fared better than non-desmoplastic patients. However the 4 year EFS for the nodular desmoplastic group was only 58%±8 with a 4 year OS of 79%±7 (this protocol did not include high dose methotrexate).

The COG 99703 phase I/II trial used a sequential high dose chemotherapy and autologous stem cell rescue backbone. This study did not demonstrate a significant survival benefit for patients with nodular desmoplastic histology. However the results from this protocol are still preliminary and the statistical analysis is limited by the small number of patients with medulloblastoma (10 with nodular desmoplastic and 13 classic medulloblastoma). Furthermore the lack of reliable data collection on the use of adjuvant radiation in this protocol precludes any meaningful comparison.

Based on these data, there is now clear evidence that a majority of young patients with nodular desmoplastic medulloblastoma can be successfully treated with conventional chemotherapy. Based on the outcome information summarized above, 2 regimens were considered for this current COG study:

1) the 9921 regimen involving prolonged conventional chemotherapy
2) the German HIT SKK regimen, which has a shorter duration

The 2 regimens are compared below in Table 3 in terms of cumulative dose of drugs used.

Table 3 Comparison of 9921 and HIT SKK Regimens with respect to Duration and Cumulative Drug Dose

	9921 Regimen A	9921 Regimen B	HIT SKK 92 or * SKK 2000
Duration of treatment	71 weeks (15 weeks induction +56 weeks maintenance)		24 weeks (3 cycles of 2 months each)
Drugs used	VCR, CDDP, CPM, VP16, CB	VCR, CB, IFOS, VP16, CPM	MTX, IT MTX, CPM, VCR, CB VP-16
Cumulative dose of drugs			
VCR	47 doses	47 doses	9 doses (* + 2 doses)
CPM	32.1 g/m^2	15.6 g/m^2	7.2 g/m^2 (*+ 2.4g/m^2)
CDDP	510 mg/m^2	0	0
CB	4.32 g/m^2	5.8 g/m^2	1.8 g/m^2 (* + 1.2g/m^2)
VP16	3.52 g/m^2	3.6 g/m^2	1.35 g/m^2*+ 0.9g/m^2
IFOS	0	36 g/m^2	0
MTX	0	0	30 g/m^2
IT MTX	0	0	36 x 2 mg

The 9921 regimen had a longer duration of treatment (71 weeks). The large cumulative dose of cisplatin is likely to induce significant hearing loss and subsequent speech development problems in these very young patients. Additionally, as infants with nodular desmoplastic medulloblastoma are expected to be long term survivors, the very high cumulative doses of cyclophosphamide and ifosfamide incorporated in this regimen are of concern since they increase the risk of infertility. Overall although this regimen appears to be associated with similar favorable outcome, its toxicity profile raises significant concern especially with regard to fertility and ototoxicity. Thus we chose to use a modified version of the HIT SKK regimen in the proposed study.

Building on the initial results of the HIT SKK 92 protocol, the German group expanded its experience with the protocol HIT SKK 2000, using the same backbone with the addition of 2 more cycles of chemotherapy. For patients with persistent residual disease after 5 cycles of chemotherapy, recommendation was made to proceed to CSI and further consolidation chemotherapy. However, with the strategy, none of the patients with ND/MBEN received more than 5 cycles of chemotherapy, as described in the current protocol and no patient underwent radiation for residual disease.[6]

Although the HIT SKK 2000 regimen still has a much shorter duration compared to the 9921 regimen, it includes methotrexate delivered both intraventricularly (through an Ommaya reservoir for a total of 32 doses of 2 mg) as well as high dose methotrexate delivered systemically. The use of intraventricular MTX poses considerable technical issues, especially for children with ventriculo-peritoneal shunts and carries significant risk of chemical peritonitis. More concerning is the evidence of MRI findings of leucoencephalopathy described in the Rutkowski publication.[3] A significant correlation was reported between the grade of leukoencephalopathy and the cumulative dose of intraventricular methotrexate (correlation coefficient, 0.53; $P<0.01$), but there was no correlation between the leukoencephalopathy grade and doses of systemic methotrexate.

Although the authors stated that the leukoencephalopathy were not associated with clinically evident symptoms, the neurocognitive performance of these children was significantly lower than that of control group of healthy children but higher than that of historical group treated with craniospinal irradiation. There was also a trend toward a higher neurocognitive status in children who received only systemic methotrexate as compared with children who received both systemic and intraventricular methotrexate.[3] In the absence of detailed information on the long term neurocognitive outcome of the German cohort, it is felt that intraventricular methotrexate should not be incorporated in the current proposal.

Therefore the intent of the current study is to investigate in a North American multi-institutional setting whether a similar progression free survival reported in the HIT SKK 2000 protocol can be achieved without incorporating intraventricular methotrexate injections to limit the risk of leukoencephalopathy and the potential associated neurocognitive impairment. Note however this trial is not designed to make a formal comparison with HIT SKK 2000 and any such comparison in outcome can only be made descriptively.

Additionally, while discussions within the different European pediatric oncology groups are ongoing to build on the German experience and to establish a common European protocol of treatment for ND/MBEN medulloblastoma in infants, it is felt that having a similar backbone chemotherapy regimen in North America will facilitate future collaborations particularly for molecular biology studies that appear increasingly essential for the development of future protocols.

2.4 The Issue of Age Cut Off for Infant Medulloblastoma

The historical definition of "infant" since the inception of so called "baby brain" clinical trials has usually been all children less than 3 years of age. However, the upper limit of baby brain protocols varies across studies and some clinical trials for young children are enrolling patients up to the age of 5 years[1] or even up to the age of 10 years as in the Headstart experience.[2]

The nodular desmoplastic subtype has predominantly been described in the group of children under the age of 3 years. However, it is estimated that between 10 and 20% of the medulloblastomas seen in children aged 3-5 years will be of nodular desmoplastic histology. (Michael Taylor personal communication)

In light of the favorable outcome of patients with nodular desmoplastic medulloblastoma, the German group has recently extended the age range of the infant group to 4 years. On their protocol HIT 2000, which involved patients enrolled on the trial from January 2001 to December 2005, there were 11 patients older than 3 years of age. Though the sample size is small, three (27%) of these 11 had nodular desmoplastic medulloblastoma, suggesting a similar rate of desmoplastic histology to that observed in the group of children less than 3 years old (10 out of 34 29%).

Looking at their entire cohort, i.e. including histology-based subtypes (classic, nodular desmoplastic, anaplastic), patients between 3 to 4 years of age had a similar OS and EFS to those less than 3 years (age limit of the previous HIT-SKK 92 trial). Specifically 5-year OS rates: 71±14%vs. 82±6%, (p=0.420) and 5y EFS: 62±15% vs. 56±9%., (p=0.981), respectively. No events were reported for the 3 patients older than3 year with nodular desmoplastic histology. (Von Bueren, personal communication)

Similarly the French and Italian groups have included in their infant protocols children up to the age of 5 years without suggestion of worse outcome in the subgroup of 3-5 year olds with desmoplastic medulloblastoma compared to the 0 to 3 years group. The 8 year EFS of 55% reported in the medulloblastoma meta-analysis[5] is based on a cohort including all children aged from 0 to 5 years with desmoplastic medulloblastoma.

The current COG protocol for older children with medulloblastoma (ACNS0331) will soon be closed to accrual. It is well described that in the group of older children (> 3 years old) receiving craniospinal radiation, younger patients (less than 7 or 8 years) are at greater risk for cognitive decline[8,9], and considering the expected excellent cure rate associated with the ND/MBEN subtype, it appears reasonable to offer a non radiation approach for the youngest of the older children with medulloblastoma. Therefore we extended the age of eligibility of the current study to 4 years.

2.5 Surgical Management of ND Medulloblastoma/MBEN

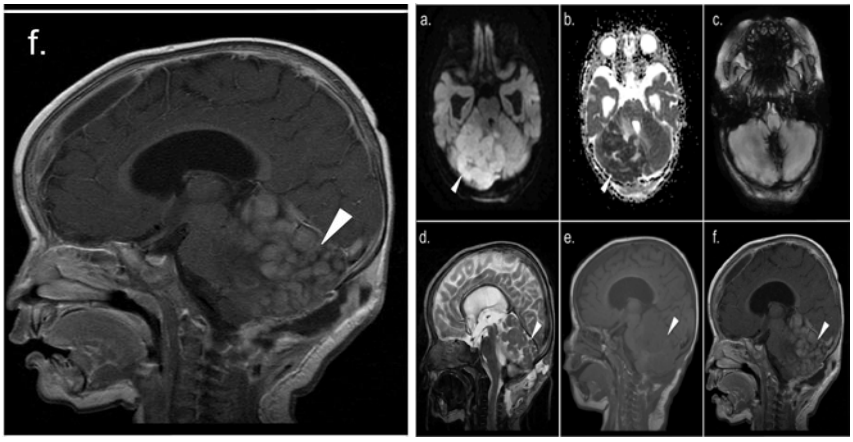
Gross total surgical resection is clearly a significant prognostic factor in medulloblastoma irrespective of the age group.[10] In the ND medulloblastoma/MBEN subgroup, gross total or near total resection is often achievable. In the 9921 cohort of desmoplastic children, STR (>90%) was achieved in 72.7% of the patient with ND/MBEN subtype. Similarly Von Bueren et al described no residual tumor in 14 out of the 19 (73.6%) patients with ND/MBEN.[6]

Although a complete resection is achievable in the vast majority of the cases at the time of definitive surgery, it has to be kept in mind that the ND/MBEN subtype is chemosensitive. Complete response after initial chemotherapy in HIT SKK 2000 series was achieved in 3/5 DMB/MBEN with residual disease.

In some instances, ND/MBEN medulloblastoma can present with diffuse involvement of the cerebellum in absence of distant metastatic seeding, which may not render them

amenable to upfront complete surgical resection. Therefore radical operations in tumors localized in areas with an increased risk of postoperative neurological deficits should be avoided in patient with ND/MBEN subtype. It is important to be cognizant of the age at presentation and radiological features suggestive of the ND/MBEN before the initial surgical procedure.

Figure 1 MRI Imaging of Nodular Medulloblastoma



On T2-weighted and post-gadolinium sequences, the tumor shows an extensive nodular grape- like appearance.[11]

However in patients with significant residual tumor after first surgery and initial chemotherapy, maximal safe secondary surgery will strongly be recommended.

2.6 Neurocognitive and Adaptive Functioning Studies

Although the major intent of the infant brain tumor treatment strategy has been to protect this very young and vulnerable population from the radiation related neurocognitive impairment, the prior track record for neurocognitive evaluation in previous COG brain tumor protocols has not been impressive. Therefore limited neurocognitive data in an infant population are available to document the benefit of such strategies in the infant population.

However, since the inception of the ALTE07C1 protocol, the Behavioral Science Committee (BSC) of COG has demonstrated significantly improved rates of neurocognitive data collection. According to the most recent study progress report for ALTE07C1, the compliance rate for the time one (T1) evaluations is approximately 90% and the compliance rate for the time two (T2) evaluations is 82%. Because of this success, ALTE07C1 is now paired with 5 separate therapeutic trials that have primary or secondary aims to examine neurocognitive outcomes. As it is well agreed that the preservation of neurocognitive outcome in very young children with brain tumors is of paramount importance, the descriptive evaluation of neurocognitive and functional outcomes for these survivors is vital to the scientific aims of this study. Therefore enrollment on ALTE07C1 will be strongly recommended for the patients enrolled on the current protocol ACNS1221.

While enrolled on ALTE07C1, ACNS1221 patients will be assessed at 3 time points: T1 (9 months), T2 (30 months), and T3 (60 months) post diagnosis (all assessments are ± 3 months).

It is anticipated that mean neurocognitive and adaptive functioning will be within the average range for normative data at T1 and that scores will not significantly decline over time (T2 and T3). One measure of neurocognitive and one measure of adaptive functioning will be used as primary outcomes for measuring children's performance over time.

To evaluate overall adaptive functioning, the General Adaptive Composite score (GAC) from the Adaptive Behavior Assessment System–II (ABAS-II) will be used, which is a parent-report measure that provides a comprehensive assessment of adaptive behavior skills.[12]

Given that this measure has norms starting at birth, these serial data will be obtained for all children enrolled on this study. The standardization sample for the ABAS-II consisted of 2100 individuals stratified by gender, race/ethnicity, and educational level according to year 2000 US Census data. Data focusing on reliability are very strong (Cronbach alpha, test re-test, and inter-rater). Satisfactory content, construct, and criterion-validity have been reported. With an emphasis on the ABAS-II, we will have potential data from 3 time points for all participating children. Interpretation of these data can utilize scores over time (slopes) and comparison to measure norms.

Beginning at age 2 years 6 months, Full Scale IQ (FSIQ) will be evaluated using key subtests (Vocabulary and Block Design) from the age-appropriate version of the Wechsler Intelligence Scale.[13] These 2 subtests allow for a reasonably accurate measure of estimated IQ (r_{ss}= .91). Since ALTE07C1 obtains data at 9, 30, and 60 months after diagnosis, all participating children will have potential data at 30 and 60 months after diagnosis (2 time points), and any child on this clinical trial diagnosed at 18 months or older will have data from 3 time points. Interpretation of these data will use scores over time (slopes) and comparison to measure norms.

2.7 Molecular Characterization of Infant Medulloblastoma

In recent years, medulloblastoma has been shown to be a heterogeneous disease divisible into distinct molecular and clinical subtypes that behave more predictably in response to therapy than current classification systems based on clinical risk.[14-19] This has fostered a movement of using subtype stratification to improve risk assignment and better tailor therapy.[16-18] Based on Northcott et al.'s and others[16] findings, medulloblastoma can be divided into 4 subgroups according to their genomic profile (WNT, SHH, Group C and Group D) with a significant correlation with outcome (Figure 1A). The SHH and the WNT driven medulloblastomas are associated with an excellent survival outcome (≥ 80%). However the complexity of these tumors goes beyond subtype divisions and, even though subtyping groups together biologically common tumors, there still exists biologic and clinical variability even within the subtypes. For example, medulloblastomas of the SHH subtype, grouped together because of common gene expression data, are some of the most heterogeneous medulloblastomas.[20] These tumors harbor a diversity of mutations in both the expected SHH genes but also in genes not immediately associable with the SHH pathway.[21-24] Additionally there are certain cytogenetic features, like MYCN amplification, chromosome 17p loss, chromosome 10q loss, chromosome 3q gain which may associate with a worse prognosis.[25]

In the infant population, most medulloblastomas are Sonic Hedgehog (SHH) driven (Figure 1B). There is a certain level of overlap between the nodular desmoplastic subgroup and the SHH group but the extent of overlap is still uncertain. About 60% of desmoplastic medulloblastomas are SHH driven.[14] Although most of the SHH driven medulloblastomas are nodular desmoplastic by histology, some classic or even anaplastic medulloblastomas may be SHH driven.

These observations suggest that an improved understanding of tumor biology even within the subtypes of the disease will be critical to maximally tailoring therapy. Currently most of our knowledge on molecular characterization of medulloblastoma have been generated from tissue samples from retrospective cohorts with limited information on treatment modalities and in the absence of homogeneous treatment. There is a need for a prospective validation of these molecular markers in a cohort of infants uniformly treated. The ACNS1221 protocol offers an excellent opportunity to collect and study a well-defined subset of medulloblastomas.

We hypothesize that disease variability arises from characteristic molecular abnormalities which carry prognostic implications These findings will help constitute a rationale for integrating targeted therapy in future trials for newly diagnosed patients, such as sonic hedgehog inhibitors which are currently undergoing phase I and phase II evaluation in recurrent patients.

Figure 1A

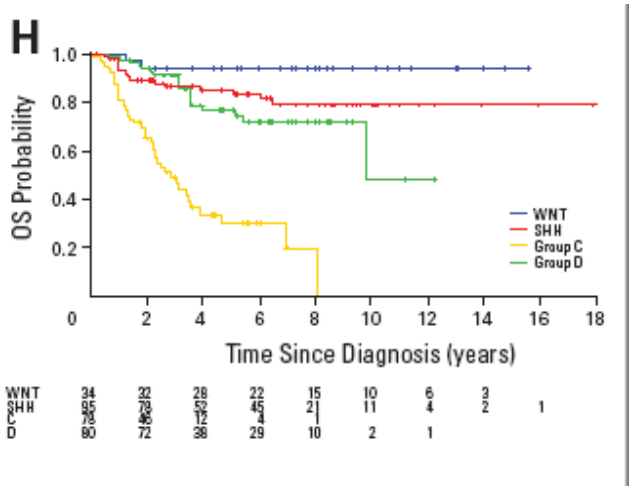
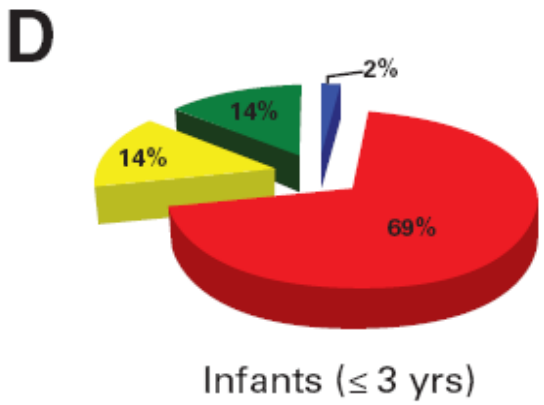


Figure 1B: Molecular subgroup distribution of medulloblastoma in children less than 3 years of age as per Northcott et al[14]



Blue : WNT pathway driven Medulloblastoma
Red SHH driven Medulloblastoma
Yellow: Group C
Green: Group D

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

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

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

Please see Appendix IV for detailed CTEP Registration Procedures for Investigators and Associates, and 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

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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

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

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

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (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 Mandatory Submission of Tissue for Rapid Central Pathology Screening Review

See Appendix III. All patients must have RAPID CENTRAL PATHOLOGY SCREENING REVIEW PRIOR TO STUDY ENROLLMENT, in order to avoid discordant diagnoses and to verify diagnosis criterion for treatment stratification**.** Pathology slides from the time of diagnosis must be sent to the COG Biopathology Center within 15 days of surgery for all potential M0 patients.

Pathology slides must be marked RAPID REVIEW and submitted by Federal Express Priority Overnight to the Biopathology Center (See **Section 14.0 for information regarding specimen submission). PLEASE DO NOT SEND SPECIMENS FOR BIOLOGY STUDIES (SECTION 14.3) UNTIL ELIGIBILITY HAS BEEN CONFIRMED AND PATIENT IS ENROLLED.** Results of rapid central review will be available within 10 calendar days of the receipt of pathology review materials.

Please Note: Patients should have no metastatic disease on spinal MRI. Patients with a pending result of the CSF cytology are eligible for the rapid central pathology screening review. Confirmation of the CSF negativity is needed for enrollment on the ACNS1221 protocol unless contraindicated.

3.1.4 Reservation Requirements

Prior to obtaining informed consent and enrolling a patient, a reservation must be made following the steps below. Reservations may be obtained 24 hours a day through the Oncology Patient Enrollment Network (OPEN) system.

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Registration system OPEN. Prior to discussing protocol entry with the patient, site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available for the patient. Once a slot-reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

If the study is active, a reservation can be made by following the steps below:

1) Log in to https://open.ctsu.org/open/ using your CTEP IAM user name and password.

2) In order to make a reservation, the patient must have an OPEN patient number. Click on the 'Slot Reservation' tab to create an OPEN patient number, under 'Patients'.
3) Using the OPEN patient number '**RESERVE'** a slot for that patient.
4) On the 'Create Slot Reservation' page, select the Protocol Number, enter the COG Patient ID, and choose the required stratum (if applicable) in order to obtain a reservation.

Refer to the 'SITE – Slot Reservation Quick Reference' guide posted under the 'Help' tab in OPEN for detailed instructions: https://www.ctsu.org/readfile.aspx?fname=OPEN/OPEN_SlotReservation_QuickReference_SiteUserGuide_102612.pdf&ftype=PDF

3.1.5 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff and the results from the rapid central pathology screening review have confirmed the patient is eligible.

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

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

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

3.2 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.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patient must be less than 48 months (4 years) of age at time of definitive surgery.

3.2.2 Diagnosis

Patients must be newly diagnosed and have a confirmed histologic diagnosis of nodular desmoplastic (ND) medulloblastoma or medulloblastoma with extensive nodularity (MBEN) from rapid central pathology screening review.

Please Note: Patients with Gorlin syndrome are eligible.

Please see exclusion criteria regarding metastatic disease below.

3.2.3 CSF Cytology

Patient must have negative lumbar CSF cytology (lumbar CSF must be obtained unless medically contraindicated). CSF cytology for staging should be performed preferably no sooner than 14 days post operatively to avoid false positive CSF, Ideally, CSF should be obtained between Day 14 and Day 21 to allow for final staging status before enrollment onto the study.

Note: Patients with positive CSF cytology obtained prior to 14 days after surgery may have cytology repeated to determine eligibility and final CSF status.

3.2.4 Imaging

Patients must have:

- Pre-operative cranial MRI (recommended with gadolinium) or pre-operative CT (recommended with contrast)
- Post-operative cranial MRI with and without gadolinium within 72 hours of surgery
- Spinal MRI pre-op with and without gadolinium or post-op with and without gadolinium preferably within 72 hours of surgery

3.2.5 Timing

Patients must be enrolled on study within 31 days of definitive surgical resection at which time tissue is acquired to determine a diagnosis.

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will be considered ineligible**.

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section.

3.2.6 Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2. Use Lansky for patients ≤ 16 years of age. See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.7 Life Expectancy

Patients must have a life expectancy of ≥ 8 weeks.

3.2.8 Concomitant Medications Restrictions

(Please see Section 4.4 for the concomitant therapy restrictions for patients during treatment.)

Steroids: Patients who are receiving dexamethasone must be on a stable dose for at least 1 week prior to study entry.

3.2.9 Organ Function Requirements

3.2.9.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 10.0 g/dL (may receive RBC transfusions)

3.2.9.2 Adequate Renal Function Defined As:

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

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[26] utilizing child length and stature data published by the CDC.

3.2.9.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.

3.2.9.4 Central Nervous System Function Defined As:

- Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled.
- Patients must not be in status, coma or assisted ventilation prior to study enrollment.

EXCLUSION CRITERIA

3.2.10 Metastatic Disease

Patients with metastatic disease by either MRI evaluation (brain and spine) or lumbar CSF cytology are not eligible.

3.2.11 Prior Therapy

Patients must not have received any prior tumor-directed therapy other than surgical intervention and corticosteroids.

REGULATORY REQUIREMENTS

3.2.11

Parents or legal guardians must sign a written informed consent.

3.2.12

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

4.0 TREATMENT PROGRAM

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).

4.1 Overview of Treatment Plan

Patients will be enrolled on the study after central rapid pathology screening confirmation of ND/MBEN and start chemotherapy within 36 days of definitive surgery. They will receive a total of 3 to 5 cycles of chemotherapy. Three cycles of Induction Therapy (63 Day Cycle) will include Methotrexate, Cyclophosphamide, Vincristine, Etoposide, and Carboplatin. Each cycle will begin when ANC > 750/μL and platelets > 75,000/μL and when off filgrastim (G-CSF) for at least 48 hours.

Patients will then have a response evaluation. For patients with complete response the treatment is complete and the patient will begin follow-up. For patients with persistent residual disease, second look surgery is strongly recommended after completion of induction (See Section 13.0) followed by 2 cycles of Continuation Therapy (42 Day Cycle) to include Cyclophosphamide, Vincristine, Carboplatin and Etoposide.

4.2 Age Specific Dose Reductions

Age specific dose reductions will be made for cyclophosphamide, vincristine and carboplatin. **Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.** No age specific dose reductions will be made for methotrexate or etoposide. See table below.

Age at the Beginning of Each Cycle	Dosage
≤ 6.99 months of age	2/3 (67%) of the m^2 dosage
7-12.99 months of age	4/5 (80%) of the m^2 dosage
≥ 13 months of age	Full m^2 dosage

4.3 Neurocognitive Function

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

4.4 Concomitant Therapy Restrictions

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Antiemetics may be used per institutional guidelines.

High Dose Methotrexate

Hold trimethoprim/sulfamethoxazole (Bactrim) on the day of HDMTX infusion and continue to hold until the methotrexate level is less than 0.1 micromolar (1×10^{-7} M).

Avoid probenecid, penicillins, aspirin, proton pump inhibitors and NSAIDS on the day of methotrexate and continue until the methotrexate level is less than 0.1 micromolar (1×10^{-7} M) as renal excretion of methotrexate is inhibited by these agents.

Avoid IV contrast media, urinary acidifiers, phenytoin, and fosphenytoin on the day of methotrexate and until the methotrexate level is less than 0.1 micromolar (1×10^{-7} M).

Vincristine

Concurrent use of enzyme inducing anticonvulsants (e.g. phenytoin, phenobarbital, and carbamazepine) should be avoided. **See Appendix II.**

Clinically significant drug interactions have been reported when using vincristine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors of cytochrome P450 3A4 include azole antifungals, such as fluconazole, voriconazole, itraconazole, ketoconazole, and strong inducers include drugs such as rifampin, phenytoin,

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

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.

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

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.5 Administration Guidelines for Induction Therapy Cycles 1, 2, 3 (63 Day Cycles)

Cycle 1 will begin when ANC ≥ 1000/μL and platelet count ≥ 100,000/μL. Subsequent cycles will begin when ANC ≥ 750/μL and platelets ≥ 75,000/μL and when off filgrastim (G-CSF) for at least 48 hours.

For the administration of Carboplatin/ Etoposide and of Cyclophosphamide/Vincristine if ANC <750/μL or platelet <75,000/μL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle.

Begin administration of methotrexate on Days 15 and 29 when ANC ≥ 250/μL and platelets ≥ 50,000/μL.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Days: 1, 15, 29
Dose: Age Based Dosing below (Maximum single dose 2 mg). Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle. Administer vinCRIStine prior to cyclophosphamide.

Age	Dose
≤ 6.99 months of age	1 mg/m^2/day
7-12.99 months of age	1.2 mg/m^2/day
≥ 13 months of age	1.5 mg/m^2/day

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide (CPM): IV over 1 hour
Days: 1-3
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6.99 months of age	533 mg/m^2/day
7-12.99 months of age	640 mg/m^2/day
≥ 13 months of age	800 mg/m^2/day

Suggested Hydration:
Prehydrate at least 2 hours at 125mL/m^2/hour before and post hydrate for at least 18 hours IV at 125 mL/m^2/hour.

Mesna: IV (short or continuous infusion)
Days: 1-3
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6.99 months of age	533 mg/m^2/day for patients
7-12.99 months of age	640 mg/m^2/day
≥ 13 months of age	800 mg/m^2/day

IV short or continuous infusion: For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily cyclophosphamide dose. Mesna can be administered in 5 divided doses by **short intravenous 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 3, 6, 9, and 12 hours after the start of cyclophosphamide.

For example: if the cyclophosphamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; 200 mg of mesna will be given 15 minutes before or with the cyclophosphamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 12 hours after the end of the cyclophosphamide infusion.

For example: if the cyclophosphamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; the 1000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the cyclophosphamide and be completed no sooner than 12 hours after **the end** of the cyclophosphamide infusion.

Methotrexate: IV over 24 hours
Days: 15, 29
Dose: 5,000 mg/m^2
See Appendix I for a flowchart of the HDMTX/LCV guidelines.

Hold any nonsteroidal anti-inflammatory medications, penicillins, proton pump inhibitors or aspirin-containing medications on the day of HDMTX infusion and for at least 72 hours after the start of the HD MTX infusion and until the MTX level is less than 0.4 μM. In the presence of delayed clearance continue to hold these medications until MTX level is less than 0.1 μM.

Suggested Hydration:

Prehydrate with D5 ¼ NS with 30 mEq $NaHCO_3$/L at 125 mL/m^2/hour until urine specific gravity is ≤ 1.010 and pH is ≥ 7.0 and ≤ 8.0. Ringers Lactate may be used as the initial fluid if a bicarbonate containing solution is unavailable. Adjust fluid volume and sodium bicarbonate to maintain urine specific gravity and pH at above parameters. A bicarbonate bolus (25 mEq/m^2 over 15 min) may be given to raise the urine pH relatively quickly, a normal saline bolus may also be helpful in facilitating hydration. Continue hydration and alkalinization throughout HDMTX infusion, and for a minimum of 48 hours after its completion and until serum methotrexate level less than 0.1 micromolar (1 x 10^{-7} molar).

Hour 0: MTX 500 mg/m^2 IV infused over 30 minutes. This is followed, immediately, by MTX 4500 mg/m^2 given by continuous IV infusion over 23.5 hours. Be certain that the HDMTX infusion is completed in the 24 hour period. Unintentional prolongation to as long as 26 hours though not encouraged is acceptable.

Hours 24, (36), 42 and 48: Draw MTX level and serum creatinine; NOTE: 36 hour level is only drawn if needed (see below)

For MTX levels that exceed these expected values modify the rescue regimen as noted below and increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If serum creatinine rises significantly, at any time point, assure appropriate urine pH and urine volume as above and draw a 42 hour level. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also consider glucarpidase (carboxypeptidase G_2) (see below). For patients with delayed clearance during a previous course, begin the following course with the increased hydration (200 mL/m^2/hr). If subsequent course is not associated with delayed clearance, attempt to use standard hydration.

If the 24 hour level is < 150 μM draw the next level at hour 42 and refer to table below.

If the 24 hour level is ≥ 150 μM and/or creatinine > 125% baseline, repeat level if MTX contamination is possible. If the value is "real" refer to the changes in hydration, etc described above and repeat the level with a serum Cr at hour 36. Then refer to the table below.

If the 42 and 48 hour levels are ≤ 1 and 0.4 μM, respectively, give Leucovorin at 15 mg/m^2 IV/PO at 42, 48 and 54 hours post the start of methotrexate loading dose. No additional levels are needed, nor is additional leucovorin.

36 Hr MTX Level	42 hr MTX level	48 hr MTX level	Leucovorin Rescue++
Only required if 24 hr level is ≥ 150 µM. See below for guidelines**	1.01 to 9.9 µM	0.41 to 5.9 µM	Continue 15 mg/m^2 q 6h until MTX level < 0.1 µM (draw q12-24 h).
	10 to 19.9 µM	6 to 9.9 µM	Increase to 15 mg/m^2 q 3h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	20 to 200 µM	10 to 100 µM	Increase to 100 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.
	> 200 µM	> 100 µM	Increase to 1000 mg/m^2 q 6h until MTX level < 0.1 µM (draw q 6-24 h). Consider glucarpidase.

** **If the 36 hour level exceeds 3** µM, increase hydration to 200 mL/m^2/hr, monitor urine pH to assure a value ≥ 7.0 and monitor urine output to determine if volume is ≥ 80% of the fluid intake, measured every 4 hours. If urine output fails to continue at 80% of the fluid intake, consider furosemide. Regardless of urine output, also **consider glucarpidase if 36 hour MTX level exceeds 10** µM.
++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤ 1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

Special precautions: IV leucovorin and sodium bicarbonate are incompatible.

Selected drug interactions: Avoid NSAIDs, TMP/SMX, penicillins, probenicid, IV contrast media, proton pump inhibitors, phenytoin and fosphenytoin. Urinary acidifiers can cause methotrexate to precipitate in the urinary tract.

Leucovorin: IV or PO (See Appendix I and guidelines for HD MTX above)
Days: 17, 31 (42 hours after the start of methotrexate infusion)
Dose: 15 mg/m^2 at hrs 42, 48, & 54 until serum methotrexate levels are less than 0.1 micromolar (1 x 10^{-7} molar).

Inject by IV push over a minimum of 3 minutes or by short infusion over 15 to 120 minutes. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL solution per minute). IV leucovorin and sodium bicarbonate are incompatible.

Etoposide: IV over 60-120 minutes
Days: 43-45
Dose: 150 mg/m^2/dose

Infuse diluted solution (concentration ≤ 0.4 mg/mL) over at least 60-120 minutes; 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. **Administer etoposide prior to carboplatin.**

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.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

CARBOplatin: IV over 1 hour
Days: 43-45
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6.99 months of age	133 mg/m^2/day
7-12.99 months of age	160 mg/m^2/day
≥ 13 months of age	200 mg/m^2/day

IV: Avoid use of aluminum containing needles or administration sets.

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

Filgrastim: Subcutaneous (preferred) or IV
Days: Daily, starting on Day 4 and Day 46 and continue for at least 7 days, or until ANC ≥ 750/μL after the expected nadir whichever comes last. Note that an ANC ≥ 750 on or before Day 7 of a cycle is **not** sufficient for discontinuing G-CSF, as the ANC may rise before Day 7 and then fall to its nadir.
Dose: 5 mcg/kg/dose.

Note: The use of filgrastim is strongly recommended, however, patients receiving PEG-filgrastim will not be excluded.

See Section 5.0 for Dose Modifications based on Toxicities.

For those patients who have not achieved a complete response after 3 cycles Induction therapy, another attempt at complete resection, if at all feasible, is strongly recommended.

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

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

The therapy delivery maps (TDMs) for Induction Therapy are on the following pages.

Following completion of this course, the next course starts on Day 64 or when ANC > 750/μL and platelets > 75,000/μL whichever occurs later and when off filgrastim (G-CSF) for at least 48 hours.

4.5.1 Therapy Delivery Map for Induction Therapy (Cycles 1, 2, 3) Induction Therapy will be given for Cycles 1, 2 and 3. Each Cycle lasts 9 weeks (63 days).	_____ Patient name or initials _____ DOB

Cycle 1 will begin when ANC ≥ 1000/μL and platelet count ≥ 100,000/μL. Subsequent cycles will begin when ANC ≥ 750/μL and platelets ≥ 75,000/μL and when off filgrastim (G-CSF) for at least 48 hours. For the administration of Carboplatin/Etoposide and of Cyclophosphamide/Vincristine if ANC <750/μL or platelet <75,000/μL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle. Begin administration of methotrexate on Days 15 and 29 when ANC ≥ 250/μL and platelets ≥ 50,000/μL.

Extensive details are in Section 4.0 (treatment overview). Each cycle lasts 63 days and the TDM for this cycle is on **2** pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute or infusion via minibag as per institutional policy	Age / Dose ≤ 6.99 months: 1 mg/m²/day 7-12.99 months: 1.2 mg/m²/day ≥ 13 months: 1.5 mg/m²/day	1, 15, 29	**Note age based dosing. Maximum single dose 2 mg.**	a. History, PE (Ht, Wt, VS) with Neurologic Exam, b.Performance Status c. CBC (differential, platelets) d. Urinalysis and Serum Creatinine or GFR e. Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium) f. Brain and spine MRI with and without gadolinium g. Audiogram or BAER h. CSF cytology **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 1 hour	Age / Dose ≤ 6.99 months: 533 mg/m²/day 7-12.99 months: 640 mg/m²/day ≥ 13 months: 800 mg/m²/day	1-3	**Note age based dosing.**	
Mesna	IV (short or continuous infusion)	Age / Dose ≤ 6.99 months: 533 mg/m²/day 7-12.99 months: 640 mg/m²/day ≥ 13 months: 800 mg/m²/day	1-3	**Note age based dosing.** Administer with Cyclophosphamide See Section 4.5	
Filgrastim (G-CSF)	SubQ (preferred) or IV	5 mcg/kg/dose	Daily, starting on Day 4 and Day 46	Continue for at least 7 days, or until ANC ≥ 750/μL after the expected nadir whichever comes last	
Methotrexate (MTX)	IV over 24 hours	5,000 mg/m²/day	15, 29	See guidelines and Appendix I.	
Leucovorin (LCV)	IV or PO	15 mg/m²/dose	17, 31	Begin 42 hours after start of methotrexate infusion. every 6 hours until serum methotrexate levels are less than 0.1 micromolar (1×10^{-7} molar).See guidelines and Appendix I	
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m²/dose	43-45	See guidelines. Administer prior to CARBOplatin.	
CARBOplatin (CARBO)	IV over 1 hour	Age / Dose ≤ 6.99 months: 133 mg/m²/day 7-12.99 months: 160 mg/m²/day ≥ 13 months: 200 mg/m²/day	43-45	**Note age based dosing.**	

4.5.1 Therapy Delivery Map for Induction Therapy (Cycles 1, 2, 3) Induction Therapy will be given for Cycles 1, 2 and 3. Each Cycle lasts 9 weeks (63 days).	_____ Patient name or initials _____ DOB

Cycle 1 will begin when ANC ≥ 1000/μL and platelet count ≥ 100,000/μL. Subsequent cycles will begin when ANC ≥ 750/μL and platelets ≥ 75,000/μL and when off filgrastim (G-CSF) for at least 48 hours. For the administration of Carboplatin/ Etoposide and of Cyclophosphamide/Vincristine if ANC <750/μL or platelet <75,000/μL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle. Begin administration of methotrexate on Days 15 and 29 when ANC ≥ 250/μL and platelets ≥ 50,000/μL.

Extensive details are in Section 4.0 (treatment overview). Each cycle lasts 63 days and the TDM for this cycle is on **2** pages.

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CPM ____mg	MESNA _____mg/dose OR by CI _____mg/day	VCR ____mg	MTX _____mg	LCV _____mg	CARBO _____mg	ETOP _____mg	G-CSF _____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#	
		2	____mg	____mg								
		3	____mg	____mg								
		4								____mcg		Indicate last day of G-CSF _____
		15			____mg	____mg					a , c, d, e	
		17					____mg					Indicate last day of LCV _____
		29			____mg	____mg					a , c, d, e	
		31					____mg					Indicate last day of LCV _____
		43						____mg	____mg		a, c, d, e, g&	
		44						____mg	____mg			
		45						____mg	____mg			
		46								____mcg		Indicate last day of G-CSF _____
		62									[a, b, c, e, f, g, h]$	
		64	Begin the next Cycle on Day 64 when blood count parameters have been met and the patient has been off G-CSF for at least 48 hours.									

- Obtain prior to Cycle 2 & - Obtain for Cycles 2 and 3.
$ - Obtain following Cycle 3

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

4.6 Administration Guidelines for Continuation Therapy (42 Days) Cycles 1, 2

Only patients with persistent disease will receive Continuation Therapy of chemotherapy. Cycles will begin when ANC ≥ 750/μL and platelets ≥ 75,000/μL and when off filgrastim (G-CSF) for at least 48 hours and patient has recovered from second surgery (if done). For the administration of Carboplatin/ Etoposide and of Cyclophosphamide/Vincristine if ANC <750/μL or platelet <75,000/μL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle.

VinCRIStine: IV push over 1 minute or infusion via minibag as per institutional policy
Day: 1
Dose: Age Based Dosing below (Maximum single dose 2 mg). Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle. Administer vinCRIStine prior to cyclophosphamide.

Age	Dose
≤ 6.99 months of age	1 mg/m^2/day
7-12.99 months of age	1.2 mg/m^2/day
≥ 13 months of age	1.5 mg/m^2/day

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

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

Cyclophosphamide (CPM): IV over 1 hour
Days: 1-3
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6.99 months of age	533 mg/m^2/day
7-12.99 months of age	640 mg/m^2/day
≥ 13 months of age	800 mg/m^2/day

Suggested Hydration:
Prehydrate at least 2 hours at 125mL/m^2/hour before and post hydrate for at least 18 hours IV at 125 mL/m^2/hour.

Mesna: IV (short or continuous infusion)
Days: 1-3
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6 months of age	533 mg/m^2/day
7-12 months	640 mg/m^2/day
≥ 13 months of age	800 mg/m^2/day

IV short or continuous infusion: For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily cyclophosphamide dose. Mesna can be administered in 5 divided doses by **short intravenous 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 3, 6, 9, and 12 hours after the start of cyclophosphamide.

For example: if the cyclophosphamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; 200 mg of mesna will be given 15 minutes before or with the cyclophosphamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as cyclophosphamide and finished no sooner than 12 hours after the end of the cyclophosphamide infusion.

For example: if the cyclophosphamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; the 1000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the cyclophosphamide and be completed no sooner than 12 hours after **the end** of the cyclophosphamide infusion.

Etoposide: IV over 60-120 minutes
Days: 21-23
Dose: 150 mg/m^2/dose

Infuse diluted solution (concentration ≤ 0.4 mg/mL) over at least 60-120 minutes; 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. **Administer etoposide prior to carboplatin.**

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.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

CARBOplatin: IV over 1 hour
Days: 21-23
Dose: Age Based Dosing below. Dose reductions must be calculated based on the patient's age at the beginning of each cycle and continued for that cycle.

Age	Dose
≤ 6.99 months of age	133 mg/m^2/day
7-12.99 months of age	160 mg/m^2/day
≥ 13 months of age	200 mg/m^2/day

IV: Infuse the diluted solution over 15-60 minutes. Avoid use of aluminum containing needles or administration sets.

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

Filgrastim: Subcutaneous (preferred) or IV
Days: Daily, starting on Day 4 and Day 24 and continue for at least 7 days, or until ANC ≥ 750/μL after the expected nadir whichever comes last. Note that an ANC ≥ 750 on or before Day 7 of a cycle is **not** sufficient for discontinuing G-CSF, as the ANC may rise before Day 7 and then fall to its nadir.
Dose: 5 mcg/kg/dose.

Note: The use of filgrastim is strongly recommended, however, patients receiving PEG-filgrastim will not be excluded.

See Section 5.0 for Dose Modifications based on Toxicities.

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

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

The therapy delivery maps (TDMs) for Continuation Therapy are on the following pages.

4.6.1 **Therapy Delivery Map for Continuation Therapy (Cycles 1, 2)** Continuation Therapy will be given for Cycles 1 and 2. Each Cycle lasts 6 weeks (42 days).	_____ Patient name or initials _____ DOB

Each cycle will begin when ANC ≥ 750/µL and platelets ≥ 75,000/µL and when off filgrastim (G-CSF) for at least 48 hours. For the administration of Carboplatin/Etoposide and of Cyclophosphamide/Vincristine if ANC <750/µL or platelet <75,000/µL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle. Extensive details are in Section 4.0 (treatment overview). Each cycle lasts 42 days and the TDM for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute or infusion via minibag as per institutional policy	Age / Dose ≤ 6.99 months: 1 mg/m²/day 7-12.99 months: 1.2 mg/m²/day ≥ 13 months: 1.5 mg/m²/day	1	**Note age based dosing. Maximum single dose 2 mg.**	a. History, PE (Ht, Wt, VS) with Neurologic Exam, b.Performance Status c. CBC (differential, platelets) d. Urinalysis and Serum Creatinine or GFR e. Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium) f. Brain and spine MRI with and without gadolinium g. Audiogram or BAER h. CSF Cytology **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Cyclophosphamide (CPM)	IV over 1 hour	Age / Dose ≤ 6.99 months: 533 mg/m²/day 7-12.99 months: 640 mg/m²/day ≥ 13 months: 800 mg/m²/day	1-3	**Note age based dosing.**	
Mesna	IV (short or continuous infusion)	Age / Dose ≤ 6.99 months: 533 mg/m²/day 7-12.99 months: 640 mg/m²/day ≥ 13 months: 800 mg/m²/day	1-3	**Note age based dosing.** Administer with Cyclophosphamide See guidelines.	
Filgrastim (G-CSF)	SubQ (preferred) or IV	5 mcg/kg/dose	Daily, starting on Day 4 and Day 24	Continue for at least 7 days, or until ANC ≥ 750/µL after the expected nadir whichever comes last	
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m²/dose	21-23	See guidelines. Administer prior to CARBOplatin.	
CARBOplatin (CARBO)	IV over 1 hour	Age / Dose ≤ 6.99 months: 133 mg/m²/day 7-12.99 months: 160 mg/m²/day ≥ 13 months: 200 mg/m²/day	21-23	**Note age based dosing.**	

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CPM ____mg	MESNA ____mg/dose OR by CI ____mg/day	VCR ____mg	CARBO ____mg	ETOP ____mg	G-CSF ____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	
		2	____mg	____mg						
		3	____mg	____mg						
		4						____mcg		Indicate last day of G-CSF ____
		21				____mg	____mg		a, c, d, e, g	
		22				____mg	____mg			
		23				____mg	____mg			
		24						____mcg		Indicate last day of G-CSF ____
		42							[a, b, c, e, f, g, h]$	
		43	Begin Cycle 2 on Day 43 when blood count parameters have been met and the patient has been off G-CSF for at least 48 hours.							

$ - Obtain following Cycle 2

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Hematological Toxicity

For the administration of Carboplatin/ Etoposide and of Cyclophosphamide/Vincristine if ANC <750/μL or platelet <75,000/μL, delay chemotherapy for 1 week and until the threshold value have been reached. If despite the use of filgrastim, there is subsequent episode of delayed recovery, omit the Day 3 of the next similar cycle.

5.2 Carboplatin

5.2.1 Nephrotoxicity

The estimation of GFR must be performed before every carboplatin containing block. If serum creatinine > 1.2 mg/dL (100 μM) **or** > 1.5 ULN **or** Creatinine clearance < 80 mL/min x 1.73 m²: Delay chemotherapy for 1 week

In case of no improvement: Perform estimation of GFR by clearance of radioisotope:
If the Isotope GFR ≥ 60 and < 80 mL/min x 1.73 m², reduce carboplatin dose to 125 mg/m²/dose. Perform estimation of GFR by clearance of radioisotope before next course.
Isotope GFR < 60 mL/min/1.73 m², replace carboplatin by cyclophosphamide at the calculated dose for age for cyclophosphamide.

Note: Institutions should verify with Nuclear Medicine Department or lab to ensure correct units are reported.

Both formulas are listed so that you can use either the Corrected GFR (that is corrected to the adult clearance of 1.73 m^2) or the Uncorrected GFR (that is the raw GFR). Use the correct version of the formula dependent on the units of measurement reported for the GFR. The GFR corrected or uncorrected is reported in the units as below:
Corrected GFR reported in mL/min/1.73 m^2
Uncorrected (Raw) GFR reported in mL/min
(To Convert Corrected to Uncorrected GFR the following formula is used: $\frac{\text{Corrected GFR}}{\text{BSA}}$ *= Uncorrected (Raw) GFR*

5.2.2 Ototoxicity

Careful monitoring of children by expert audiologist and by serial audiometry throughout the treatment with carboplatin is recommended as clinically indicated. Otoacoustic emissions (OAE) are the clinical methodology of choice for initial testing. If not feasible BAER is suggested. Do not adjust dose for unilateral hearing loss related to initial or second surgery. Adjust dose as below for unilateral or bilateral hearing loss.
If decrease threshold ≤ 15 dB at 1000-3000 Hz or ≤ 40 dB at 4000-8000 Hz : No dose modification needed
If decrease threshold between >15- ≤ 30 dB at 1000-3000 Hz or > 40 dB at 4000-8000 Hz– Reduce carboplatin from 200 mg/m^2 to 125 mg/m²/day prior to adjusting dose for age.

If decrease threshold > 30 dB at 1000-3000 Hz: Replace carboplatin by cyclophosphamide at the calculated dose for age for cyclophosphamide.

5.2.3 Allergic Reactions

In subsequent cycles of carboplatin, it is recommended to infuse carboplatin over 2 hours

and premedicate with diphenhydramine 1mg/kg (max dose 50 mg) and steroids (if reaction is more than a mild reaction), and ranitidine 1 mg/kg/dose IV (max dose 50 mg) or equivalent H2-receptor antagonist (e.g., famotidine dose 0.5 mg/kg, maximum single dose 20 mg) if unresponsive to diphenhydramine and steroid.

5.3 Cyclophosphamide

5.3.1 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. If mesna originally given as short infusion boluses, change to continuous infusion. If mesna originally given as 100% via continuous infusion, increase hydration for subsequent doses.

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.

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 120% of the cyclophosphamide dose at the next cycle.

5.3.2 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 dose. Use hydration and continuous infusion mesna at 120% of the cyclophosphamide dose.

5.4 Etoposide (VP-16)

5.4.1 Allergic Reaction

Premedicate with diphenhydramine (1-2 mg/kg slow IV push, maximum dose is 50 mg). If symptoms persist, add hydrocortisone 100-300 mg/m^2. Continue to use premedication before etoposide in future. Also consider substituting an equimolar amount of etoposide phosphate, in the face of significant allergy and/or hypotension. Etoposide phosphate is a water soluble prodrug that does not contain polysorbate 80 and polyethyleneglycol, the solubilizing agent in etoposide that may induce allergic reactions and hypotension. Etoposide phosphate is rapidly converted to etoposide *in vivo* and provides total drug exposure, as represented by AUC (0-infinity), that is statistically indistinguishable from that measured for etoposide at equimolar doses.

To substitute etoposide with etoposide phosphate, doses should always be expressed and calculated as the desired ETOPOSIDE dose, not as the etoposide phosphate (salt) dose. Etoposide phosphate 113.5 mg is equivalent to etoposide 100 mg; each vial of Etopophos contains 100 mg of etoposide. An etoposide dose of 100 mg/m^2 is equal to Etopophos 100 mg/m^2.

5.4.2 Hypotension

If diastolic or systolic blood pressure (BP) falls 20 mm Hg during infusion, reduce infusion rate by 50%. Start a simultaneous infusion of NS 10 mL/kg if BP fails to recover or falls further. Stop infusion if BP does not recover, continue NS. If the patient has had any episode of hypotension, prehydrate with 0.9% NaCl at 10 mL/kg/hr for 2 hours prior to any subsequent infusion.

5.5 High-Dose Methotrexate (HDMTX) and Leucovorin Rescue

5.5.1 Nephrotoxicity

Postpone course if pre-treatment (MTX) serum creatinine is > 1.5 x baseline or GFR creatinine clearance < 65 mL/minute/1.73m^2. If renal function does not recover, omit MTX. Do not give HDMTX to a patient with this degree or renal impairment, assuming that prolonged excretion can be managed with glucarpidase.

NOTE: For patients who have markedly delayed MTX clearance secondary to renal dysfunction, consider using glucarpidase (carboxypeptidase G_2, Voraxaze™). ASD Healthcare is the sole supplier of glucarpidase (carboxypeptidase G_2, Voraxaze™) in the US. To obtain supplies of glucarpidase in the US contact the Voraxaze 24-hour Customer Service line at 855-786-7292. Additional information can be found at http://www.btgplc.com/products/specialty-pharmaceuticals/voraxaze. Canadian sites should contact McKesson at (877) 384-7425 for further information. Sites in Australia and New Zealand should contact Hospira at 1300-046-774 (local) or medicalinformationAUS@hospira.com.

5.5.2 Liver Dysfunction

Samples for the determination of ALT value must be drawn within 72 hours, PRIOR to a course of intravenous MTX. Blood samples for ALT should not be drawn following the start of MTX infusions as MTX causes significant short term elevation in ALT levels.

ALT	IV MTX
< 10 X ULN	Continue with therapy as scheduled
10 – 20 X ULN	Continue with therapy as scheduled for 1 cycle
10 – 20 X ULN for 2 consecutive cycles	Discontinue TMP/SMX* Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption.
> 20 X ULN	Hold therapy until ALT < 10 X ULN, then resume at full doses at point of interruption.
> 20 X ULN for > 2 weeks	Evaluate with AST, Bili, Alkaline phosphatase, PT, albumin, total protein, and hepatitis A, B, C, CMV, and EBV serologies. Consider liver biopsy before additional therapy given. Notify Study Chair.

* Please see COG Supportive care Guidelines at: https://members.childrensoncologygroup.org/prot/reference_materials.asp for TMP/SMX substitutions.

Hold IV MTX for direct hyperbilirubinemia of > 2.0 mg/dL.

5.5.3 Mucositis

For Grade 3-4 mucositis, withhold IV MTX until resolved. Increase leucovorin rescue following the next course from 3 to 5 doses on a q6 hr schedule. If subsequent course is not associated with Grade 3-4 mucositis, attempt to decrease the leucovorin. If mucositis recurs despite the extended leucovorin, decrease the dose of MTX by 25%, increase hydration to 200 mL/m^2/hr and continue increased leucovorin as above. Should subsequent courses be well tolerated, use a stepwise approach to resuming a standard approach to drug delivery. Consider culturing lesions for herpes simplex if mucositis persists or recurs.

5.6 Vincristne

5.6.1 Vincristine Neurotoxicity

Seizures: Hold one (1) dose of vincristine, then reinstitute at 1 mg/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.

Severe neuropathic pain (Grade 3 or greater): Hold dose(s). When symptoms subside, resume at 50% previous dose, 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.

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. Drugs such as gabapentin may be of value.

Vocal Cord Paralysis: Hold dose(s). When symptoms subside, resume at 50% of previous dose, then escalate to full dose as tolerated.

5.6.2 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.

5.6.3 Constipation or Ileus

Every effort should be made to prevent the development of constipation and ileus through judicious use of stool softeners/laxatives to prevent dose alterations. For greater than Grade 3 toxicity, hold vincristine dose(s). Institute aggressive regimen to treat constipation, if present. When symptoms abate then resume vincristine at 50% dose and escalate to full dosage as tolerated.

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." This manual is provided under Standard Sections for Protocols at: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations During Protocol Therapy

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. **Obtain other studies prior to start of phase unless otherwise indicated.**

STUDIES TO BE OBTAINED	Baseline	Prior to Each Cycle of Induction Therapy	During Each Cycle of Induction Therapy	Following Completion of Induction Therapy (Cycle 3)	Following Second Look Surgery	Prior to Each Cycle of Continuation Therapy	During Continuation Therapy	Completion of Continuation Therapy
History	X	X	X (Day 15, 29, 43)	X		X	X (Day 21)	X
Physical Exam (Ht, Wt, VS)	X	X	X (Day 15, 29, 43)	X		X	X (Day 21)	X
Performance Status	X	X		X		X		X
CBC (differential, platelets)	X	X	X (Day 15, 29, 43)	X		X	X (Day 21)	X
Urinalysis	X	X	X (Days 15, 29)			X	X (Day 21)	
Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium)	X	X	X (Day 15, 29, 43)	X		X	X (Day 21)	X
Serum Creatinine, Creatinine Clearance or GFR	X	X	X (Day 15, 29, 43)			X	X (Day 21)	
Audiogram or BAER	X		X (Day 43)[4]	X			X (Day 21)	X
Brain MRI with and without gadolinium	X[1]	X (Prior to Cycle 2)[3]		X[3]	X[3]			X[3]
Spinal MRI with and without gadolinium	X[2]	X (Prior to Cycle 2)[3]		X[3]	X[3]			X[3]
CSF cytology	X			X				X
Tissue Submission for Biology Studies (See Sections 7.3and 14.3	X				X			

1- The pre-operative MRI evaluation will include an MRI of the brain (recommended with gadolinium) or pre-operative CT (recommended with contrast). The brain MRI should be repeated within 72 hours of surgery with and without gadolinium and this study will serve as the baseline for future comparisons.
2- The spinal MRI will include pre-op with and without gadolinium or post-op with and without gadolinium preferably within 72 hours of surgery.
3- Required for disease evaluation.
4- Obtain for Cycles 2 and 3.

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 Observations Following Completion of Protocol Therapy

Observation	3 Months, 6 Months, 9 Months	Every 4 Months up to 24 Months (Months 12, 16, 20, 24)	Annually up to 72 Months (Months 36, 48, 60, 72)
Physical Exam with neurologic exam including growth curve (Height and Weight)	X	X	X
Brain MRI with and without gadolinium	X	X	X
Spine MRI with and without gadolinium	X	X	X[1]
Audiogram or BAER		X[2]	X[1]

1 – Obtain if clinically indicated or if abnormal at completion of therapy.
2 – Obtain at 12 and 24 months.

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

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

7.3 Required Studies

7.3.1 Biology Specimens

The following specimens are required. Send tumor tissue and peripheral blood according to collection and shipping instructions in Section 14.0. **NOTE: Biology specimens should not be submitted until after the rapid central pathology screening review has been completed and the patient is found to be eligible for and enrolled on ACNS1221.**

Sample	When Obtained	Study
Peripheral Blood (5 ml of blood in a purple top tube [EDTA])	Prior to treatment and at the time of second surgery.	Germline DNA and SNP analysis
Formalin Fixed Paraffin Embeded (FFPE) Sections: 25 (5µm) unstained slides and up to 10 (10µm) scrolls	At time of diagnosis and second surgery	1)IHC: 9 GAB1, βcatenin, Filamin A, and YAP1 2) FISH studies: Loss of 9q and 10q Isochromosome 17q MYCN and MYCC amplification, GLI2 amplification

7.4 Optional Studies

7.4.1 Neurocognitive 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 (IQ) and specific areas of neuropsychological functioning, emotional-behavioral functioning, and quality of life. Total testing time should be approximately 1 hour at each assessment point.

7.4.2 Optional Biology Specimens

The following specimens are optional. Send snap frozen tumor tissue according to collection and shipping instructions in Section 14.0

Sample	When Obtained	Study
50-100 mg pieces Snap frozen tumor tissue	At time of diagnosis and second surgery	1) High throughput gene expression analysis 2) SNP analysis on tumors 3) Whole exome sequencing 4) Targeted gene sequencing

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.

b) Refusal of further protocol therapy by patient/parent/guardian.

c) Completion of protocol therapy.

d) Physician determines it is in patient's best interest.

e) Development of a second malignancy.

f) Repeat eligibility studies (if required) are outside the parameters required for eligibility.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.

b) Lost to follow-up.

c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).

d) Withdrawal of consent for any further data submission.

e) The sixth anniversary of the date the patient was enrolled on this study.

f) Patient did not receive protocol treatment after study enrollment.

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size and Study Duration

Background

The primary objective of this trial is to estimate the PFS distribution of patients 0-<4 years of age with newly-diagnosed M0 desmoplastic (ND/MBEN) medulloblastoma treated with ACNS1221 therapy. While this study is not designed for a formal comparison, outcome for patients treated on the current trial will be assessed for evidence that the 2-year PFS rate is unacceptably low given what was observed for patients treated on HIT SKK 2000 trial, which enrolled newly diagnosed non-metastatic medulloblastoma patients within this age group and treated them with a chemotherapy-only regimen.[6] HIT SKK 2000 enrolled 19 evaluable desmoplastic patients (13 ND+6 MBEN), 14 of whom were R0 (9 ND+5 MBEN) after initial surgery. All 19 patients have been followed for over 2 years and the only progression (local) was observed 1.7 years after diagnosis in a patient who was R0 after initial surgery. Hence the percentage of patients who were progression free during the first 2 years for this cohort is 94.74% with a Blyth-Still-Casella 95% lower bound estimate of 79.13%.

While the follow-up is less complete, preliminary results from Head Start III trial for a similarly defined patient cohort indicate a similar outcome (G Dhall personal communication). Specifically, 15 M0/R0 desmoplastic patients less than 4 years of age were enrolled on the Head Start III study and only 1 failure was observed during the first 2 years. Hence the percentage of patients who were progression free during the first 2 years in the associated Head Start III cohort is 93.33% with a

Blyth-Still-Casella 95% lower bound estimate of 75.29%, which is quite similar to the outcome observed in the HIT SKK 2000 trial.

With respect to the COG studies, the recent report by Leary et al[4] indicate that 18 M0 desmoplastic patients aged 0-3 years were treated on CCG-9921 protocol. All 18 were followed for at least 2 years from on-treatment date and 4 failed during the first 2 years leading to a "proportion of success" estimate of 77.78%. In other words 77.78% of patients were failure free at the end of 2 years with a standard error of 9.47%. The Blyth-Still-Casella 95% lower bound estimate of the proportion of patients who are failure free at the 2-year mark is 58.12%.

Primary Endpoint and Sample Size

The intent of the current study is to estimate the PFS distribution associated with the current treatment which uses the same chemotherapy regimen as HIT SKK 2000 but without the intraventricular MTX. Note however that this study is an independent assessment of the efficacy associated with the proposed treatment regimen and this trial is not designed to directly compare its outcome to the one observed on HIT SKK 2000 trial.

While the primary objective is estimating the PFS distribution, for the purpose of sample size determination we will frame the design in the context of hypothesis testing with the following primary outcome: proportion of eligible patients who receive at least 1 dose of the chemotherapy regimen and who complete the first 2 years from diagnosis without progression or death. Since this trial proposes a reduction in treatment, we will base the design on a one-sided test and the following hypotheses: the true, unknown 2-year success rate is at least 90% (null) vs. less than 74% (alternative). The values for the null and the alternative hypotheses were chosen based on the outcome observed on recent trials especially HIT SKK 2000. Though 90% is slightly lower than what was achieved on HIT SKK 2000, this was felt to be a reasonable target taking into account the small sample sizes from which these outcome information were derived, the variability observed in the outcome across trials and the previous variability associated with identifying ND/MBEN medulloblastoma. Moreover the study team firmly believes that 90% 2-year PFS without IT-MTX would be a very desirable outcome for this patient population.

Because the desirable outcome is stated in the null hypothesis which is consistent with the treatment reduction objective of this study, we used a relatively large α and a small β in order to maximize the power to detect erosion in PFS rates and control the risk of falsely concluding that the modified treatment is not associated with worse outcome. Based on the above-mentioned parameters, a sample size of 37 patients results in α=0.16 and power=0.945 for the associated 1-sided hypothesis which would lead us to declare the proposed treatment regimen as promising if no more than 5 failures are observed during the first 2 years from diagnosis among the 37 patients. In other words, the 2-year PFS rate associated with the proposed treatment regimen will be considered desirable if 32 or more of the 37 patients enrolled (86.5%) complete the two year observation period without an event. Otherwise the proposed regimen will be rejected. Final analysis will be conducted once 37 eligible and evaluable patients have been enrolled and all have been followed for 2 years from diagnosis or until failure, whichever comes first. Considering the unlikely event of patients being declared ineligible or inevaluable after enrolling on the trial, we estimate that we will enroll at most 42 patients in total.

In the recent infant trials conducted by COG or its predecessors, namely CCG-9921, CCG-99703 and P9934, there were no M0 medulloblastoma patients who were censored in the first 2 years of the study. In addition, based on the currently open trials whose eligibility criteria include medulloblastoma patients younger than 4 years of age, specifically ACNS0331, ACNS0332 and

ACNS0334, there was only 1 medulloblastoma patient younger than 4 years of age who was lost to follow-up within 2 years of enrollment. Hence we expect that in the current study no patient will be lost to follow-up within two years of diagnosis. This is important since the parameter on which this design is based is a proportion derived from a Binomial distribution. The definition of this proportion requires all patients who fail to be evaluated at the 2-year time point to be considered as failures. These would include patients who discontinue treatment due to toxicity and refuse further follow-up, withdraw from the study or who are lost to follow-up within the first two years. Definition of an "event" also includes second malignancy or death for any reason within the first 2 years from diagnosis.

9.2 Accrual Duration

The study team estimates that the accrual rate to this trial will be approximately15 patients/year. Hence we expect that accrual to this study will be complete in 2.5-3 years barring any unforeseen circumstances.

To estimate our expected accrual we reviewed the enrollment profile of previous infant studies and extracted the number of M0 Desmoplastic patients enrolled per year according to the central pathology review of these trials. The following table summarizes the accrual of several infant studies which ran during the last 2 decades, some of which overlapped:

Table 4: Accrual Summary of Infant M0 ND/MBEN Medulloblastoma Patients on Previous Trials

Protocol	Years of study	No. of M0 ND/MBEN	No./year
9934	10/2000-6/2006	30	5
9921	4/1993-7/1997	18	4.5
99703	3/1998-10/2004	13	1.7
Head Start I,II	1991-2003	21	1.6
Head Start III	2003-2009	28	4.6

The following facts are part of our rationale for anticipating higher accrual than what has been listed above:

- The 9934 trial did not include patients < 8 months and was only opened in 33 out of the 250 COG institutions. Note that while the accrual rate for this study had to be adjusted from 25 patients/year to 16 patients/year, at the time the adjustment was made the study team had speculated that the slower accrual was likely related to the mandated XRT rather than competition from other studies.
- 99703 study was closed to accrual frequently as part of the study design to evaluate safety which resulted in many patients being treated off protocol.
- The addition of 1 to 2 patients per year to account for accrual of patients aged between 3 and 4 years (estimate based on A9961 series)

Also based on CBTRUS data applied to the US population estimates (2004-2007) of children ages 0-4 years, an annual incidence of approximately 185 cases of medulloblastoma would be expected. Based on the reported frequencies of desmoplastic medulloblastoma summarized in Table 1, we estimate that 40% of these 185 new cases annually will be ND/MBEN which results in a population size of 74 patients/year in the US alone with additional patients who would be eligible to enroll from COG member institutions in Canada and Australia. Although some concurrent studies will be competitive (next Head Start study and the currently open St Jude SJYC07 trial), we do not

anticipate that they will alter our ability to reach our target accrual rate of 15 patients/year. This trial is the only opportunity for many centers to treat ND/MBEN medulloblastoma patients with a regimen specific to their histology and without high dose chemotherapy, which we believe will help boost accrual.

9.3 Analysis Plan for the Primary Objective

At the time of the final analysis, 95% exact confidence interval estimate of the binomial probability of completing two years of therapy free of failure will be calculated. In addition Kaplan-Meier estimates of PFS and overall survival distributions will be provided. PFS will be measured from diagnosis to the earliest of disease progression or death from any cause. Similarly OS will be measured from diagnosis to death from any cause. Patients who have not experienced one of these events will be censored at their last date of contact. In the event that any patient experiences a second malignancy we will also provide an estimate of event free survival distribution. For patients with measureable disease we will assess response rates after induction therapy as well as at the end of continuation therapy. Estimates of response rates as well as the associated exact confidence intervals will be reported. If accrual estimates as discussed above prove accurate, these analyses are expected 5-6 years after the trial is activated.

Interim Analysis

Given the excellent outcome which is being targeted, the long follow-up needed to assess the primary endpoint and the relatively small number of patients to be enrolled on this study, devising an interim analysis with reasonable operating characteristics is difficult. Keeping this limitation in mind, we will conduct an interim analysis once 15 patients have been enrolled and have been observed for the 2-year outcome. If 10 or fewer patients complete the 2-year observation period without progression/death, this would suggest that the modified therapy is inferior. Note however that unless these events occur relatively early or that the reduced treatment has a substantially lower success rate, it is likely that at the time of the interim analysis, most patients would have been accrued since accrual will not be suspended in order to wait for the interim analysis results. Based on this interim analysis rule, if the modified treatment has a 74% 2-year success rate, there is a 34.7% chance that this boundary will be crossed at the interim analysis. However if the 2 year success rate is 60%, the trial will stop with 78.3% probability based on the proposed interim analysis rule. In addition since only 6 failures are needed overall in order to declare the proposed strategy a failure, this will also serve as a stopping rule. More specifically, we will stop accrual to the trial if at any point 6 failures have been observed within the first 2 years from diagnosis, which may be more effective than the interim analysis rule in stopping early if the proposed regimen is indeed inferior. Note that an earlier time point could not be considered for the design as no failures were observed on the HIT SKK 2000 study or on the CCG-9921 trial among patients who would have been eligible for this study during the first year of treatment and only 1 patient had failed by 18 months.

9.4 Correlative Science Objectives

Rapid Central Pathology Screening Review

Evaluate the feasibility of a rapid central pathology screening review for treatment allocation according to histology and assess agreement between institutional and central pathology review diagnoses as well as among central pathology review diagnoses.

While the nodular/desmoplastic histology subtype is more common among the infant group, the reported rates vary widely among studies, ranging from 29% to 75%. The discrepancy in the rates of desmoplasia may be related to selection bias among the various infant medulloblastoma series

(different ages for inclusion, different eras of diagnostic tools and awareness of the diagnosis) or may be due to under-reporting since most protocols to date did not have specific reporting requirements for subtypes of medulloblastoma. However, there is also evidence that lack of consensus on the definition of desmoplastic medulloblastoma is another contributing factor to this discrepancy. Therefore, a rapid central pathology screening review appears essential in the context of a protocol that is intending to treat according to histologic subtype. Hence this protocol will require pre-screening and rapid central pathology screening review to confirm eligibility.

Patients with an institutional diagnosis of medulloblastoma will undergo a rapid central review and only those with confirmed ND/MBEN histology will be eligible to be treated on the current study. The central pathology panel will include 3 pathologists who will review the pathology slides via a web-based system. All 3 pathologists are expected to review all cases and eligibility will be based on majority opinion. More specifically, if at least 2/3 pathologists agree that the patient has ND/MBEN medulloblastoma that patient will be declared eligible. In cases where one of the 3 pathologists is not available and the remaining 2 pathologists are not in agreement, they will be expected to discuss the case and reach a consensus about eligibility. Given the web-based review system and the relatively long period allocated for review, the study team believes it is highly unlikely that there will be a case where more than one pathologist will be unavailable for review.

The feasibility of this central prescreening process will be monitored and the central review results are expected to be made available within 10 days of the receipt of the slides at the Biopathology Center. We will monitor the success rate of timely central pathology review based on the expectation that at least 95% of the cases will be reviewed within 10 days. Note that while the sample size of this trial is 37 eligible and evaluable patients, up to 100 patients may have to be pre-screened in order to achieve it. The following somewhat ad-hoc monitoring rules will be used to assess feasibility of this approach and if at any time one of the thresholds is met, a re-evaluation of the central pathology screening review process will be initiated so that corrective action can be taken. These thresholds are based on an exact binomial design with H_0:$p \geq 0.95$ vs. H_A:$p < 0.95$ which leads to a sample size of 98 and is powered to detect an effect size of 9% (i.e. p=0.86) with an actual α=0.057 and actual power=0.943. The associated interim monitoring rules based on monitoring for rejection of H_0 only are given in the table below:

Number of Patients Screened	**Re-evaluate pathology review process if number of patients whose central path screening review is not complete within 10 days of receipt of slides at Biopathology Center**	**Cumulative boundary crossing probability under the assumption that the true success rate ≤86%**
35	≥8	21.1%
55	≥9	51.7%
80	≥10	80.9%
98	≥10	94.3%

At the end of the trial the feasibility of such a prescreening process will be assessed by reporting various performance statistics including the percentage and the associated confidence interval of cases where the central review was obtained within 10 days from receipt of slides as well as summary statistics of the actual review times. Further frequency tables and other descriptive statistics will be provided summarizing the agreement between the site pathologists and the central pathology reviewers as well as among the central pathology reviewers.

Molecular Profile

Prospectively evaluate the molecular profile of ND/MBEN medulloblastoma in young children

The proposed secondary biology objective is quite broad and aims to scrutinize the available tumor material via a variety of molecular studies. Given the high dimensionality of the genomic information which will be generated from these samples, the optional nature of some of these studies and the relatively small sample size planned for this study, the number of patients with available tissue will be the limiting factor in determining the feasibility and the utility of these studies. The eligible cohort for this trial is relatively homogeneous from a clinical and histological perspective which will help reduce the number of other variables that may need to be accommodated in the resulting models.

As indicated above accrual is expected to last approximately 3 years. Tumor tissue will be collected from consenting patients during this time however the sample and array processing will not be performed until the accrual is complete. This will eliminate various sources of variability which would otherwise be introduced into the data. Further, in light of the rapidly progressing sample and array processing methodologies, waiting until the end of the accrual period to perform the necessary analyses would allow us to utilize the most up-to-date methods available at that time. The same rapid emergence of new approaches is also true for statistical methodology regarding genomic data therefore the approaches detailed below reflect the current state of knowledge and may be modified at the time of analysis which is expected to be performed approximately 4 years after study initiation. At the time the protocol is closed to accrual but prior to the analysis of the procured samples, a separate protocol (to include analytical and statistical methodology) will be developed for use of the samples collected for the ACNS1221 trial for correlative biology studies and submitted and approved in accordance with the National Clinical Trials Network. The following therefore is an overview of studies which may be performed, though are subject to change based on above-outlined reasons:

Unsupervised clustering algorithms, such as hierarchical clustering or non-negative matrix factorization[27] may be used descriptively to explore the possibilities of discovering novel subgroups based on gene expression. We may also combine our data with previously collected data for other medulloblastomas and perform subgroup discovery analysis on the combined cohort including bootstrap-based resampling of subjects[28] to determine the stability of subgroup assignments.

We may explore the association of gene expression with clinical features, histological features, and prognosis, via appropriate hypothesis tests and models. We may use false discovery rate methods[29] or other similar approaches to address multiple testing.

We may use SNP microarrays to identify copy number abnormalities in these tumors. We will adjust for potential aneuploidy while normalizing signal data and then use an appropriate segmentation algorithms [30,31,32,33] to identify change-points in the series that may indicate regions of deletion or amplification. We may also explore whether the constellation of deletions and amplifications appear to be associated with target specific pathways as well as with clinical features and prognosis.

We may use sparse canonical correlation[34] or similar approaches to characterize the association of genome-wide copy number alterations with genome-wide gene expression.

Using the most appropriate methods available at the time, the whole exome sequencing data, will be mapped to the reference genome, will be transformed and adjusted for GC-effects, and then segmented to identify copy number changes. Additionally, we may explore the presence of

translocations and other structural alterations in the whole exome data. The clinical and prognostic relevance of copy number and structural abnormalities may be studied by screening their association with clinical and prognositic variables.

All patients who enroll on this study will have FFPE tissue available for analysis. The percentage of tumor sub-types identified via expression of four IHC markers (GAB1, Bcatenin, Filamin A and Yap1) along with their exact confidence intervals will be provided. Similar statistics will also be computed for percentage of patients with a variety of molecular aberrations such as loss of chromosome 9q, 10q and 17p, gain of chromosome 3q and 17q, amplification of MYCN and GLI2 as well as other specific targets which may be identified in the near future. Contingency table analysis will be used to examine the association of molecular abnormalities with other categorical characterizations of tumors. If appropriate, associations of continuous markers with specific tumor types will be examined using ANOVA or the Kruskal-Wallis tests. Significance will be determined using exact, permutation, or resampling methods. Finally associations of such abnormalities with outcome will be explored via Cox models.

Neurocognitive Functioning

Due to early closure of the study, the neuropsychological function studies were removed as part of Amendment #3.

Monitor and describe the neurocognitive and adaptive functioning of young children with ND/MBEN medulloblastoma treated on this protocol using the ALTE07C1 protocol

Neurocognitive and adaptive functioning outcome assessment is an important secondary objective of this trial and the intent is to provide preliminary evidence that the treatment regimen proposed in this study will not lead to substantial decline in neuropsychological and adaptive functioning as assessed in an exploratory fashion. The proposed assessments and time points (9, 30, and 60 months post diagnosis (± 3 months)) are consistent with the approved COG ALTE07C1 protocol. Since the proposed hypotheses are in the form of non-inferiority, it will not be possible to test these definitively. Instead provided adequate data is available to make such analyses viable, we will provide confidence intervals of the average scores obtained at each time point both for Full Scale IQ score (FSIQ) and General Adaptive Composite score (GAC) and see if these confidence intervals include the normative values. Additionally we will describe changes between T1 and T2, T2 and T3 and T1 and T3 via paired tests and confidence intervals both for FSIQ and GAC scores in order to capture any deterioration over time. We will also consider repeated measures analyses incorporating all three time points to describe change over time.

Given the optional nature of these studies, the consent rate to participate in ALTE07C1 trial and compliance with data submission will determine whether adequate data will be available to provide meaningful information. Hence a monitoring rule will be in place to ensure that the consent and compliance rates are not unacceptably low. We will base this monitoring rule on T1 and on GAC score, since FSIQ score availability will be dependent on the age distribution of patients at T1 whereas GAC will be potentially available on everyone since it is a parent report measure. Based on a 1-sample t-test and a null hypothesis that the mean GAC score for patients on this study will be similar to the norms vs. the mean GAC score will be lower, we will need 27 patients to detect a 0.5 std dev drop in average GAC scores with 10% type 1 error and 90% power. This sample size requires approximately 75% consent and compliance rate. So we will check the consent and compliance rate after 20 patients have been enrolled on the study and have reached T1, if the number of patients who consented and provided data for GAC score is less than 15, then we will review and revise our approach to ensure that the compliance improves for future patients.

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	1	2	3
Not Hispanic or Latino	17	22	39
Ethnic Category: Total of all subjects	18	24	42
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	2	3
Native Hawaiian or other Pacific Islander	0	0	0
White	17	22	39
Racial Category: Total of all subjects	18	24	42

This distribution was derived from enrollment patterns in prior COG trials with similar patient populations and incorporates the slightly larger likelihood of medulloblastoma in males.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 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 v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

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 its perpendicular. FLAIR, T2 or post contrast T1 weighted images may be used - whichever gives the best estimate of tumor size.

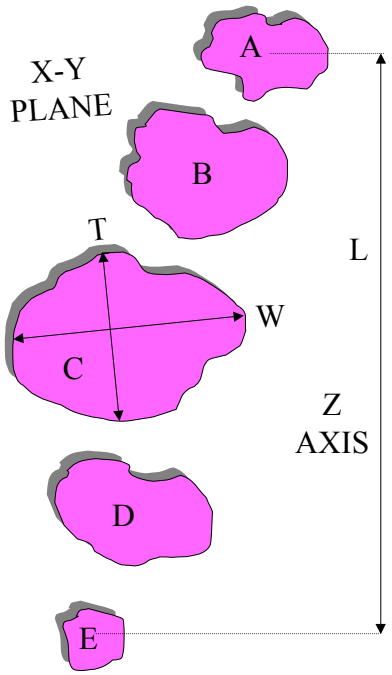
Since many tumors contain nonenhancing components (or, in some cases, the tumor may not enhance at all), both the enhancing and the non-enhancing components must be evaluated – on post contrast T1 weighted images and on FLAIR/T2 weighted images respectively. Increase in

enhancement on T1 weighted images without accompanying increase in disease bulk on T2 or FLAIR images is not considered tumor progression. In return, enlarging areas of nonenhancing tumor (defined as mass effect/tissue thickening) are evidence of tumor progression. Conversely, decrease in enhancing tumor component without decrease in overall FLAIR/T2 extent may represent change in tumor permeability (commonly observed with antiangiogenic therapies) rather than represent tumor response.

The following section describes the methodology. (See Figure 10.1 below for illustration.)

1. For MRI imaging the longest measurement of the tumor (or width, W) should be determined. It 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. Longest diameter of target lesion(s) should be selected in the axial plane only for CT.
2. The measurement (transverse (T)) perpendicular to the width in the selected plane should be determined. NOTE: A measurable lesion should have a minimal transverse measurement that is at least twice the combined thickness of the image slice and the interslice gap. For example, with a 4 mm slice and a 0.4 mm gap, minimal measurable lesion diameter is 8.8 mm. Smaller lesions would not be measurable for study purpose.
3. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis composes 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, and change in extent/thickness assessed on follow up studies.

Figure 10.1: COG Guidelines for Measurement of Tumor Size



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

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

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.

Overall Response Assessment

Target Lesions	New Lesions*	Overall Response
CR	No	**CR**
PR	No	**PR**
SD	No	**SD**
PD	Yes or No	**PD**
Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease
IR – Incomplete Response

*If CSF cytology becomes positive, it will be considered a new lesion and progressive disease.

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

10.3 Selection of 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, a minimum of the 2 largest lesions should be measured; a maximum of 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements.
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 (eg, 8 mm lesion for a 4 mm slice).

10.4 Response Criteria for Target Lesions

Response criteria are assessed in 2 dimensions – the product of WxT.

To assess response/progression, the ratio is calculated:

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

Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – eg, when multiple lesions show opposite responses, the progressive disease takes precedence.

Complete Response (CR): The disappearance of all target lesions.

Partial Response (PR): ≥ 50% decrease in the sum of the products of the 2 perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in sum of the products of the 2 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% 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 lesions. If CSF cytology becomes positive, it will be considered a new lesion and progressive disease.

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.

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

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

- Leukemia secondary to oncology chemotherapy
- Myelodysplastic syndrome
- Treatment related secondary malignancy

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

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 NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

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 that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

11.4 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 toxicities reported via CTEP-AERS and all Grade 4 and higher Adverse Events.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are 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). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (eg, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

13.0 SURGICAL GUIDELINES

13.1 Assessment of Residual Tumor

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

13.2 Size of Post-Surgical Residual Tumor

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

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

13.3 Extent of Tumor Resection

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

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

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

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

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

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

13.4 Imaging Confirmation of Extent of Resection

All patients will have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI scan, with and without contrast. This scan should be carried out after surgery, within 72 hours.

13.5 Peri-operative Corticosteroids

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

13.6 Second Surgery

The purpose of the second operation is to remove as much tumor that persists after induction chemotherapy as safely possible. As outlined in the Background section of this protocol, complete

resection of disease at diagnosis confers a survival advantage to patients. The goal of this intervention is to confer the advantage of complete resection of disease to as many patients as possible. If it is determined pre-operatively that residual tumor cannot be removed in its entirety, serious consideration should be made for tumor maximal safe debulking instead.

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.

14.0 PATHOLOGY GUIDELINES AND SPECIAL STUDIES

Before entering patients on this trial, clinicians should discuss this protocol with their pathologist and provide them with pathology section of the protocol and list of the required materials that will need to be submitted for the rapid central pathology screening review. (Requirements are listed on the Data Submission Schedule in the CRF packet and below.)

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed and to request that all M0 patients up to 4 year of age at definitive surgery specimens be forwarded to the COG Biopathology Center (BPC), as required. The BPC will NOT request materials.

14.1 Required Rapid Central Pathology Screening Review (See Appendix III)

The pathologic classification of tumors is becoming increasingly complex since there is considerable variation in the histological features of patients. Central review is therefore critical to ensuring that the diagnosis is accurate and that patients are treated appropriately. Central pathologic review will be performed on all diagnostic specimens (whether resected or biopsied). Results of the review will only be given to the treating institution for patients who receive rapid central pathology screening review.

If there is a discrepancy between the institutional diagnosis and the diagnosis on the rapid screening central review of a patient, then a discussion between the local and study pathologists will take place to attempt to reach a consensus, however, the decision of the study pathologists will be used to confirm eligibility. Slides will be stored at the COG Biopathology Center for quality control purposes.

Specimen Requirements

Patients must have a centrally confirmed histologic diagnosis of nodular desmoplastic (ND) medulloblastoma or medulloblastoma with extensive nodularity (MBEN) to enroll on the ACNS1221 study. The tumor should show significant nodular features encompassing 10% or more of the overall specimen. **Please do not submit tissue for Biology Studies (Section 14.3) until eligibility is confirmed and patient is enrolled on the study.**

Required Materials for Rapid Central Pathology Screening Review

1) 1 x H&E stained slide from **ALL** available paraffin blocks
2) 1 reticulin stained slide from a representative block
3) 1 synaptophysin stained slide if useful for institutional diagnosis

4) 5 unstained slides from most representative block
5) Institutional pathology reports
6) Operative report(s)
7) ACNS1221 Rapid Review Transmittal Form

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

Cases sent for Rapid Central Pathology Screening Review must be marked for RAPID REVIEW and shipped within 15 days of diagnosis by Federal Express Priority Overnight 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.

Results of rapid central pathology screening review will be available within 10 calendar days of the receipt of pathology review materials.

14.2 Virtual Microscopy (VIPER) System

This study will use virtual microscopy (VIPER) online automated pathology review system at the COG BPC for the rapid central pathology screening review. Representative H&E and reticulin slides will be scanned at the BPC into an ACNS1221 digital tissue review database. Synaptophysin stained slides will be scanned if available. The three study pathologists (Drs. Eberhardt, Hawkins and Horbinski) will be notified by email that a case is ready for central review. If 2 of the 3 pathologists confirm a diagnosis of nodular desmoplatic medulloblastoma or medulloblastoma with extensive nodularity using VIPER (Virtual Imaging for Pathology Education and Research), eligibility is confirmed. The institution will be notified of patient eligibility by email within 10 days of receipt of the slide at the Biopathology Center. At that time the patient may be enrolled on the protocol if all eligibility criteria are met and consent has been obtained.

14.3 Required Special Studies Specimen Requirements

Participation in biology studies is mandatory and specimens must be submitted no later than 3 working days after enrollment on ACNS1221. In addition, institutions are encouraged to enroll and submit specimens for ACNS02B3.

Required Materials:

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

1) **Peripheral Blood**: 5 ml of peripheral blood in a purple top tube (EDTA) should be sent at kept at 4°C. During warm weather, blood should be shipped on a cold pack. For second surgeries, please send blood at this time also.

2) **Formalin Fixed Paraffin Embedded Material (FFPE):** 25 (5um) unstained slides and up to 10 (10μm) scrolls should be sent
3) **COG Generic Specimen Transmittal Form** must accompany each shipment. Please use current form available at http://memberschildrensoncologygroup.org/prot/generic.asp.

Optional Materials:
It is highly recommended that snap frozen tumor tissue (a minimum of > 0.5 cm^2 is preferred) be submitted if available. As many 50-100 mg pieces of tissue as possible should be frozen in foil in liquid nitrogen within 10 minutes of removal. Wrap the aliquots in foil or place in cryopreservation tube if the tumor is semi-liquid. Use waterproof marker to label samples. Snap freeze the foil or cryopreservation tube containing the tumor material in vapor phase liquid nitrogen. Store in a -80°C freezer until shipment. Samples should be shipped to the BPC on dry ice.

Please label biology specimens with the COG Patient ID number, collection date and specimen type. For slides, document whether tissue is primary (P) or metastatic (M).

Specimen Shipment
If frozen tissue is submitted then biology specimens can be shipped together in a Specimen Procurement Kit. This 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. This kit contains most of the supplies necessary for shipping specimens to the BPC. To request a Specimen Procurement Kit, click on the 'Biopathology Center Application' link on either the Protocol or the CRA Home Page of the COG web site. On the Biopathology Center Applications page, select the BPC Kit Management link to enter the Kit Management application. For packing and shipping instructions please see **Shipping Specimens in a Dual Chambered Kit** at https://members.childrensoncologygroup.org/prot/biology.asp.

Ship the kit by Priority Overnight using a FedEx shipping label obtained through the BPC Kit Management application. Specimen procurement kits are to be shipped Monday through Thursday for delivery Tuesday through Friday. If blood is collected on a Friday, it may be shipped for Saturday delivery. Please do not ship tissue on Friday.

Note: If frozen tissue is not submitted, then a shipping label for the blood sample can be obtained through the BPC Kit Management application, but slides must be shipped either by mail or using the institution's courier account.

Ship specimens 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.

All specimens will be processed and then banked at the COG Biopathology Center (BPC). Specimens will be forwarded to Dr. Giles Robinson for biology studies.

14.4 Rationale for Biology Studies

High throughput molecular analysis on fresh frozen tumor tissue

Studies detailing subtype differences have utilized high quality RNA and DNA from fresh frozen material.[14-17,35] These studies have radically improved our understanding of medulloblastoma. Similarly, we plan to improve our understanding of this histologically defined subset of ND/MBEN medulloblastoma with high throughput gene expression analysis. SNP analysis on tumors and other upcoming new technologies that will be available at the time of analysis, where fresh frozen tissue is requested. Isolation, collection and storage of genomic material on ND/MBEN tumors will allow for identification of currently identified and other candidate mutations via targeted sequencing studies or whole exome sequencing

Rationale for Studies on FFPE

The majority of medulloblastoma samples attained from surgery do not have fresh frozen tissue available on which to perform studies. This current protocol will enroll patients from many different sites and, despite our emphasis on receiving fresh frozen tissue from every patient, we still anticipate to not have fresh frozen tissue on all of the medulloblastoma samples enrolled. Therefore, on this current protocol we will continue to collect and store FFPE upon which we aim to gather molecular and genomic information. While we anticipate that rapidly changing technology will enhance extraction of molecular data from of this medium there remains a lot of valuable information that can currently be gained from already available testing. Immunohistochemistry (IHC) and interphase fluorescence in situ hybridization (FISH) can be used to identify molecular abnormalities associated with clinicopathologic variables. These studies are robust, rapidly performed, and relatively inexpensive. IHC can be used to determine subtype classification. On ACNS1221 expression of four IHC markers (GAB1, Bcatenin, Filamin A and Yap1) will be performed on all FFPE tumor samples. Immunoreactivity profiles of these 4 markers will allow for the classification of ND/MBEN tumors into the WNT, SHH and non-WNT/non-SHH molecular subgroups. [27] Since we anticipate the majority of the ND/MBEN tumors will fall into the SHH subgroup[36,37] this analysis will provide useful data on the exclusivity of this histology to the SHH subtype and may allow for improved identification of a SHH specific ND/MBEN subgroup. FISH can also be used to uncover specific molecular abnormalities with clinicopathologic associations. Losses of chromosome 9q, 10q and 17p, gains of chromosome 3q and 17q, as well as amplification of MYCN and GLI2 will be assessed in this population. In addition FISH and IHC will be used to validate and explore genetic abnormalities revealed by high throughput molecular studies on the entire ND/MBEN population.

14.5 Methods

Methods for biology studies advance with technology and are subject to change. Samples on this trial will be analyzed by the most advanced methods available and the following methods are to be considered representative of those which will be used. Current patient derived materials needed to perform these analyses include (1) Fresh Frozen tumor tissue (2) Formalin Fixed Paraffin Embedded Tumor Material (3) Constitutional DNA Whole Blood Sample.

Fresh frozen tissue will be processed for RNA and DNA extraction. One or more pea sized aliquots of tumor should be collected from patients at time of initial resection and any subsequent tumor surgery.

Constitutional DNA Whole Blood Sample 5 mL of whole blood will be needed to extract germline DNA. This will serve as a comparative germline sample to tumor for sequencing studies. Whole blood anti-coagulated with EDTA will need to be collected, kept at 4°C and shipped on wet ice. Using waterproof marker, label the tubes with patient identifying number.

Formalin Fixed Paraffin Embeded Material (FFPE) for IHC, FISH studies. FFPE tissue will be processed by Neuropathology. For IHC FFPE sections (5μm) will be taken to assess the following:

- GAB1, Bcatenin, Filamin A, and YAP1 immunoreactivity for subtype classification
  For FISH FFPE sections (8 μm) will be taken to assess the following
- Loss of 9q and 10q
- Isochromosome 17q
- MYCN and MYCC amplification, GLI2 amplification

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

15.1 Timing of MRIs

To document the degree of residual tumor, standard whole brain MRI with and without contrast (gadolinium) and spine MRI with and without contrast (gadolinium) must be performed at the following time points:

- Pre-operative to include an MRI of the brain (recommended with gadolinium) or pre-operative CT (recommended with contrast).
- Pre-operative Spinal MRI with and without gadolinium or post-op with and without gadolinium preferably within 72 hours of surgery
- Post-operative cranial MRI within 72 hours of surgery
- Prior to Cycle 2 of Induction Therapy
- Completion of Induction Therapy
- Post-operative MRI within 72 hours of second surgery if done.
- Following Completion of Continuation Therapy

15.2 Whole Brain MRI With and Without Contrast

Recommended 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 gradient echo (susceptibility sequence); 4-5 mm skip 1-2 mm. TE=20, flip angle =20.
7. Axial T1 with contrast; 4 mm skip 0.4 mm

8. Sagittal T1 with contrast; 4 mm skip 0.4 mm
9. Axial T2 FLAIR with contrast; 4 mm skip 0.4

Optional sequences (depending on tumor)
Precontrast :
1. Sagittal or coronal FSET2; 4 mm skip 0.4 mm, depending on tumor configuration/orientation
2. Axial diffusion tensor

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

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

15.3 Spine MRI With Contrast

The MRI scan must be performed of the entire spine with and without contrast, and must be performed in at least two planes.

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

16.0 RADIATION THERAPY GUIDELINES

No radiation therapy is planned for this study.

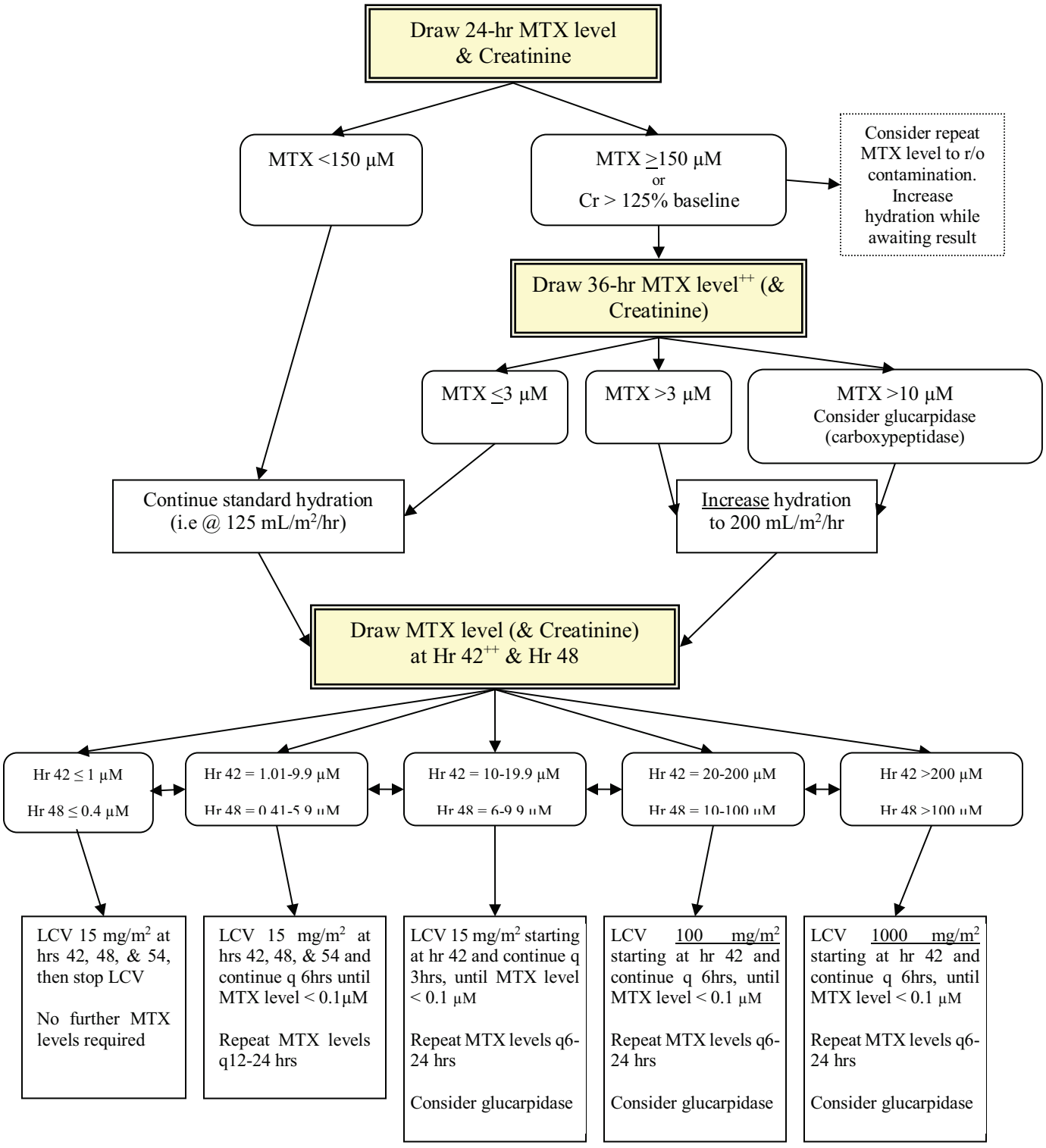
17.0 NEUROPSYCHOLOGICAL FUNCTION STUDY

Due to early closure of the study, the neuropsychological function studies were removed as part of Amendment #3.

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.

APPENDIX I: HIGH DOSE METHOTREXATE FLOW CHART

(Please refer to Section 4.5 for complete details; all levels are timed from the start of the HDMTX infusion)



++ If the level is high at hour 36 or 42, but then the patient "catches up" and the level falls to the expected values of ≤1 and/or ≤ 0.4 µM at hours 42 and 48, respectively, resume standard leucovorin and hydration as long as urine output remains satisfactory.

APPENDIX II: CYP3A4 INDUCERS AND INHIBITORS

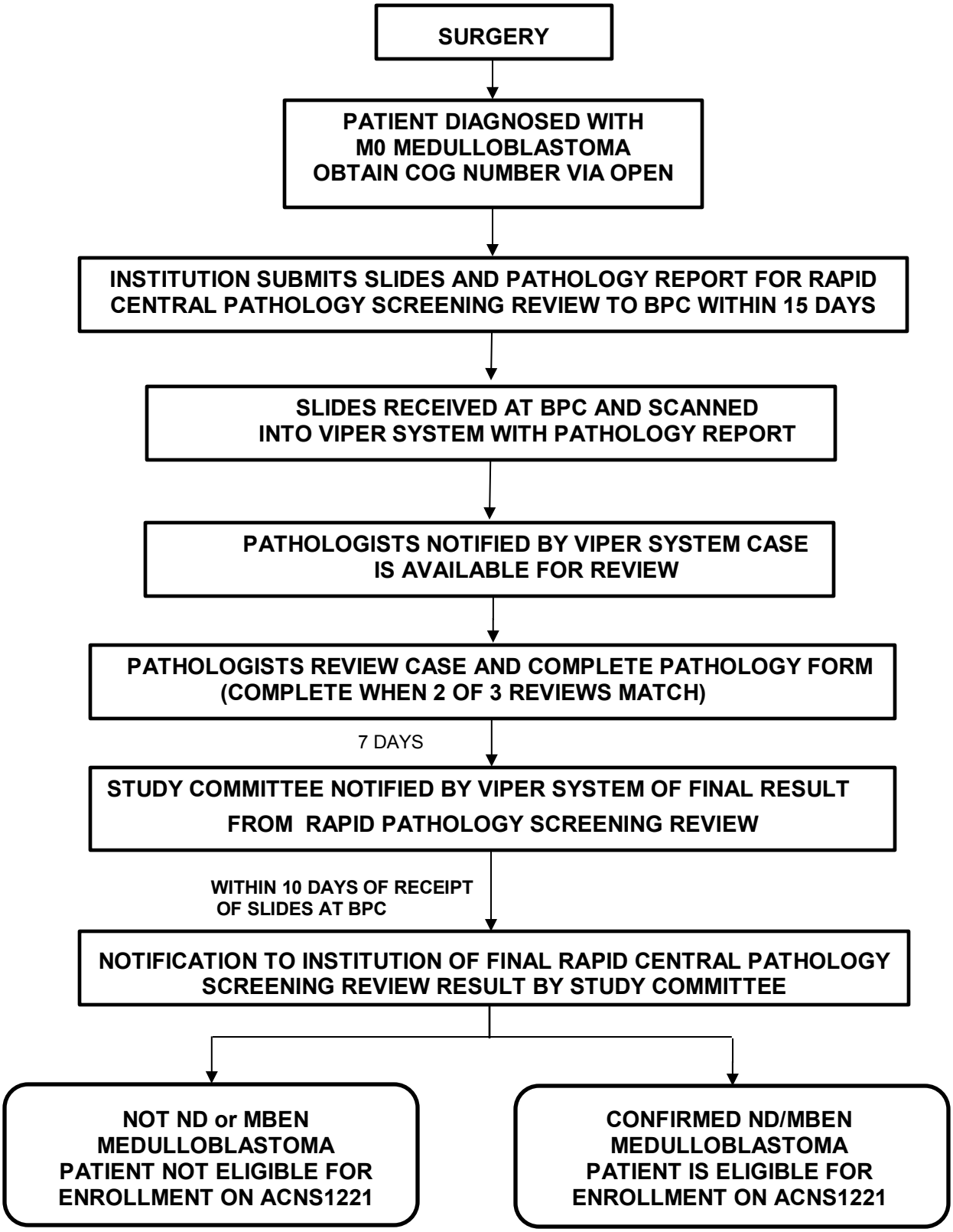
The use of the following medications should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list; please refer to other resources such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx for additional information.

CYP3A4 substrates	Strong Inhibitors*	Moderate Inhibitors	Weak Inhibitors	Inducers
alfentanil	atazanavir	aprepitant	amiodarone	armodafinil
amiodarone	boceprevir	atazanavir	ciprofloxacin	barbiturates
aprepitant	clarithromycin	cimetidine	doxycycline	bosentan
benzodiazepines	cobicistat	crizotinib	mifepristone	carbamazepine
bortezomib	conivaptan	cyclosporine	metronidazole	deferasirox
brentuximab	delavirdine	desipramine	nicardipine	efavirenz
budesonide	fosamprenavir	diltiazem	propofol	etravirine
calcium channel blockers	indinavir	erythromycin	quinidine	fosphenytoin
cisapride	itraconazole	fluconazole	sertraline	glucocorticoids**
citalopram/escitalopram	ketoconazole	fluvoxamine	tacrolimus	modafinil
glucocorticoids**	nefazodone	fosaprepitant		nafcillin
crizotinib	nelfinavir	grapefruit		nevirapine
cyclosporine	posaconazole	grapefruit		oxcarbazepine
cyclophosphamide	ritonavir	juice		phenobarbital
dapsone	saquinavir	imatinib		phenytoin
dasatinib	telaprevir	norfloxacin		pioglitazone
dihydroergotamine	telithromycin	tetracycline		primidone
docetaxel	voriconazole	verapamil		rifabutin
doxorubicin				rifampin
ergotamine				rifapentin
erlotinib				ritonavir
esomeprazole				St. John's wort
estrogens				topiramate
etoposide				
fentanyl				
fosaprepitant				
gefitinib				
haloperidol				
HIV antiretrovirals				
HMG Co-A inhibitors				
ifosfamide				
imatinib				
irinotecan				
itraconazole				
ketoconazole				
lansoprazole				
lapatinib				
losartan				
lovastatin				
macrolide antibiotics				
medroxyprogesterone				

methadone midazolam modafinil monteleukast nefazodone nilotinib omeprazole ondansetron paclitaxel pazopanib quinidine sildenafil sirolimus sunitinib tacrolimus terfenadine telaprevir tamoxifen temsirolimus teniposide trimethoprim vinca alkaloids zolpidem				

* Certain fruits and fruit juices (star fruit, Seville oranges, pomegranate) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
**Refer to Section 3.2.8 regarding use of corticosteroids.

APPENDIX III: ACNS1221 RAPID CENTRAL PATHOLOGY SCREENING REVIEW SCHEMA (PRIOR TO STUDY ENROLLMENT)



APPENDIX IV: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

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

Registration requires the submission of:

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

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

CTEP Associate Registration Procedures / CTEP-IAM Account

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

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

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

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

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

CTSU REGISTRATION PROCEDURES

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

Requirements for ACNS1221 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

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

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

APPENDIX V: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Carboplatin

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

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

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

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

Cyclophosphamide

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

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

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

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

Etoposide

Drugs that may interact with etoposide*

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

Food and supplements that may interact with etoposide**
• Echinacea • Glucosamine • St. John's Wort • 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.*

Methotrexate

Drugs that may interact with methotrexate*
• Some antibiotics (amoxicillin, Bactrim, chloramphenicol, ciprofloxacin, penicillin, piperacillin, tetracycline) • Some anti-inflammatory drugs (aspirin, acetaminophen, ibuprofen, naproxen, ketorolac) • Some heartburn medications (esomeprazole, lansoprazole, omeprazole, pantoprazole) • Several other specific agents, including the following: amiodarone, clozapine, cyclosporine, eltrombopag, leflunomide, phenytoin, pimecrolimus, probenecid, pyrimethamine, retinoids, theophylline, warfarin

Food and supplements that may interact with methotrexate**
• Alcohol • Echinacea • Some vitamins, including those that contain folic acid or high doses of vitamin C

**Sometimes these drugs are used with methotrexate 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.*

Leucovorin

Drugs that may interact with leucovorin*
• Some antiepileptics (fosphenytoin, phenobarbital, phenytoin, primidone)

Food and supplements that may interact with leucovorin**
• Folic acid

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

Food and supplements that may interact with vincristine**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

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

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

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