J1403 - Pilot Study of a Surgery and Chemotherapy-Only Approach in the Upfront Therapy of Children with Wnt Positive Standard Risk Medulloblastoma

NCT02212574

September 12, 2016

PILOT STUDY OF A SURGERY AND CHEMOTHERAPY-ONLY APPROACH IN THE UPFRONT THERAPY OF CHILDREN WITH WNT POSITIVE STANDARD RISK MEDULLOBLASTOMA

JHU Protocol #: J1403/NA_00091840

Study Phase: Pilot

Study Products: None

Protocol Chair/Principal Investigator: Kenneth J. Cohen, MD, MBA

Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University

Co-Principal Investigators: **Pratiti Bandopadhayay, MBBS, PhD**
Susan Chi, MD

Dana-Farber Cancer Institute
Harvard Medical School

Co-Investigators:

Dr Mark Kieran, Dana-Farber Cancer Institute

Statistician: Dr Wendy London, Dana-Farber Cancer Institute

Coordinating Center
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University
Bloomberg 11379
1800 Orleans St.
Baltimore, MD 21287
Phone: 410-614-5055
kcohen@jhmi.edu

IRB: Institutional Review Board
Johns Hopkins School of Medicine
1620 McElderry Street
Reed Hall, Suite B-130
Baltimore, MD 21205-1911

Protocol Revision Record
Version #1: December 19, 2013
Version #2: February 17, 2014
Version #3: August 25, 2014 (Amendment #1)
Version #4: September 14, 2015 (Amendment #2)
Version #5: April 28, 2016 (Amendment #3)
Version #6: September 12, 2016 (Amendment #4)

Dr Amy Smith
M D Anderson Cancer Center- Orlando
Pediatric Hematology/Oncology
92 West Miller MP 318
Orlando, FL 32806
USA
Phone (321) 841-8588
EMail amy.smith@orlandohealth.com
Fax: (321) 841-8560

Dr Kellie Nazemi
Oregon Health and Science University
Pediatric Hematology/Oncology
3181 SW Sam Jackson Park Road
Mail Code: CDRCP
Portland, OR 97239-3098
USA
Phone: (503) 494-1543
EMail: nazemik@ohsu.edu
Fax: 503 494-0714

Dr Joshua Rubin
Washington University School of Medicine
Pediatric Hematology/Oncology
1 Children's Place, 9 South
St. Louis, MO 63110
USA
Phone: 314 454-6018
EMail: rubin_j@kids.wustl.edu
Fax: 314 454-2780

Dr Sarah Leary
Seattle Children's Hospital
Hematology/Oncology
4800 Sand Point Way NE
M/S B-6553
Seattle, WA 98105
USA
Phone: (206) 987-2106
EMail: sarah.leary@seattlechildrens.org
Fax: (206) 987-3946

Dr Kathleen Dorris
Children's Hospital Colorado
Center for Cancer & Blood Disorders
13123 East 16th Avenue B115
Aurora, CO 80045
USA
Phone: 720 777-6772
EMail: kathleen.dorris@childrenscolorado.org
Fax: 720 777-7279

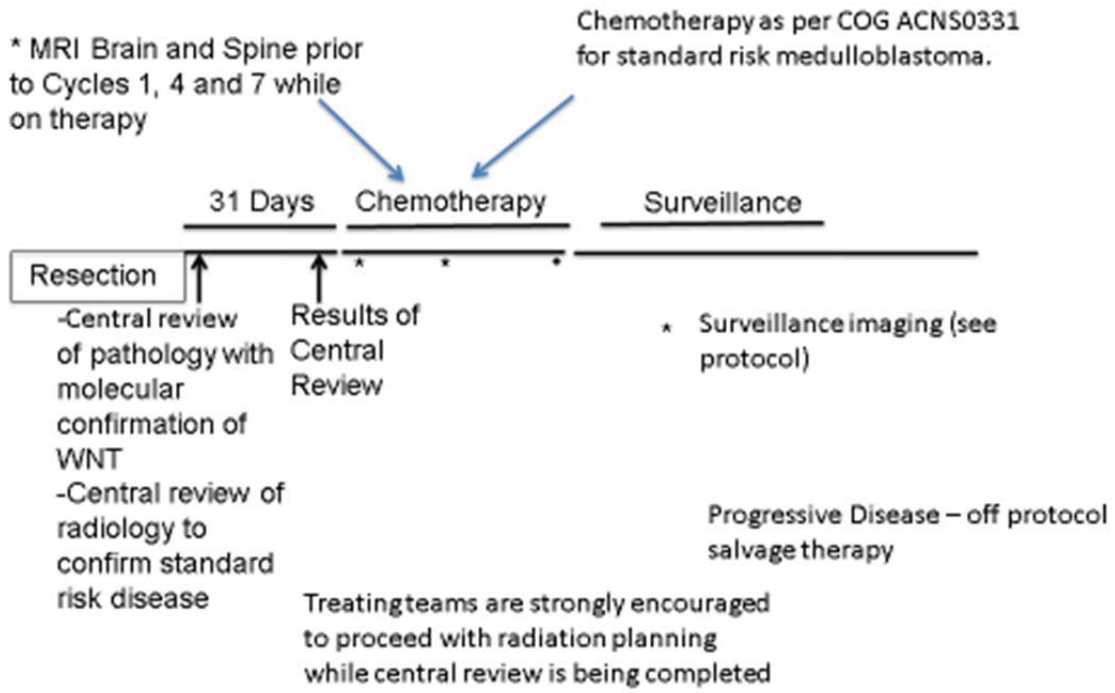
Dr Stacie Stapleton
All Children's Hospital
Pediatric Hematology/Oncology
601 5th Street South
Suite 140
St. Petersburg, FL 33701
USA
Phone: 727 767-4176
EMail: Stacie.Stapleton@allkids.org
Fax: 727 767-4379

Dr Jason Fangusaro
Ann and Robert H Lurie Children's Hospital of Chicago
Hematology/Oncology
225 E Chicago Ave Box # 30
Chicago, IL 60611
USA
Phone: (312) 227-4844
EMail: JFangusaro@luriechildrens.org
Fax: (312) 227-9756

Dr Tobey MacDonald
Children's Healthcare of Atlanta - Egleston
Pediatric Neuro-Oncology
Aflac Cancer Ctr & Blood Disorders Service
2015 Uppergate Drive NE, Suite 442
Atlanta, GA 30322
USA
Phone: (404) 727-1447
EMail: tobey.macdonald@emory.edu
Fax: (404) 727-4455

Dr. Derek Hanson
Hackensack University Medical Center
Program Head, Pediatric Neuro-oncology
Institute for Pediatric Cancer and Blood Disorders
Joseph M. Sanzari Children's Hospital
30 Prospect Avenue
Hackensack, NJ 07601
USA
Phone: 551-996-5437
Fax: 201-487-7340
Email: dhanson@hackensackumc.org

1. SCHEMA



Chemotherapy dosing, schedule and administration will be the same as was used for the COG ACNS0331 standard risk medulloblastoma.

Patients with classical non-metastatic Wnt positive medulloblastoma will be identified by the presence of monosomy 6 by array CGH, and gene transcript detection by NanoString. Pathology samples will be centrally analyzed at Johns Hopkins to confirm Wnt-positivity and radiology studies will be prospectively reviewed at DFCI. Results of central review will be released within fourteen days, and before the chemotherapy is due to start (by day 31 following definitive surgery).

Local teams should proceed with radiation planning so that if central analysis does not confirm Wnt-positivity or patient/family elect not to forego irradiation there is no delay in the commencement of standard therapy.

Table of Contents

2. OBJECTIVES

This is a prospective, single arm, multi-center international pilot study designed to assess the effectiveness based on progression free survival (PFS) of a surgery and chemotherapy only approach for the treatment of children with non-metastatic Wnt positive medulloblastoma. This protocol tests the hypothesis that children with Wnt positive medulloblastoma can be treated effectively with maximum surgery and chemotherapy only without the need for radiation. Ten evaluable children will be enrolled to this study. This pilot study will provide information regarding the safety of this approach to allow for the planning of a larger clinical trial to assess the outcomes of children treated without radiation. Chemotherapy will be based on the current standard chemotherapy approach for average risk medulloblastoma. Primary outcome measure will be progression free survival.

2.1 Study Design

This is a prospective, single arm pilot study which will enroll ten evaluable children (it is anticipated that up to three children might be inevaluable, such that 13 children may be enrolled). Children will be treated with maximal surgical resection followed by chemotherapy. Pathology and radiology will be centrally reviewed at enrollment to ensure only children confirmed to have a Wnt-positive, non-metastatic medulloblastoma are enrolled on study.

2.2 Primary Objectives

To determine the occurrence of relapse, progression, or death due to disease in the first two years after study enrollment of newly diagnosed children with non-metastatic, standard risk, Wnt positive medulloblastoma with a chemotherapy-only approach. Primary outcome measure of this study will be progression-free survival.

2.3 Secondary Objectives

1. To describe overall survival of children with newly diagnosed non-metastatic, standard risk, Wnt positive medulloblastoma who are treated with a maximal surgical resection and chemotherapy-only approach.
2. To determine the pattern of failure in those children with progressive disease.
3. To correlate the frequency of nuclear β-catenin with other measures of Wnt-positivity

3. Background and Rationale

3.1 Background

Medulloblastoma is the most common malignant central nervous system tumor in childhood. Historically the tumors have been classified according to Chang staging and histological appearance. It has been recently recognized that medulloblastoma includes a heterogeneous group of tumors that carry distinct genomic signatures and prognostic features (1-5).

Children with Wnt positive medulloblastoma have been recognized to have an excellent prognosis. Wnt positive medulloblastomas account for approximately 10% of all pediatric medulloblastomas, are most commonly of the classical histology subtype and carry a favorable prognosis when compared to other molecular signatures such as *MYC* amplification (4, 6). Children with Wnt positive medulloblastoma are generally older, with a median age at diagnosis of 10.4 years (range 6-20)(6). Retrospective analysis has demonstrated long term progression free survival rates of up to 90% in children with non-metastatic Wnt positive medulloblastoma (7, 8).

The Wnt positive subgroup of tumors can be identified by immunohistochemistry staining for nuclear β-catenin accumulation (5, 7-9). This provides an easily reproducible method of

identifying Wnt positive medulloblastoma with paraffin embedded material. However, findings and interpretation can be challenging, leading to inconsistent results.

The current therapeutic approach to standard risk medulloblastoma involves maximal surgical resection, adjuvant radiation (focal boost of 30.6Gy with craniospinal irradiation of 23.40Gy and concurrent Vincristine) followed by maintenance chemotherapy comprising vincristine, cisplatin, CCNU and cyclophosphamide. This approach is for treatment of children with standard risk medulloblastoma and currently includes all of the molecular subtypes.

Treatment results for five year overall survival rates in standard risk medulloblastoma range between 70-80% (10, 11), however long term morbidity from therapy, in particular radiation therapy remains of concern. Treatment with radiation therapy has been correlated with neurocognitive morbidity[Ris, 2001 #8, 12) increases the risk of secondary radiation induced tumors including meningiomas and high grade gliomas (13, 14), endocrinopathy, vasculopathy and growth deficits.

Accordingly, strategies to reduce doses of craniospinal and posterior fossa radiation have been investigated. The current COG study for standard risk medulloblastoma ACNS 0331 is investigating further reduction in craniospinal doses of irradiation with a randomization of CSI doses of 23.40 Gy or 18 Gy.

In young children, infant protocols have demonstrated that radiation can be safely delayed or omitted with the use of post-operative chemotherapy. Studies have shown that a large number of children can be salvaged on relapse after upfront chemotherapy only treatment (15-17). Using a chemotherapy regimen containing carboplatin, procarbazine, etoposide, cisplatin, vincristine and cyclophosphamide, the French SFOP trial treated children with medulloblastoma with a chemotherapy only approach. These children were infants and thus unlikely to be Wnt positive. Salvage therapy included high dose chemotherapy with

busulfan and thiotepa followed by involved field irradiation therapy. Using this approach, children with non-metastatic disease with no radiological residual disease at diagnosis had a progression free survival of 29% (95% CI 18-44) with a 5 year overall survival of 73% (59-84%)(16). Importantly although the event free survival was low for these children with non Wnt medulloblastoma, this study was important in demonstrating that children with medulloblastoma who progressed after treatment with a chemotherapy only approach were able to be salvaged with further chemotherapy and involved field irradiation therapy (18).

Head Start I and II protocols comprising maximal surgical resection followed by five cycles of induction chemotherapy with Cyclophosphamide, Etoposide, Cisplatin and Vincristine followed by myeloablative stem cell support consolidation were tested in an endeavor to omit irradiation therapy in young children (15). Using this treatment approach, the five year event free survival for children with non-metastatic medulloblastoma was 52% (±11) and again children that relapsed were able to be salvaged, with the overall five year survival of children treated with this approach of 70% (±10)(15).

Given the good outcomes reported in children with Wnt positive medulloblastoma with the current standard therapy, the possibility of reducing long-term therapy related morbidity by reducing radiation therapy is being considered in this protocol. Treatment strategies that omit radiation are attractive as they stand to reduce the devastating long term morbidity associated with radiation therapy including neuro-cognitive deficits, radiation induced malignancies, endocrinopathy, vasculopathy and growth deficits.

Children will be treated on this protocol with chemotherapy for standard risk medulloblastoma. The chemotherapy is as per the COG ACNS0331 clinical trial for standard risk medulloblastoma. Dosing and modification for toxicity is based on the chemotherapy regimen of COG ACNS0331. This chemotherapy is the standard approach in the USA as

the chemotherapy regimen for children with standard risk medulloblastoma, and thus will be able to be administered by all centers.

3.2 Rationale

The rationale for this study is as follows:

1. Children with Wnt positive medulloblastoma have an excellent overall survival and can be easily identified at diagnosis.
2. The current treatment strategy for standard risk medulloblastoma includes radiation therapy, which carries significant long-term morbidity including neuro-cognitive deficits, secondary high-grade malignancy, vasculopathy, endocrinopathy, and growth deficit.
3. Chemotherapy only approaches for medulloblastoma in infants have demonstrated that many children with medulloblastoma can be cured without radiation. For those that relapse, they can be salvaged with therapy including radiation therapy.

   We will therefore examine the progression free survival of children with non-metastatic Wnt positive medulloblastoma treated without radiation. If children progress without radiation, radiation therapy can then be used as a component of salvage strategy.

4. Participant Selection

Children with non-metastatic completely resected medulloblastoma will be enrolled on study. Wnt positive medulloblastoma will be identified by the presence monosomy 6 by array CGH and by gene transcript detection by NanoString. Central review of pathology and imaging will be performed after enrollment, prior to the commencement of therapy to confirm eligibility criteria.

4.1 Eligibility Criteria

The study will be conducted in two parts:

Screening: To determine if the tumor meets protocol criteria for non-metastatic Wnt positive medulloblastoma

Treatment: For those subjects whose tumor meets protocol criteria for non-metastatic Wnt positive medulloblastoma based on Screening.

Patients will be consented to Treatment only after screening confirmation of Wnt positive medulloblastoma. Patients must be enrolled before chemotherapy commences. Treatment must begin by day 31 following definitive surgery.

4.2 Screening for enrollment on treatment portion

Participants must meet the following criteria at Screening to be potential candidates for the Treatment portion of the study:

- Children at least 3 years of age and less than or equal to 18 years of age at diagnosis
- Participants must have classical histology posterior fossa medulloblastoma as determined by institutional neuro-pathological evaluation.
- Sufficient pathologic material must be available for central analysis and review (see Section 4.5 below)

Tumors will be deemed Wnt positive if, at the time of central analysis, there is:

- Monosomy 6 as determined by array CGH
- Gene transcript detection by NanoString supporting Wnt+ medulloblastoma
- Absence of large-cell, anaplastic histology
- Nuclear β-catenin IHC result will be determined, but not required for the diagnosis

Participants who meet the Screening requirements must meet the following eligibility criteria to participate in the Treatment portion of the study:

- Absence of residual or disseminated disease as defined by the following criteria:

  - Minimal residual disease as determined by post-operative imaging preferably performed within 48 hours of resection (and at most 28 days post-surgery), i.e. gross total resection or residual disease of <1.5cm2 on post-operative imaging.

  - No evidence of metastatic disease in the brain, spine or CSF. Assessments must include MRI imaging of the brain and spine with and without contrast and a lumbar puncture for CSF cytology

- Diagnostic imaging (pre and post contrast) must be forwarded to DFCI for central review to confirm eligibility.
- Patients must not have had any radiation therapy or chemotherapy for medulloblastoma prior to study enrollment
- Patients must have a Lansky performance status of ≥ 30 for children ≤ 10 years of age or a Karnofsky performance status of > 30 for children > 10 years of age.
- Participants must have normal organ and marrow function as defined below:

  -Hemoglobin greater than 10gm/dL (can be transfused).

  -Hemoglobin < 10gm/dL due to operative blood loss is permitted.

  -Absolute neutrophil count ≥ 1,000/uL

  -Platelets ≥ 100,000/uL (non-transfused)

  -Total bilirubin <1.5 x upper limit normal

  -SGOT (AST) or SGPT (ALT) <2.5 x upper limit normal for age

  -Creatinine clearance or radioisotope GFR >70 ml/min/1.73m^2 or normal serum creatinine for patient's age and gender

- The effects of cisplatin, lomustine, vincristine and cyclophosphamide on the developing human fetus are presumed to be teratogenic. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Pregnant or breast-feeding females are not eligible for study enrollment. All females of child-bearing age must have a negative pregnancy test before being enrolled on study. All patients of child-bearing age must practice an effective method of birth control whilst undergoing chemotherapy on study.
- No history of allergic reactions attributed to compounds of similar chemical or biologic composition to cisplatin, lomustine, vincristine or cyclophosphamide.
- Ability to understand and the willingness to sign a written informed consent document for both Screening and Treatment. Signed informed consent must be obtained prior to screening or treatment.
- All Institutional, FDA and NCI requirements for human studies must be met.
- Eligibility criteria cannot be waived.

4.3 Inclusion of Women, Minorities and Other Underrepresented Populations

This protocol is open to males and females of all races.

4.4 Neuropathological guidelines and specimen requirements.

Tumors will be classified according to the World Health Organization classification of central nervous system brain tumors.

At the time of central neuropathologic analysis, the following criteria will used to classify the tumor as a Wnt-positive medulloblastoma (all criteria must be met):

1. Histological classification of medulloblastoma that is not large cell/anaplastic
2. Monosomy 6 as determined by array CGH
3. Gene transcript detection by NanoString consistent with Wnt+ medulloblastoma

4.5 Mandatory Submission of Tissue for Rapid Central Pathology Review

Pathology slides (mandatory) should be submitted for rapid central pathology review and molecular analyses on all consenting patients with an institutional diagnosis of medulloblastoma to confirm eligibility for Treatment.

The following samples are required:

1. Two (2) representative H&E slide supporting the diagnosis of medulloblastoma

and either:

2. Tissue block

or:

3. Ten (10) unstained slides on plus glass and ten (10) 10 um shavings

Results of rapid central review of pathology and molecular classification **will be available within 14 days of submission**.

Pathology Samples should be sent to:

Dr. Fausto Rodriguez
The Johns Hopkins Hospital
Department of Pathology
Sheikh Zayed Tower M2101
1800 Orleans St.
Baltimore, MD 21231
Phone 410-955-8378
Fax 410-614-9310

4.6 Central radiology review

Mandatory Submission of Imaging for Rapid Central Radiology Review

The following imaging is required and must be submitted for central review within sufficient time to allow for all centralized testing and review to take place prior to Day 30 following surgery

1. Pre-operative MRI of the brain with contrast
2. Post-operative MRI of the brain with contrast
3. Either pre-operative MRI of the total spine or post-operative MRI of the total spine obtained at least 10 days, but no more than 21 days following surgery.

Results of rapid central review of radiology **will be available within 7 days of submission.**

De-identified MRI images should be saved on a CD disk (DICOM format) and sent by FedEx or courier to:

Dana-Farber Cancer Institute
Mark Kieran, MD, PhD, D3154
450 Brookline Ave
Boston, MA 02215

Treating physicians should also notify the investigational team by emailing:

Pratiti_Bandopadhayay@dfci.harvard.edu

MRI Brain – Imaging Guidelines (recommended in the absence of an institutional standard)

Recommended sequences:

-Sagittal T1 localizer, 4-5mm skip 1mm

-Axial FSE T2:4-5mm, skip 0-1mm

-Axial FLAIR:4-5mm skip 0 (may also do post contrast). Can substitute 2 and 3 with axial spin echo proton density/T2, 5mm skip 1mm(if FSET2/FLAIR not available)

-Axial diffusion:4-5mm skip 0 (single shot, matrix 128 x 128 or 128 x 192, B=1000)

-Axial T1:4mm skip 1mm

Contrast

-Axial T1: 4-5mm skip 0-1mm

-Coronal T1:4-5mm skip 0-1mm

Optional sequences:

Precontrast:

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

MRI Spine with contrast – Imaging Guidelines

1, Whole spine-sagittal T1:3mm skip 0mm

Technical notes:

-Acquire 2 separate acquisitions (one cervical and upper thoracic, the second lower thoracic and lumbosacral) to optimize placement of presaturation pulse.

-Phase direction AP, frequency direction SI

-Place anterior saturation pulse close to the anterior margin of the spinal column-to minimize motion artifacts from chest/abdomen.

-Pixel size 1mm2 or less (example: for 26cm FOV, use 256 x 256 matrix)

-Keep TE to minimum (<15msecs)

-Fat saturation not necessary

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

Technical notes:

-Phase direction RL, frequency direction AP

-Keep TE to minimum (<15 msecs)

-Do not interleave

5. REGISTRATION PROCEDURES

This study will be conducted in accordance with the Sidney Kimmel Comprehensive Cancer Center's Coordinating Center Protocol.

Patient Registration

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an institutionally approved IRB consent form.

All patients must be registered centrally at the Sidney Kimmel Comprehensive Cancer Center.

5.1 Registration for Screening

To register a patient for screening, the following documents must be completed and faxed (443-287-3975) or e-mailed (Tammy Scott scottta@jhmi.edu) at the Coordinating Center:

Signed patient consent form for Screening

- Screening registration Form

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process, the Coordinating Center will:

- assign a patient study number
- register the patient on the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- fax or e-mail the patient study number to the participating site.

5.2 Registration for Treatment

To enroll a patient for treatment who has met the screening criteria, the following documents must be completed and faxed (443-287-3975) or e-mailed (Tammy Scott scottta@jhmi.edu) at the Coordinating Center:

- Signed patient consent form for Treatment
- Treatment eligibility checklist

The Coordinating Center will review the documents to confirm eligibility. To complete the registration process for Treatment, the Coordinating Center will:

- Register the patient on the Treatment portion of the study with the Sidney Kimmel Comprehensive Cancer Center's Clinical Research Office
- Send a fax or e-mail to the institution confirming eligibility and the last eligible start date for treatment.

6. Multicenter Guidelines

Protocol Chair

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.

- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

7. Quality Assurance

This is a Level 1 study under the SKCCC Data Safety Monitoring Plan. Data monitoring of this protocol will occur on a regular basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally at SKCCC by Kenneth J. Cohen, MD, MBA monthly and externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee at SKCCC.

Authorized representatives of the Coordinating Center may visit participating sites to perform

audits or inspections, including source data verification. The purpose of these audits or inspections is to systematically and independently examine all trial related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

8. Data Submission

Data and/or completed eCRFs must be transmitted to the Coordinating Center following the completion of each cycle as detailed in Section 16.1.1.

9. Adverse Event Reporting

Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical trials, from the time of signing an informed consent, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no trial treatment has been administered.

Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any trial phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Protocol Chair

The Protocol Chair is ultimately responsible for the required reporting of all serious adverse events.

Coordinating Center

The Coordinating Center is the central location for the collection and maintenance of documentation of serious adverse events and is responsible for submitting serious adverse event reports to the Protocol Chair promptly. The Coordinating Center will maintain documentation of all serious adverse event reports for each participating site. Adverse event reports submitted to the Coordinating Center must be signed and dated by the participating site's Principal Investigator. The Coordinating Center will provide appropriate forms to be used by all participating sites for reporting serious adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites

Participating sites are responsible for reporting serious adverse events to their IRB according to its specific requirements and to the Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Progressive Disease as defined as recurrence or progression of medulloblastoma within the brain, spine or CSF must be reported within 7 days.

Serious and Unanticipated Adverse Events (considered an adverse event of special interest by the treating physician) as defined above must be reported to the Coordinating Center within **24 hours** of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within **three (3) working days** of the participating site Principal Investigator's learning of the event.

Serious adverse event reports are to be faxed to the Coordinating Center at SKCCC. Follow-up reports are faxed, mailed, or sent electronically to the Coordinating Center as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the protocol therapy. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

10. TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from 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.

Treatment will be administered on an inpatient or outpatient basis. Expected toxicities and potential risks as well as dose modifications for vincristine, cisplatin, CCNU and cyclophosphamide are described in Section 11 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The chemotherapy backbone of this protocol is the current standard chemotherapy for average risk medulloblastoma, which is currently administered widely in multiple centers in North America. Chemotherapy must begin within thirty days of definitive surgery. A central venous catheter is recommended prior to commencement of chemotherapy. Each cycle will begin at full dose when ANC >1000/μl and platelet count ≥ 75,000/μl. Granulocyte colony stimulating factor (GCSF) will be used if there is a delay in two consecutive weeks in initiating chemotherapy due to neutropenia. Chemotherapy will be given according to the

following schema of cycles/regimens: 1A, 2A, 3B, 4A, 5A, 6B, 7A, 8A, 9B. Cycle A is for 42 days and cycle B is for 28 days.

Week/Cycle	Regimen	Chemotherapy
Week 1, Cycle 1	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 7, Cycle 2	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 13, Cycle 3	B (28 Days)	Cyclophosphamide (1000mg/m^2) IV over 1 hour days 1 and 2 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8 Mesna (360mg/m^2/dose) IV infusion over 15-30 minutes starting 15 minutes prior to, or at the same time as cyclophosphamide (based on institutional standards) and then repeated at 4 or 8 hours
Week 17, Cycle 4	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 23, Cycle 5	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 29, Cycle 6	B (28 Days)	Cyclophosphamide (1000mg/m^2) IV over 1 hour days 1 and 2 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8 Mesna (360mg/m^2/dose) IV infusion over 15-30 minutes starting 15 minutes prior to, or at the same time as cyclophosphamide (based on institutional standards) and then repeated at 4 or 8 hours
Week 33, Cycle 7	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 39, Cycle 8	A (42 Days)	Cisplatin (75mg/m^2) IV over 6 hours day 1 Lomustine (CCNU) (75mg/m^2) orally day 1 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8, 15
Week 45, Cycle 9	B (28 Days)	Cyclophosphamide (1000mg/m^2) IV over 1 hour days 1 and 2 Vincristine (1.5mg/m^2, maximum 2.0mg) IV push day 1, 8 Mesna (360mg/m^2/dose) IV infusion over 15-30 minutes starting 15 minutes prior to, or at the same time as cyclophosphamide (based on institutional standards) and then repeated at 4 or 8 hours

10.1 Pre-treatment Hematologic Criteria (please see Section 11.2 for other criteria for dose modifications or delays)

10.1.1 Cycle 1, Day 1

10.1.1.1 ANC >1000/μl

10.1.1.2 Platelet count ≥ 75,000/μl.

10.1.2 Subsequent Cycles

10.1.2.1 ANC >1000/μl

10.1.2.2 Platelet count ≥ 75,000/μl.

10.2 Agent Administration

10.2.1 Lomustine

- 75mg/m^2 given orally on day 1 per institutional guidelines
- Doses will be rounded up or down to the nearest 10mg. Round down for doses < *5 and round up for doses ≥ *5 (e.g. 84 mg round to 80 mg; 85 mg round to 90 mg)
- Doses will be administered on an empty stomach, 1 hour before or 2 hours after a meal, with oral fluids.
- Doses are usually administered at bedtime.

10.2.2 Cisplatin

- 75mg/m^2 given intravenously over 6 hours x 1 dose on Day 1
- Suggested hydration and supportive care

- -2 to 0 hours prehydration 500ml/m^2 D5 1/2NS with mannitol 10 GM/m^2 at 250ml/ m^2/hr
- 0 to 6 hours Cisplatin 75mg/m^2 with 10 GM/m2 mannitol in D5 ½ NS 1000ml/m^2 IV at 167 ml/m^2/hr for 6 hours.
- 6 to 24 hours Continue hydration with D5 ½ Normal Saline with magnesium sulfate 0.5-1mEq/kg in post-hydration fluid to run at 125ml/m^2/hr for at least 6 hours. If children tolerating oral intake after 6 hours the remainder of post hydration can be given orally. 24 hours after the cisplatin continue magnesium supplementation.
- Urine output must be monitored during administration of cisplatin. If the urine output falls below 3ml/kg/hr for two hours consecutively, mannitol 0.5g/kg with a 10ml/kg bolus of normal saline are recommended.
- Children are likely to require magnesium supplementation after commencing treatment with cisplatin. Aluminum containing needles and giving sets should be avoided because of the risk of precipitation.

10.2.3 Vincristine

- 1.5mg/m^2 (maximum dose 2mg) given as an IV push on days 1, and 8 and 15 (Day 15 dose for Regimen A only). Doses are to be rounded down to the nearest 0.1mg.
- Vincristine is vesicant and should be administered through a central line to prevent extravasation

SPECIAL PRECAUTIONS: Intrathecal injection of vincristine is FATAL.

10.2.4 Cyclophosphamide

- 1000mg/m^2 IV over 1 hour day 1 and 2

- Prehydrate with D5W and ½ Normal Saline for 2 hours pre and 6 hours post cyclophosphamide at 125ml/m^2/hr or as per local institutional guidelines

10.2.5 Mesna

- 360mg/m^2/dose intravenously over 15-30 minutes on days 1 and 2.
- Administer either 15 minutes before or during the cyclophosphamide infusion (based on institutional standards) and then repeat at hours 4 and 8.
- The total dose of Mesna can also be given as a continuous infusion, starting at the same time as the cyclophosphamide infusion and continuing for at least eight hours post cyclophosphamide (or given as per institutional policy).

10.3 General Concomitant Medication and Supportive Care Guidelines

If a cycle of chemotherapy is delayed for over 2 weeks due to neutropenia, subsequent cycles of chemotherapy should include filgrastim (G-CSF) or pegfilgrastrim. Filgrastim (G-CSF) may be used to maintain treatment schedule if there is a 2 week delay in initiation of subsequent chemotherapy cycles due to low ANC. The standard dose of filgrastim is 5mcg/kg/day subQ to commence 24 hours after the completion of chemotherapy. Filgrastim must be stopped at least 24 hours before the next chemotherapy cycle but may be continued without regard to vincristine administration. Pegfilgrastim can be used instead of GCSF for children greater than 1 year of age (and greater than 10kg). The recommended dose is one subQ injection of 0.1mg/kg at least 24 hours after completion of chemotherapy (maximum 6 mg).

10.4 Duration of Therapy

Duration of protocol therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until the prescribed chemotherapy course of nine cycles is complete or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Completion of prescribed therapy

10.5 Duration of Follow Up

Participants will be followed for 5 years following enrollment. In the event the patient is taken off study protocol therapy, survival outcomes will still be collected, unless the patient denies consent.

10.6 Criteria for Removal from Study

Participants will be removed from study in the following events: a, patient/family no longer wish to participate or b, the treating physician deems it is not in the patient’s best interest to remain on study.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Dr Kenneth Cohen at 410-614-5055.

11. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

11.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

11.1.1 Adverse Event Lists for Lomustine

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate within 1-2 days	Nausea, vomiting		Disorientation, lethargy, ataxia, and dysarthria
Prompt(within 2-3 weeks prior to next course			Liver dysfunction (↑ alkaline phosphatase, SGOT (AST) and bilirubin) (L), stomatitis

Delayed: Any time later during therapy, excluding the above conditions			Pulmonary fibrosis and/or infiltrates (usually with high cumulative dose ≥ 1100mg/m² (L), progressive renal dysfunction, renal failure (large doses)(L), decrease in kidney size, optic atrophy, visual disturbances, blindness,
Late: Any time after completion of treatment			Secondary malignancy, death secondary to pulmonary fibrosis
Unknown Frequency and Timing:	**Fetal and teratogenic toxicities:** Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. It is not known whether this drug is excreted in human milk.		

* ***(L) Toxicity may also occur later***.

11.1.2 Adverse Event List for Cisplatin

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate within 1-2 days	Nausea (L), vomiting (L)	Metallic taste (L)	Anaphylactic reaction (facial edema, wheezing, tachycardia, and hypotension), phlebitis, extravasation (rare) but if occurs = local ulceration (only in concentration > 0.5mg/mL)
Prompt(within 2-3 weeks prior to next course	Anorexia (L), myelosuppression, hypomagnesemia (L), high frequency hearing loss (L), nephrotoxicity (↑ Cr, BUN, Uric Acid) (L)	Electrolyte disturbances (L) (hypocalcemia, natremia, kalemia, & phosphatemia) peripheral neuropathy, (paresthesias in a stocking-glove distribution) (L)	Vestibular dysfunction, tinnitus (L), rash, seizure (L), elevated liver function tests (L)
Delayed: Any time later during therapy, excluding the above conditions		Hearing loss in the normal hearing range	Areflexia, loss of proprioception and vibratory sensation, (very rarely loss of motor function) (L), optic neuritis, papilledema, cerebral blindness, blurred vision and altered color perception (improvement or total recovery usually occurs after discontinuing), chronic renal failure, deafness
Late: Any time after completion of treatment			Secondary malignancy
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cisplatin have been noted in animals and cisplatin can cause fetal harm in humans. Cisplatin is excreted into breast milk.		

* ***(L) Toxicity may also occur later***.

11.1.3 Adverse Event List for Vincristine

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate within 1-2 days		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt(within 2-3 weeks prior to next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy, excluding the above conditions	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

11.1.4 Adverse Event List for Cyclophosphamide

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate within 1-2 days	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt(within 2-3 weeks prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Any time later during therapy, excluding the above conditions	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)1 (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1].Dependent on dose, age, gender, and degree of pubertal development at time of treatment.

[2] Risk increased with pulmonary chest irradiation and higher doses.

* ***(L) Toxicity may also occur later***.

11.2 Toxicity Management, dose modifications and delays

11.2.1 Neurotoxicity

11.2.1.1 For grade 3 to 4 neurotoxicity including foot drop, paresthesia, ileus or paresis, withhold the next dose of Vincristine and then resume at lower dose (1mg/m^2, maximum dose 1.5mg) and then escalate to full dose when symptoms resolve.

11.2.1.2 For seizures, withhold dose then recommence at reduced dose (1mg/m^2, maximum dose 1.5mg) and then escalate to full dose (if seizures do not recur) whilst continuing anticonvulsants. Exclude syndrome of inappropriate secretion of antidiuretic hormone (SIADH) as a cause of seizures.

11.2.1.3 Vincristine should not be withheld for jaw pain which should be treated symptomatically with analgesics (not salicylates).

11.2.2 Hepatotoxicity

11.2.2.1 Vincristine should be withheld for a direct bilirubin of greater than 1.9mg/dL. For direct bilirubin levels of 1.5mg/dL to 1.9mg/dL a reduced dose (1mg/m^2, maximum dose 1.5mg) should be administered.

11.2.3 Hematological toxicity

If chemotherapy is due and the absolute neutrophil count remains below 750/ L the next cycle of chemotherapy should be delayed. Repeat CBC weekly.

If the next cycle of Maintenance is due and ANC < 750/ L hold chemotherapy until ANC ≥ 750/ L.

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

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

- If the patient is due to receive Regimen A, the dose of Lomustine (CCNU) should be reduced by 50% (38 mg/m^2)
- If the patient is due to receive Regimen B, the dose of Cyclophosphamide should be reduced by 25% (750 mg/m^2/day) on Days 1 and 2.
- If the ANC is less than 750/ L when the next cycle is due, despite the dose reduction in CCNU, hold chemotherapy until the ANC is greater than or equal to 750/ L. For the next cycle of Regimen A, reduce Lomustine (CCNU) to 20mg/m^2.

If a cycle of chemotherapy is delayed for over 2 weeks due to neutropenia, subsequent cycles of chemotherapy should include filgrastim (G-CSF). Filgrastim (G-CSF) will be used to maintain treatment schedule if there is a delay in initiation of chemotherapy due to low white cell count (see section 10.3).

11.2.4 Hemorrhagic Cystitis (Hematuria)

11.2.4.1 Microscopic Hematuria

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

For persistent microscopic hematuria (> 2 abnormal urinalyses during a cycle of therapy), increase hydration to 3500-4000 mL/m2/day.

11,2,4,2 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 judgment.

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

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

For persistent gross hematuria occurring during a cycle of cyclophosphamide, interrupt the cyclophosphamide. Withhold further cyclophosphamide until the next cycle of therapy or until urine clears. For subsequent cycles give mesna

by continuous infusion. For occurrence of a second episode of gross hematuria or persistence of microscopic hematuria on the continuous infusion regimen, continue the cyclophosphamide when the urine clears to less than gross hematuria.

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

11.2.5 Nephrotoxicity

11.2.5.1

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

11.2.5.2

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

11.2.5.3

If the creatinine clearance or GFR does not rise above 30 ml/min/1.73 m2, the cisplatin should be deleted from treatment.

11.2.5.4

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

11.2.6 Ototoxicity

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

12. DRUG FORMULATION AND ADMINISTRATION

12.1 Cisplatin

Description

Cisplatin (Cis-diamminedichloroplatinum II, CDDP, cis-DDP, Platinol-AQ) NSC #119875 is an inorganic, water-soluble complex containing a central platinum atom, 2 chlorine atoms, and 2 ammonia molecules. In aqueous solution, the chloride ions are slowly displaced by water generating a positively charged aquated complex. This activated complex is then available to react with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bi-functional covalent links, very similar to alkylating reactions. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Cisplatin has a rapid distribution phase of 25-80 minutes with a slower secondary elimination half-life of 60-70 hours. The platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Platinum is present in tissues for as long as 180 days

after the last administration. Both cisplatin and platinum are excreted through the kidneys ranging from 10-50%. Fecal elimination is minimal. Cisplatin's penetration into the CNS is poor.

Form

Available as an aqueous solution containing 1 mg/mL of cisplatin and 9 mg (1.54 mEq)/mL of sodium chloride in 50 mL, 100 mL, and 200 mL multi-dose non-preserved vials.

Storage and Stability

Store at 15°-25°C (68º-77ºF). Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. Cisplatin removed from its amber container should be protected from light if not used within 6 hours

Compatibility

Cisplatin is incompatible with sodium bicarbonate and alkaline solutions. Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin causing precipitate formation and a loss of potency

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Preparation

Cisplatin may be further diluted in dextrose and saline solutions provided the solution contains >0.3% sodium chloride. The final infusion solution should contain ≥ 0.2% sodium chloride. Dextrose/saline/mannitol containing solutions, protected from light, are stable refrigerated or at room temperature for 24 to 72 hours, however, cisplatin solutions should not be stored in the refrigerator to avoid precipitation.

Administration

75mg/m^2 given intravenously over 6 hours x 1 dose on Day 1.

Suggested hydration and supportive care

-2 to 0 hours Prehydration 500ml/m^2 D5 1/2NS with mannitol 10 GM/m^2 at 250ml/m^2/hr

0 to 6 hours Cisplatin 75mg/m^2 with 10 GM/m2 mannitol in D5 ½ NS 1000ml/m^2 IV at 167 ml/m^2/hr for 6 hours.

6 to 24 hours Continue hydration with D5 ½ Normal Saline with magnesium sulfate 0.5-1mEq/kg in post-hydration fluid at 125ml/m^2/hr for at least 6 hours. If children are tolerating oral intake after 6 hours the remainder of post hydration can be given orally.

Urine output must be monitored during administration of cisplatin. If the urine output falls below 3ml/kg/hr for two hours consecutively, mannitol 0.5g/kg with a 10ml/kg bolus of normal saline are recommended.

Ordering

Commercially available from various manufacturers. See package insert for more detailed information.

12.2 Cyclophosphamide

Description

Cyclophosphamide (Cytoxan) NSC #26271 is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine

as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Form: Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide.

Storage and Stability: Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30ºC (86ºF).

Compatibility *NA*

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Availability

Commercially available from various manufacturers. See package insert for more detailed information.

Preparation

Cyclophosphamide for Injection: Reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. If administered as undiluted drug at the 20 mg/mL concentration, reconstitute with NS only to avoid a hypotonic solution. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration.

Administration

1000mg/m^2 IV over 1 hour day 1 and 2

Prehydrate with D5W and ½ Normal Saline for 1 hour pre and 6 hours post cyclophosphamide at 125ml/m^2/hr

Ordering

Commercially available from various manufacturers. See package insert for more detailed information.

12.3 Lomustine

Description

Lomustine (Cyclohexylchloroethylnitrosourea CCNU, CeeNU®) NSC #79037) alkylates DNA and RNA, causes interstrand cross-linking of DNA, prevents the repair of DNA, and alters the structure of RNA and the structure and function of many proteins and enzymes. It is not cross resistant with other alkylators and it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins. Lomustine is cell-cycle non-specific and is thought to act in the late G1 or early S phase. Time to peak concentration after oral administration is 1 to 4 hours. Lomustine is rapidly and completely absorbed. Metabolism of lomustine is through hydroxylation of the cyclohexyl moiety by hepatic microsomal enzymes. The parent drug lomustine has not been detected in blood, but the peak concentrations of the ring hydroxylated metabolites are approximately 3 μM after doses of 130 mg/m^2. Following oral administration of radioactive lomustine at doses ranging from 30 mg/m^2 to 100 mg/m^2, about half of the radioactivity given was excreted in the urine in the form of degradation products within 24 hours. Approximately 10% is excreted through the lungs and 5% through the feces. The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels. Due to the high lipid solubility and the relative lack of ionization at physiological pH, lomustine crosses the blood-brain barrier. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma

Form

Lomustine is supplied as 100 mg capsules, 40 mg capsules and 10 mg capsules. Inactive ingredients in lomustine capsules are: magnesium stearate and mannitol.

Storage and Stability

Store in well-closed containers at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F). Avoid excessive heat (over 40°C or 104°F).

Compatibility -NA

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Patients should be told to wear gloves when handling lomustine capsules.

Availability

Commercially available from various manufacturers. See package insert for more detailed information.

Preparation and Administration

Round dose to the nearest 10mg. Round down for doses < *5 and round up for doses ≥ *5 (e.g. 84 mg round to 80 mg; 85 mg round to 90 mg). Give orally no more frequently than every 6 weeks. Give with fluids on an empty stomach and at bedtime to reduce nausea and vomiting. No food or drink should be given for at least 2 hours after administration. In order to provide the proper dose of lomustine patients should be aware: that there maybe two or more different types and colors of capsules in the container dispensed by the pharmacist; lomustine is given as a single oral dose and will not be repeated for at least 6 weeks; and patients should be told to wear gloves when handling lomustine capsules.

Ordering

Commercially available from various manufacturers. See package insert for more detailed information.

12.4 Vincristine

Description

Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Form

Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution.

Storage and Stability

Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use

Compatibility

Do not mix with any IV solutions other than those containing dextrose or saline

Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Administration

1.5mg/m^2 (maximum dose 2mg) given as an IV push on days 1, and 8 and 15 (Day 15 dose for Regimen A only). Doses are to be rounded down to the nearest 0.1mg.

Vincristine is vesicant and should be administered through a central line to prevent exravasation

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vincristine. Vincristine should NOT be delivered to the patient at the same time with any medications intended for central nervous system administration. **Vincristine is fatal if given intrathecally.** Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

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.

PLEASE NOTE:

The warning statement in the vincristine USP monograph has been revised as stated above to the following: "Do not remove covering until moment of injection. For intravenous use only. Fatal if given by other routes." The prescribing information for the product by Teva USA has been

revised to reflect this information. At the writing of this monograph, the Hospira prescribing information had not yet been revised.

This revision can be found in Pharmacopeial Forum 36(6) which is available free of charge on the USP website at http://www.usp.org/USPNF/pf/. The notice of intent to revise can be found at the following website: http://www.usp.org/USPNF/compendialNotices/vincristineSulfate.html.

The official FDA-approved labeling can be found at the NIH's DailyMed website: http://dailymed.nlm.nih.gov/dailymed/search.cfm?startswith=vincristine.

Ordering

Commercially available from various manufacturers. See package insert for more detailed information.

13. Required and Recommended Evaluations

13.1 Evaluations During Therapy that must be reported to the Coordinating Center

Test	At Diagnosis/Prior to Cycle 1	Prior to Each Cycle of Chemotherapy	Completion of Treatment
MRI Brain	Pre-op and Post-Op2	X Prior to cycle 4 and 7)	X
MRI Spine	Pre or post-op1	X (Prior to Cycles 4 and 7)	X
CSF evaluation	Post-op3		
Audiogram	X	X (Prior to Cycles 4, and 7)	
Height/Weight	X		
Performance Status	X		
GFR or CrCl or serum creatinine based on age/gender	X		X
Complete Blood Count, Diff and Platelet count	X	X	X
Liver Function, BUN Creatinine, electrolytes (Ca, Mg)	X		
History and Physical Exam	X		
Pathology Central Review	X		
Radiology Central Review	X		
Neuropsych testing**	Timing based on institutional standards and subject readiness		

1 - Spinal MRI to include an enhanced complete (cervical, thoracic, lumbar and sacral) pre-op or post-op between 10 and 21 days after surgery. 2 - Assessment must include pre-op and post-op MRI performed with and without contrast preferably within 48 hours and at most 21 days after surgery. 3 – Lumbar CSF evaluation should occur no sooner than 10 days following surgery and no later than 21 days following surgery . **-neuropsychologic testing should be obtained based on institutional standards and available resources as a standard of care procedure. If testing is obtained, results should be reported

13.2 Recommended Evaluations During Therapy that are not reported to the Coordinating Center

Note: The following observations are considered standard of care for children undergoing treatment for medulloblastoma. It is anticipated that most/all of these data points will be obtained as part of good clinical care but they will not be reported centrally to the coordinating center since they do not impact the interpretation of the primary or secondary objectives and associated statistical analyses of this protocol

Test	**Prior to Each Cycle of Chemotherapy (beginning with Cycle 2 of treatment)**	**Completion of Treatment**
Height/Weight	X	
History and Physical Exam	X	X
GFR or CrCl or serum creatinine based on age/gender	X (Prior to Cycles 4 and 7)	X
Liver Function, BUN Creatinine, electrolytes (Ca, Mg)	X	

13.3 Required Evaluations Following Completion of Therapy that must be reported to the Coordinating Center

	3 m	6 m	9 m	1 year	1.5 years	2 years	2.5 years	3 years	Annual after 3 years until year 5	At relapse/disease progression
MRI Brain	X	X	X	X	X	X	X	X	X	X
MRI Spine (complete spine)		X		X	X	X	X	X	X	X
CSF Evaluation										X
Audiogram (per institutional standards)				X						
Complete Blood Count, Diff and platelet count	X									
Neuropsych testing**	Timing based on institutional standards and subject readiness									

**-neuropsychologic testing should be obtained based on institutional standards and available resources as a standard of care procedure. If testing is obtained, results should be reported

13.4 Recommended Evaluations Following Therapy that are not reported to the Coordinating Center

Note: The following observations are considered standard of care for children who have completed treatment for medulloblastoma. It is anticipated that most/all of these data points will be obtained as part of good clinical care but they will not be reported centrally to the coordinating center since they do not impact the interpretation of the primary or secondary objectives and associated statistical analyses of this protocol

	3 m	6 m	9 m	1 year	1.5 years	2 years	2.5 years	3 years	Annual after 3 years until year 5	At relapse/disease progression
History and physical with neurological exam	X	X	X	X	X	X	X	X	X	X
Height/Weight	X	X	X	X		X		X	X	X
Audiogram (per institutional standards)								X		
Complete Blood Count, Diff	X									
Endocrinology evaluation (per institutional standards)				X		X		X	X	

14. MEASUREMENT OF EFFECT

14.1 Antitumor Effect

For the purposes of this study, participants should be re-evaluated for response prior to cycle 4 and 7 (while on therapy) and then as described in section 13.3.

14.1.1 Response Assessment, Definitions

14.1.1.1 Definition of a New Lesion

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered. Demonstration of CSF cytopathology positive for medulloblastoma will also be evidence of tumor recurrence independent of any associated imaging findings on MRI.

15. ADVERSE EVENT REPORTING REQUIREMENTS

15.1 Definitions

15.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

15.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Prolongs inpatient hospitalization (prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed

before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned). Routine febrile neutropenia admissions (less than one week duration, no requirement of ICU admission) are expected toxicity of the therapy and will not be considered a serious adverse event

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission

- respite care
- Routine febrile neutropenia admissions (less than one week duration, no requirement of ICU admission)

15.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

15.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

15.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

15.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

15.2 Procedures for SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific eCRFs. AEs, unless deemed to be of special interest by the treating investigator, will not be reported since the toxicity of standard of care medulloblastoma therapy is well defined and previously reported.

.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

15.3 Reporting Requirements

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

15.4 Reporting to the Study Team

15.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Principle Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.
- Progressive disease will be reported within 7 days

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the overall Principal Investigator within one business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within one business day of learning of it and document the time of his or her first awareness of the adverse event.

Report serious adverse events by telephone, email or facsimile to:

Kenneth J. Cohen, MD, MBA

Telephone Number: 410-614-5055

Email: kcohen@jhmi.edu

Fax: 410-955-0028

Emergency Contact #: 410-375-8281 (mobile)

Within the subsequent 1-2 business day from initial report, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

15.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will not be reported since the chemotherapy regimen is standard of care.

15.5 Reporting to the Institutional Review Board (IRB)

Investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Kenneth J. Cohen, MD, MBA

Telephone Number: 410-614-5055

Email: kcohen@jhmi.edu

Fax: 410-955-0028

Emergency Contact #: 410-375-8281 (mobile)

15.6 Reporting to the Food and Drug Administration (FDA)

N/A

15.7 Reporting to the NIH Office of Biotechnology Activities (OBA)

N/A

15.8 Reporting to the Institutional Biosafety Committee (IBC)

N/A

15.9 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

15.10 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution SAEs (with dates) should be documented on the appropriate eCRF and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the Overall Investigator or respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

16. DATA AND SAFETY MONITORING

16.1 Data Reporting

eCRFs will be provided for all study mandated data points and should be submitted based on the deadlines detailed in Section 16.1.1

16.1.1 Data Submission

eCRFs will be submitted electronically via CRMS (information will be provided to each site for access to CRMS):

The schedule for completion and submission of eCRFs to the coordinating center is as follows:

Form	**Submission Timeline**
Screening Registration Form	Complete prior to registration with coordinating center
Treatment eligibility checklist	By Day 28 following surgery
Start Cycle Form	Within 14 days from the start of each cycle. Note that Start Cycle Form for Cycles 4 and 7 will include response assessment information
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

16.2 Safety Meetings

The SKCCC Safety Monitoring Committee (SMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be raised and addressed by the Principal Investigator and study team as needed.

The SMC will meet according to SKCCC standards or more often if required to review toxicity and accrual data for the study. Information to be provided to the committee may include: up-to-date participant accrual; DLT information; all grade 2 or higher unexpected adverse events; summary of all deaths while being treated and during active follow-up; any response information; protocol deviations; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

16.3 Auditing/Monitoring

This is a DSMP Level I study under the SKCCC Data Safety Monitoring Plan (12/6/2012). The SKCCC Clinical Research Office QA Group will perform an audit after the first JHU research participant has enrolled. The JHU Study team (coordinating center) will then periodically audit data from participating satellite sites depending on the rate of accrual and prior audit results (this satellite site auditing will be accomplished remotely or via on-site visits as applicable). In addition, the SKCCC Data Safety Monitoring Committee will review every relapse in real time to ensure that the safety stopping rule is not triggered. All trial monitoring and reporting will be reviewed annually by the SKCCC Safety Monitoring Committee. The PI at each site is responsible for internally monitoring the trial. Data must be reviewed to assure the

validity of data, as well as, the safety of the research participants. Each PI will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study. JHU agrees to (1) promptly notify Collaborating Investigator in writing promptly of information such as new and unexpected serious adverse safety events arising from JHU monitoring of the Study that could affect the safety of Subjects, and (2) trends or patterns of non-serious or expected adverse events that occur at a specificity or severity that is inconsistent with prior observations, including results obtained for a period of two years after Study Conclusion or termination, that could affect the safety or medical care of subjects who were at any point enrolled in the Study, influence the conduct of the Study, or alter the IRB's approval.

17. REGULATORY CONSIDERATIONS

17.1 Protocol Review and Amendments

This protocol, the proposed informed consents, all forms of participant information related to the study and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location. This will occur following approval by the Coordinating Center IRB.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The overall Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

17.2 Informed Consent

All participants must be provided a consent form describing each portion of this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

17.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html

- Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
- Title 21 Part 56 – Institutional Review Boards
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
- Title 21 Part 312 – Investigational New Drug Application
  www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

17.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the eCRFs include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

17.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

17.6 Multi-center Guidelines

- This protocol will adhere to the policies and requirements of the SKCCC.

- Overall Principal Investigator/Coordinating Center is responsible for distributing all Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

18. STATISTICAL CONSIDERATIONS

Overview: This is a single arm, prospective pilot study to explore the strategy of omitting radiation therapy in pediatric patients with standard risk, WNT positive standard risk medulloblastoma. This is not an intent-to-treat design; some eligible patients will be excluded from the assessment of the primary objective due to receiving radiation or starting chemotherapy too late.

Accrual and study duration: 10% of all medulloblastoma belong to the Wnt-positive subgroup. We would therefore anticipate there to be approximately 45 children diagnosed with Wnt-positive medulloblastoma in the USA each year. Ten 'evaluable' children will be required to provide adequate operating characteristics for the stopping rule below. We estimate at most 3 children will be inevaluable. Therefore a total of up to 13 children will be enrolled (fewer, if there are less than 3 inevaluable patients). At an accrual rate of 5-6 children per year, these 13 children can be enrolled within 2-3 years. Study duration will be at least 4-5 years (2-3 years for accrual, plus a minimum of 2 years follow up on the last patient enrolled).

Endpoints: The primary endpoint will be the occurrence of relapse, progression, or death due to disease within the first two years after study enrollment. Secondary endpoints are the patterns of failure in those children that do have progressive disease, progression-free survival (PFS) (calculated from the time of enrollment until the first occurrence of relapse, progressive disease or death due to disease, or until last contact if no event occurs), and overall survival (OS).

Evaluability: To be evaluable for inclusion in the stopping rule for assessment of the primary objectives, children:

a) must be eligible;

b) must commence treatment with chemotherapy by day 31 after resection;

c) must not receive radiation therapy within two years after study enrollment. However, any child who has a relapse or progression prior to receiving radiation therapy is evaluable.

Safety Monitoring and Stopping Rule

To address the primary objective of the utility of eliminating radiation therapy, the following one-stage monitoring rule will be used: Of the first 10 evaluable patients enrolled, if at any time 3 or more patients have an event (relapse, progression, or death due to disease), then the study will be stopped and we will conclude that removal of radiation therapy is unsafe in children with standard risk, Wnt-positive medulloblastoma. If there are 2 or fewer children who have an event out of 10, then we will conclude that removal of radiation therapy in children with standard risk, Wnt-positive medulloblastoma is feasible. This rule tests the null hypothesis that the proportion of patients with relapse/progression/disease-death by 2-years is ≤0.1versus the alternative that it is ≥0.45, with 90% power and alpha=0.07. The choices of the null and alternative were based on the results of Packer et al (10).

Methods to address study objectives: To address the primary objective, the stopping rule above will be applied. To address the secondary objectives, the data will be descriptively summarized. Kaplan-Meier curves of PFS and OS will be generated. Toxicities will be tabulated.

19. PUBLICATION PLAN

The study team will aim to publish the study results within 24 months of the end of data collection in a peer reviewed journal.

20. Appendix A: Performance Status Criteria

Lansky Play- Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
100	fully active, normal	100	Normal, no complaints, no evidence of disease.
90	minor restrictions with strenuous physical activity	90	Able to carry on normal activity; minor signs or symptoms of disease.
80	active, but gets tired more quickly	80	Normal activity with effort; some signs or symptoms of disease.
70	both greater restriction of, and less time spent in, active play	70	Cares for self, unable to carry on normal activity or to do active work.
60	up and around, but minimal active play; keeps busy with quieter activities	60	Requires occasional assistance, but is able to care for most of his/her needs.
50	lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities	50	Requires considerable assistance and frequent medical care.
40	mostly in bed; participates in quiet activities	40	Disabled, requires special care and assistance.
30	stuck in bed; needs help even for quiet play	30	Severely disabled, hospitalization indicated. Death not imminent.
20	often sleeping; play is entirely limited to very passive activities	20	Very sick, hospitalization indicated. Death not imminent.
10	does not play nor get out of bed	10	Moribund, fatal processes progressing rapidly.
0	unresponsive	0	Dead.

21. References

1. Ellison DW, Kocak M, Dalton J, et al. Definition of disease-risk stratification groups in childhood medulloblastoma using combined clinical, pathologic, and molecular variables. J Clin Oncol; 29: 1400-7.
2. Tamayo P, Cho YJ, Tsherniak A, et al. Predicting relapse in patients with medulloblastoma by integrating evidence from clinical and genomic features. J Clin Oncol; 29: 1415-23.
3. Northcott PA, Korshunov A, Witt H, et al. Medulloblastoma comprises four distinct molecular variants. J Clin Oncol; 29: 1408-14.
4. Cho YJ, Tsherniak A, Tamayo P, et al. Integrative genomic analysis of medulloblastoma identifies a molecular subgroup that drives poor clinical outcome. J Clin Oncol; 29: 1424-30.
5. Schwalbe EC, Lindsey JC, Straughton D, et al. Rapid diagnosis of medulloblastoma molecular subgroups. Clin Cancer Res; 17: 1883-94.
6. Kool M, Koster J, Bunt J, et al. Integrated genomics identifies five medulloblastoma subtypes with distinct genetic profiles, pathway signatures and clinicopathological features. PLoS One 2008; 3: e3088.
7. Ellison DW, Onilude OE, Lindsey JC, et al. beta-Catenin status predicts a favorable outcome in childhood medulloblastoma: the United Kingdom Children's Cancer Study Group Brain Tumour Committee. J Clin Oncol 2005; 23: 7951-7.
8. Fattet S, Haberler C, Legoix P, et al. Beta-catenin status in paediatric medulloblastomas: correlation of immunohistochemical expression with mutational status, genetic profiles, and clinical characteristics. J Pathol 2009; 218: 86-94.
9. Taylor MD, Northcott PA, Korshunov A, et al. Molecular subgroups of medulloblastoma: the current consensus. Acta Neuropathol; 123: 465-72.
10. Packer RJ, Goldwein J, Nicholson HS, et al. Treatment of children with medulloblastomas with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. J Clin Oncol 1999; 17: 2127-36.
11. Merchant TE, Kun LE, Krasin MJ, et al. Multi-institution prospective trial of reduced-dose craniospinal irradiation (23.4 Gy) followed by conformal posterior fossa (36 Gy) and primary site irradiation (55.8 Gy) and dose-intensive chemotherapy for average-risk medulloblastoma. Int J Radiat Oncol Biol Phys 2008; 70: 782-7.
12. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol 2004; 5: 399-408.
13. Relling MV, Rubnitz JE, Rivera GK, et al. High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 1999; 354: 34-9.
14. Mulhern RK, Kepner JL, Thomas PR, Armstrong FD, Friedman HS, Kun LE. Neuropsychologic functioning of survivors of childhood medulloblastoma randomized to receive conventional or reduced-dose craniospinal irradiation: a Pediatric Oncology Group study. J Clin Oncol 1998; 16: 1723-8.
15. Dhall G, Grodman H, Ji L, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer 2008; 50: 1169-75.
16. Grill J, Sainte-Rose C, Jouvet A, et al. Treatment of medulloblastoma with postoperative chemotherapy alone: an SFOP prospective trial in young children. Lancet Oncol 2005; 6: 573-80.

17. von Bueren AO, von Hoff K, Pietsch T, et al. Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. Neuro Oncol; 13: 669-79.
18. Ridola V, Grill J, Doz F, et al. High-dose chemotherapy with autologous stem cell rescue followed by posterior fossa irradiation for local medulloblastoma recurrence or progression after conventional chemotherapy. Cancer 2007; 110: 156-63.