

Activated: March 26, 2007

Closed:

Version Date:

12/24/10

Amendment #:

1B

CHILDREN'S ONCOLOGY GROUP

ACNS0332

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

A Groupwide Phase III Study

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

THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, AND SHOULD NOT BE COPIED, REDISTRIBUTED OR USED FOR ANY OTHER PURPOSE. MEDICAL AND SCIENTIFIC INFORMATION CONTAINED WITHIN THIS PROTOCOL IS NOT INCLUDED TO AUTHORIZE OR FACILITATE THE PRACTICE OF MEDICINE BY ANY PERSON OR ENTITY. *RESEARCH* MEANS A SYSTEMATIC INVESTIGATION, INCLUDING RESEARCH DEVELOPMENT, TESTING AND EVALUATION, DESIGNED TO DEVELOP OR CONTRIBUTE TO GENERALIZABLE KNOWLEDGE. THIS PROTOCOL IS THE RESEARCH PLAN DEVELOPED BY THE CHILDREN'S ONCOLOGY GROUP TO INVESTIGATE A PARTICULAR STUDY QUESTION OR SET OF STUDY QUESTIONS AND SHOULD NOT BE USED TO DIRECT THE PRACTICE OF MEDICINE BY ANY PERSON OR TO PROVIDE INDIVIDUALIZED MEDICAL CARE, TREATMENT, OR ADVICE TO ANY PATIENT OR STUDY SUBJECT. THE PROCEDURES IN THIS PROTOCOL ARE INTENDED ONLY FOR USE BY CLINICAL ONCOLOGISTS IN CAREFULLY STRUCTURED SETTINGS, AND MAY NOT PROVE TO BE MORE EFFECTIVE THAN STANDARD TREATMENT. ANY PERSON WHO REQUIRES MEDICAL CARE IS URGED TO CONSULT WITH HIS OR HER PERSONAL PHYSICIAN OR TREATING PHYSICIAN OR VISIT THE NEAREST LOCAL HOSPITAL OR HEALTHCARE INSTITUTION.

STUDY CHAIR

James M. Olson, MD
Seattle Children's Hospital
Division of Hematology and Oncology, MS 6D-1
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 667-7955
Fax: (206) 667-2917
E-mail: jolson@fhcrc.org

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

TABLE OF CONTENTS

<u>SECTION</u>	<u>PAGE</u>
STUDY COMMITTEE	5
ABSTRACT	8
EXPERIMENTAL DESIGN SCHEMA	9
1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)	10
1.1 Primary Objectives	10
1.2 Secondary Objectives	10
2.0 BACKGROUND	10
2.1 Rationale for Selected Approach and Trial Design	10
2.2 Rationale for Concurrent Carboplatin and Radiation Therapy	10
2.3 Rationale for Concurrent Isotretinoin and Adjuvant Chemotherapy	11
2.4 Gender and Race Differences	13
3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY	13
3.1 Study Enrollment	13
3.2 Patient Criteria	14
4.0 TREATMENT PLAN	18
4.1 Regimen A and Regimen C Administration Schedule for Radiation Therapy	18
4.2 Regimen B and Regimen D Administration Schedule for Radiation Therapy	21
4.3 Regimen A or Regimen B Maintenance (Without Isotretinoin)	24
4.4 Regimen C or Regimen D Maintenance (With Isotretinoin)	27
4.5 Regimen C or D Isotretinoin Continuation Therapy Cycles 7-12	30
5.0 DOSE MODIFICATIONS FOR TOXICITIES	32
5.1 Dose Modifications During Radiation Therapy	32
5.2 Dose Modifications during Maintenance Chemotherapy	32
5.3 Modifications for Toxicity for Isotretinoin (Regimen C and D)	34
6.0 DRUG INFORMATION	35
7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED	35
7.1 Required Observations, Pre-Treatment and During Radiation Therapy for Regimens A & C	36
7.2 Required Observations, Pre-Treatment and During Radiation Therapy for Regimens B & D (With Carboplatin)	37
7.3 Required Observations During Maintenance Chemotherapy for Regimens A and B	38
7.4 Required Observations During Maintenance and Continuation Chemotherapy for Regimens C and D (With Isotretinoin)	39
7.5 Required Observations Following Therapy	40
7.6 Optional Studies	41
8.0 SUPPORTIVE CARE GUIDELINES	41
8.1 Venous Access	41
8.2 Antiemetics	41
8.3 Fever and Neutropenia	41
8.4 Prophylactic Antibiotics	41
8.5 Azole Anti-fungal Agents	42
8.6 Blood Products	42

8.7	Nutritional Support	42
9.0	CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA	42
9.1	Criteria for Removal from Protocol Therapy	42
9.2	Off Study Criteria	43
10.0	STATISTICAL CONSIDERATIONS	43
10.1	Design Considerations	43
10.2	Patient Accrual	44
10.3	Study Duration	44
10.4	Study Endpoints For Analysis Of Treatment Efficacy	44
10.5	Statistical Analysis Of Difference In Long-Term EFS Rate	44
10.6	Interim Monitoring	45
10.7	Statistical Analysis of the Post-RT Response	45
10.8	Stratification	46
10.9	Neuropsychological and Quality of Life	46
10.10	Laboratory Correlates	47
10.11	Gender and Ethnicity Considerations	47
11.0	EVALUATION CRITERIA	48
11.1	Common Terminology Criteria for Adverse Events v4.0 (CTCAE)	48
11.2	Methodology to Determine Tumor Measurement	48
11.3	Selection of Target and Non-Target Lesions	50
11.4	Response Criteria for Target Lesions	50
11.5	Response Criteria for Non-target Lesions	51
12.0	ADVERSE EVENT REPORTING REQUIREMENTS	51
12.1	Purpose	51
12.2	Determination of Reporting Requirements	51
12.3	Reporting of Adverse Events for Commercial Agents - AdEERS abbreviated Pathway	51
12.4	Routine Adverse Event Reporting	52
13.0	RECORDS AND REPORTING	52
13.1	Categories of Research Records	52
13.2	CDUS	53
14.0	SURGICAL GUIDELINES	53
14.1	Neurosurgical Procedure	53
14.2	Shunts	54
14.3	Assessment of Residual Tumor	54
14.4	Extent of Tumor Resection	54
14.5	Imaging Confirmation of Extent of Resection	55
14.6	Peri-operative Corticosteroids	55
15.0	PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS	55
15.1	Neuropathology Goals	55
15.2	Requirements for Handling Biopsy or Surgical Resection Tissue	55
15.3	Pathology Review Materials	55
15.4	Central Review Process	56
16.0	SPECIMEN REQUIREMENTS FOR BIOLOGY STUDIES	56
16.1	Optional Biology Studies	56
16.2	Specific Aims	58

16.3	Aim 1. To identify <i>ex vivo</i> prognostic indicators of therapy failure in high-risk medulloblastomas/SPNETs	59
16.4	Aim II. Predicting Medulloblastoma Outcome with Molecular Markers	63
16.5	Aim III To Prioritize Targeted Therapies for Future Clinical Trials	66
16.6	Aim IV. Tissue Banking	69
17.0	IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING	70
17.1	Whole Brain MRI With and Without Contrast	70
17.2	MR Spine With and Without Contrast	71
17.3	Central Review	71
18.0	RADIATION THERAPY GUIDELINES	72
18.0.1	General Guidelines	72
18.1	Timing of Radiation Therapy	73
18.2	Equipment	73
18.3	3-D Target Volume and Organ At Risk Definitions	74
18.4	Dosimetry	77
18.5	Treatment Technique	79
18.6	Normal Tissue Sparing	80
18.7	Dose Calculations and Reporting	81
18.8	Quality Assurance Documentation	82
18.9	Definitions of Deviation in Protocol Performance	83
19.0	QUALITY OF LIFE AND NEUROPSYCHOMETRIC GUIDELINES	84
	APPENDIX I: PERFORMANCE STATUS SCALES/SCORES	85
	APPENDIX II: M-STAGING SYSTEM FOR POSTERIOR FOSSA AND NON POSTERIOR FOSSA PNET	86
	APPENDIX III: YOUTH INFORMATION SHEETS	87
	REFERENCES	91
	SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM	94

STUDY COMMITTEE

Calls related to general questions about the protocol can be directed to Sara Muchinsky (CRA) at (206) 884-1591.

Calls that require PI input from institutions East of the Mississippi River should be directed to Dr. Roger Packer at (202) 476-2120 or rpacker@cnmc.org and west of the Mississippi River should be directed to Dr. Jim Olson at (206) 667-7955 or jolson@fhcrc.org or Dr. Russ Geyer at (206) 987-2106 or russ.geyer@seattlechildrens.org.

STUDY CHAIR

James M. Olson, M.D.
Seattle Children's Hospital
Division of Hematology and Oncology, MS 6D-1
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 667-7955
Fax: (206) 667-6524
E-mail: jolson@fhcrc.org

Andrew Hallahan, M.D. (Biology)
Royal Children's Hospital, Brisbane
The Oncology Unit
Herston Road
Herston, QLD 4029
Australia
Phone : 61 7 3636 1357
Fax : 61 7 3636 9051
E-mail: Andrew_Hallahan@health.qld.gov.au

STUDY VICE CHAIR

Roger Packer, M.D.
Children's National Medical Center - D.C.
Executive Dir., Ctr for Neuro. Sci & Behav. Med
Chairman, Dept of Neurology
111 Michigan Avenue NW
Washington, DC 20010-2970
Phone: (202) 476-2120
Fax: (202) 476-5226
E-mail: rpacker@cnmc.org

Nancy Heideman (Pharmacist)
University of New Mexico School of Medicine College of Pharmacy
2502 Marble NE
Albuquerque, NM 87131
Phone: (505) 272-8134
Fax: (505) 272-8699
E-mail: nheideman@salud.unm.edu

STUDY STATISTICIAN

Tianni Zhou, Ph.D.
Children's Oncology Group - Operations Center
440 E. Huntington Dr.
Arcadia, CA 91006
Phone: (626) 241-1534
Fax: (626) 445-4334
E-mail: Tzhou@childrensoncologygroup.org

Linda Heier, MD (Diagnostic Imaging)
Diagnostic Imaging
Weill Medical College of Cornell Univ. Medical Center
Dept. Of Radiology
450 E. 63rd St. #11D
New York, NY 10065
Phone: (212) 746-2581
Fax: (212) 746-8597
E-mail: laheier@med.cornell.edu

STUDY COMMITTEE MEMBERS

Peter Burger, M.D. (Pathology)
Johns Hopkins Hospital
Pathology/NeuroPathology Room 710-A
600 North Wolfe Street Pathology 7
Baltimore MD 21287
Phone: (410) 955-8378
Fax: (410) 614-9310
E-mail: pburger@jhmi.edu

Regina Jakacki MD (Pediatric Oncology)
Pediatric Hematology/Oncology
Children's Hospital of Pittsburgh of UPMC
One Children's Hospital Dr.
4401 Penn Ave, Faculty Pavillion Bldg, 5th Floor
Pittsburgh, PA 15224
Phone: (412) 692-7056
Fax: (412) 692-7693
e-mail: Regina.Jakacki@chp.edu

Michael Taylor, M.D. (Neurosurgery)
Hospital for Sick Children
Neurosurgery
555 University Ave. Suite 1504
Tormoto, ON M5G 1X8
Phone: (416) 813-7564
Fax: (416) 813-4975
E-mail: Michael_d.taylor@sickkids.ca

Nicole Larrier, M.D. (Radiation Oncology)
Duke University Medical Center
Radiation Oncology
Box 3085
Durham, NC 27710
Phone: (919) 668-5213
Fax: (919) 684-3953
E-mail : larrier@radonc.duke.edu

Jeff Michalski, M.D. (Radiation Oncology)
Washington University Medical Center
Radiation/Oncology
4921 Parkview Place Box 8224
St Louis, MO 63110
Phone: (314) 362-8566
Fax: (314) 747-9557
E-mail: michalski@radonc.wustl.edu

Sara Muchinsky (Data Management)
Seattle Children's
Hematology/Oncology
1900 Ninth Ave
M15 C9S-9C
Seattle, WA 98101
Phone : (206) 884-1591
Fax : (206) 792-3062
E-mail: sara.muchinsky@seattlechildrens.org

Ingrid Shieh (Research Coordinator)
Children's Oncology Group – Operations Center
440 E. Huntington Drive
Arcadia, CA 91006
Phone: (626) 241-1533
Fax: (626) 445-4334
E-mail: ishie@childrensoncologygroup.org

Karin Walsh, PhD (Psychology)
Children's National Medical Center
Neuropsychology
111 Michigan Ave. NW
Washington, DC 20010
Phone: (202) 476-3923
Fax: (202) 476-5039
E-mail : kwalsh@cnmc.org

Mark Krieger, M.D. (Neurosurgery)
Children's Hospital Los Angeles
Neurosurgery
1300 North Vermont Ave. Suite 1006
Los Angeles, CA 90027
Phone : (323) 663-8128
Fax : (323) 668-1870
E-mail : mkrieger@chla.usc.edu

Vikki Nussbaum, Pharm.D. (Pharmacist)
University of Wisconsin Hospital and Clinics
Pharmacy
P4
1675 Highland Ave.
Madison, WI 53792
Phone: (608) 263-1290
Fax: (608) 263-9424
E-mail: vnussbaum@uwhealth.org

Ian Pollack, M.D. (CNS Disease Committee Chair)
Children's Hospital of Pittsburgh of UPMC
One Children's Hospital Dr.
4401 Penn Ave
Pittsburgh PA 15224
Phone: (412) 692-5881
Fax: (412) 692-5921
E-mail: ian.pollack@chp.edu

Denis Shrieve, M.D. (Radiation Oncology)
Primary Children's Medical Center
University of Utah
Radiation Oncology
100 North Mario Capecchi Dr.
Salt lake City, UT 84132
Phone: (801) 581-8793
Fax: (801) 662-4707
E-mail: dennis.shrieve@hci.utah.edu

Chris Williams-Hughes (Protocol Coordinator)
Children's Oncology Group – Operations Center
5312 W. Roxbury Place
Littleton, CO 80128
Phone: (303) 904-8527
Fax: (303) 904-8407
E-mail: chrishughes@Q.com

J. Russell Geyer, MD (Pediatric Oncology)
Seattle Children's
Dept. of Pediatric Hem-Onc
4800 Sand Pt. Way NE
Mail Stop B6553
Seattle, WA 98105
Phone: (206) 987-2106
Fax: (206) 987-3946
E-mail: russ.geyer@seattlechildrens.org

Bonnie Carlson-Green, PhD
Children's Hospitals and Clinics of Minnesota
Psychological Services
360 Sherman St.
Mail Stop 62-200
St. Paul, MN 55102
Phone: (651) 220-6813
Fax: (651) 220-6707
E-mail : bonnie.carlson-green@childrensmn.org

Nancy Tarbell, M.D. (Radiation Oncology)
Massachusetts General Hospital
Bulfinch 360
55 Fruit Street
Boston, MA 2114
Phone: (617) 724-1836
Fax: (617) 724-4808
E-mail: nancy_tarbell@hms.harvard.edu

Kathleen Perko, RN (Nursing)
Oregon Health and Science University
3181 SW Sam Jackson Park Road, Mail Code: DC 10N
Portland, OR 97239
Phone: (503) 418-5172
Fax: (503) 494-0714
E-mail: perkok@ohsu.edu

For Group Operations (GOC) and
Statistics and Data Center (SDC) contacts see:
<http://members.childrensoncologygroup.org>
Telephone: (626) 447-0064

<u>AGENT</u>	<u>NSC#</u>
Carboplatin (Paraplatin®)	241240
Cisplatin	119875
Cyclophosphamide	026271
Filgrastim (G-CSF)	614629
Isotretinoin (13-cis Retinoic Acid)	329481
Vincristine	067574

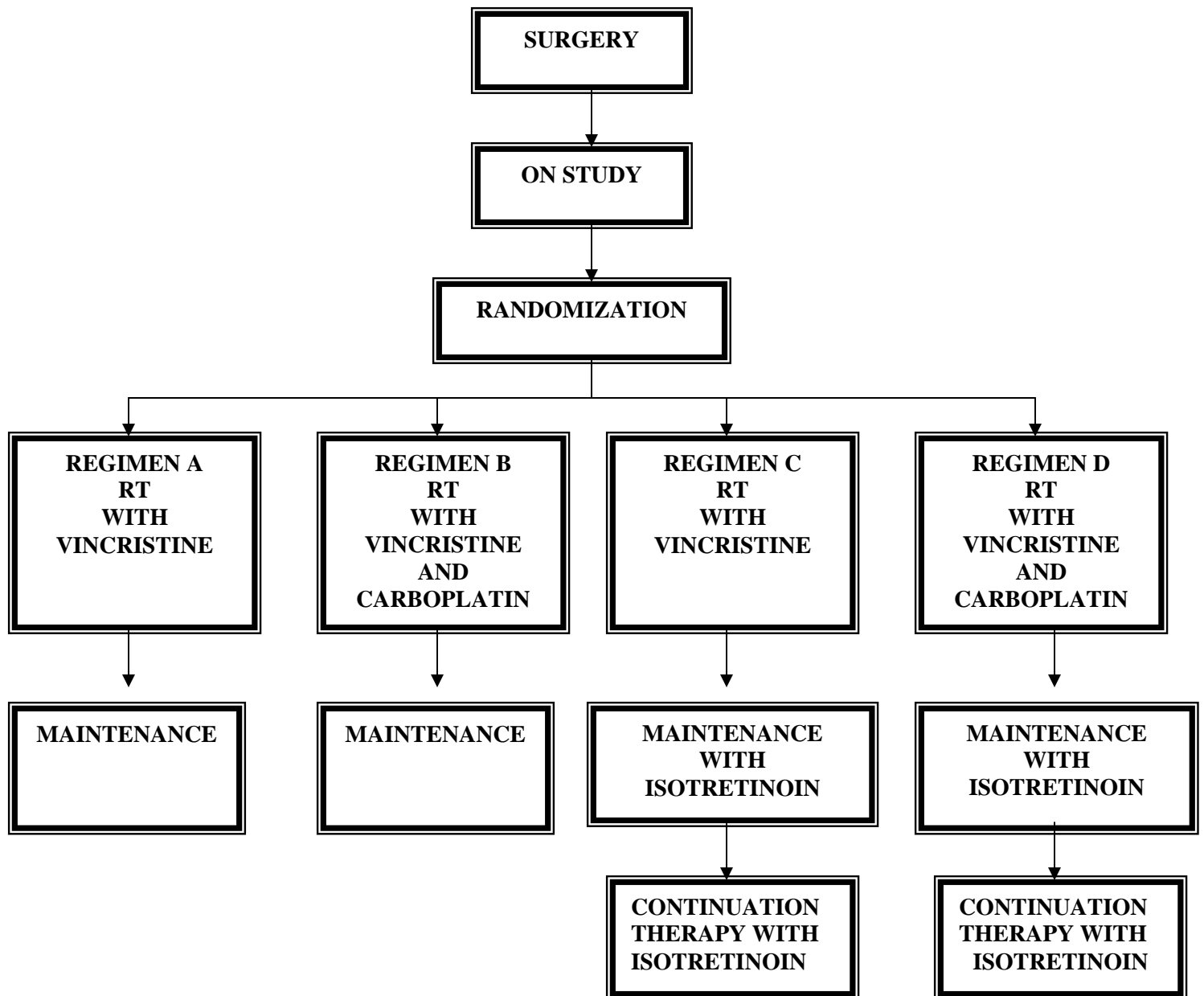
The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

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

ABSTRACT

Medulloblastoma/PNET is the most common malignant childhood brain cancer. The goal of this study is to determine whether radiosensitization with carboplatin or the addition of Isotretinoin to maintenance therapy improves cure rates for children with other than average risk medulloblastoma/PNET. All patients will receive standard therapy consisting of surgery, radiation therapy and chemotherapy. Subsets of patients will be randomly assigned to receive carboplatin radiosensitization, Isotretinoin during maintenance, both, or neither. Carboplatin has activity as a single agent against medulloblastoma and it has been shown to enhance radiation-induced tumor cell kill. A previous study, CCG-99701, demonstrated that it was feasible and safe to administer carboplatin on a daily basis during radiation therapy. Laboratory-based studies have shown that Isotretinoin effectively kills patient-derived medulloblastoma cells *ex vivo* and in animal models of medulloblastoma. Furthermore, this agent acts synergistically with cisplatin *in vitro* and in animal models. Isotretinoin has previously been safely administered to neuroblastoma patients at the same dose planned for this study. Correlative biology studies are incorporated into the research design.

EXPERIMENTAL DESIGN SCHEMA



1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1

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

1.1.2

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

1.2 Secondary Objectives

1.2.1

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

1.2.2

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

1.2.3

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

1.2.4

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

2.0 BACKGROUND

2.1 Rationale for Selected Approach and Trial Design

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

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

2.2 Rationale for Concurrent Carboplatin and Radiation Therapy

Carboplatin as a single agent is effective for medulloblastoma/PNET patients, with complete or partial responses observed in 7 out of 15 recurrent disease patients receiving 100-210 mg/m²/week.⁵⁻⁷ Most of these patients received 175/mg/m²/week as a single dose. In the proposed study, patients will receive 175/mg/m²/week divided into five daily 35 mg/m²/day doses. Based on the efficacy data in relapsed patients, co-administration of carboplatin and radiation in the post-surgical period would be justified even

in the absence of laboratory studies showing positive interaction between the two modalities. In addition, multiple laboratory and clinical studies show that cancer cell response is greater in the presence of carboplatin and radiation than either modality alone.⁸⁻¹⁴

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

Concurrent administration of carboplatin and radiation has been well tolerated by adults and elderly patients in clinical trials and has led to improved response rates compared to radiation alone. In patients with advanced head and neck cancer, concurrent administration of carboplatin at AUC of 0.4 per week, docetaxel at 10 mg/m² and 64-82 Gy radiotherapy resulted in 81% complete response and 19% partial response rates.¹⁵ Elderly patients with small cell lung cancer were treated with daily carboplatin (30 mg/m²/day x 4 weeks) and 50-60 Gy radiotherapy and achieved a 50% response rate (1 CR, 18 PR, 38 patients total).¹⁶ A phase III trial of 283 patients with unresectable stage III lung cancer showed an 18% CR rate in patients that received carboplatin (100 mg/m²/week) plus 60 Gy radiation versus 10% in the radiation only arm (P = 0.1).¹⁷

Concurrent administration of carboplatin (35 mg/m²/day x 30 doses) and radiation therapy in high risk medulloblastoma/PNET patients has been shown to be safe in protocol CCG 99701. In that study, carboplatin, rather than cisplatin was selected for reduced toxicities in addition to radiosensitization based primarily on pharmacokinetic properties, as both have been reported to have similar radiosensitizing activity.¹⁸ Because carboplatin binds to plasma proteins more slowly than cisplatin, more free drug is available to cross the blood brain barrier.^{19,20} Following intravenous administration of comparable doses in a primate model cerebrospinal AUC levels were 10-fold higher for carboplatin compared to cisplatin.²¹ Brain tumor levels of carboplatin sufficient for radiosensitization can be obtained with doses of carboplatin as low as 20 mg/m².²²⁻²⁴

2.3 Rationale for Concurrent Isotretinoin and Adjuvant Chemotherapy

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

Cultured medulloblastoma cells undergo apoptosis as the predominant response to retinoids. In two medulloblastoma cell lines, D283 and D341, Isotretinoin and all-trans retinoic acid (ATRA) induced apoptosis in a dose- and time-dependent fashion at concentrations that are readily achievable in the central nervous system. Efficacy was observed at concentrations ranging from 10 nM to 1 μM.²⁵ The response increased with duration of treatment so that by 6-8 days, 79% +/- 4% of D283s and 67% +/- 4% of D341s were apoptotic.²⁵ Because cultured tumor cells do not always faithfully represent primary tumors, patient-derived medulloblastoma specimens were placed in tissue culture media within 20 minutes of resection from their blood supply, mechanically triturated into near single-cell suspensions and then treated with RA. Eight of 10 primary medulloblastoma/primitive neuroectodermal tumor specimens tested showed significantly increased cell death in response to these retinoids. Only 32 ± 5.2% of cells remained viable after 48 hours of ATRA exposure compared to 70 ± 5.5% of vehicle-treated cells (P < 0.0006). In both established cultures and patient-derived specimens, cell cycle arrest and neuronal differentiation was observed in a subset of the cells that failed to apoptose. Importantly, little or no

retinoid-induced apoptosis was observed in neuroblastoma or glioma cells indicating that retinoids interfere with a pathway that is uniquely critical for medulloblastoma cell survival. This would suggest that retinoids might have even more efficacy in medulloblastoma patients than has been observed with neuroblastoma patients.

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

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

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

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

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

Isotretinoin acts synergistically with cisplatin in cultured medulloblastoma cells. Cisplatin serves as a key agent in medulloblastoma therapy because of its demonstrated efficacy against medulloblastoma cells and because of improved outcomes in clinical trials that utilized platinum-based chemotherapy regimens. Preliminary studies show that Isotretinoin acts synergistically with cisplatin both in vitro and in vivo,

increasing apoptosis of D283 cells by as much as three fold compared to either agent alone (Hallahan and Olson, unpublished). In an earlier study, the combination of 1 µg/ml cisplatin and 10 µM/l Isotretinoin led to complete cessation of growth of Med-3 medulloblastoma cells.³³ In other studies, retinoid agonists increased the efficacy of cisplatin against skin squamous cell carcinoma cell lines, oral squamous cell carcinoma xenografts, ovarian adenocarcinoma cells, ovarian carcinoma xenografts, and squamous head and neck cancer cells.³⁴⁻³⁷ In addition, durable responses were observed when retinoid agonists and cisplatin were co-administered in patients with recurrent or advanced squamous cell carcinoma of the head and neck, advanced squamous cell carcinoma of the skin, advanced non-small-cell lung cancer.^{34,38}

Cisplatin and Isotretinoin have largely non-overlapping toxicities. Prevalent cisplatin toxicities include hearing loss, renal dysfunction, nausea and marrow suppression. Isotretinoin has been safely administered in pediatric neuroblastoma patients. The most common untoward effects of Isotretinoin included dry skin, xerostomatitis, and headache, though the frequency of headache is much lower than seen with other retinoids such as ATRA. In a study of 43 adults treated with Isotretinoin for glioma, there were no instances of headache or pseudotumor cerebri.³⁹ Because cisplatin and Isotretinoin act synergistically, they have been combined in multiple clinical trials that involved adult patients. In one study, that involved administration of ATRA at 150 mg/m² on an every day basis without breaks, ATRA was poorly tolerated and discontinued by some patients. In three other trials that utilized breaks in the Isotretinoin dosing regimen, the combination was well tolerated establishing that the drugs can be safely co-administered.^{34,38} The current study follows a two weeks on, two weeks off schedule for Isotretinoin, similar to the schedule that has been well tolerated in children with neuroblastoma.

2.4 Gender and Race Differences

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

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 IRB Approval

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

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

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

3.1.2 Patient Registration

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

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

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

3.1.3 Study Enrollment

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

3.1.4 Neurocognitive Testing

Enrollment onto ALTE07C1 is strongly encouraged.

3.1.5 Timing

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

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

3.1.6 Bilingual Services

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

3.1.7 Randomization

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

3.2 Patient Criteria

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

3.2.1 Age

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

3.2.2 Diagnosis

Newly diagnosed, previously untreated: (1) M0 Medulloblastoma with $>1.5 \text{ cm}^2$ residual; (2) M+ Medulloblastoma; (3) M0 or M+ Supratentorial PNET (including pineoblastoma). Patients with diffusely anaplastic medulloblastoma are eligible regardless of M-stage or residual tumor. See Appendix II for M-Staging.

All patients with M4 disease are not eligible.

3.2.3 Cranial and Spinal MRI

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

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

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

3.2.4 Evaluation of Lumbar CSF Cytology

Lumbar CSF cytology examination must be obtained pre-operatively or within 31 days following surgery. The optimal time for obtaining CSF is prior to surgery or 1-3 weeks following surgery. Ventricular CSF (either pre- or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M₃). Patients who are categorized as M₁ must have either an intra-operative positive CSF (via lumbar puncture at the end of the procedure) or a positive lumbar CSF obtained > 7 days post-operatively (to rule out surgically induced false positives).

3.2.5 Performance Level (See Appendix I)

Patients must have a Karnofsky performance level of ≥ 30 for patients > 16 years of age or a Lansky performance scale of ≥ 30 for patients ≤ 16 years of age and life expectancy > 8 weeks.

3.2.6 Prior Therapy

No previous chemotherapy or radiation therapy.

3.2.7 Concomitant Medications Restrictions

3.2.7.1

Patients taking Accutane (Isotretinoin) for acne must discontinue drug use with this indication prior to enrollment. Corticosteroids should not be used during chemotherapy administration as an antiemetic because of their effect on the blood-brain barrier.

Isotretinoin is contraindicated in patients with parabens allergy as the capsule is preserved with the agent and patients with soybean allergy since Isotretinoin is suspended in soybean oil. Concurrent use

with tetracyclines should be avoided due to reports of cases of pseudotumor cerebri with concurrent use. Isotretinoin may increase clearance of carbamazepine and diminish the therapeutic effect of oral contraceptives. Intake of vitamin A should be limited for the duration of isotretinoin treatment.

3.2.7.2

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

3.2.7.3

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

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

3.2.7.4

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

3.2.7.5

No other experimental therapy is permitted while on study.

3.2.8 Organ Function Requirements:

3.2.8.1 Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR $\geq 70\text{mL/min/1.73m}^2$ OR
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

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

3.2.8.2 Adequate liver function defined as:

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

3.2.8.3 Adequate bone marrow function defined as:

- ANC \geq 1,000/ μ L
- Platelets \geq 100,000/ μ L (untransfused)
- Hemoglobin \geq 8 g/dl (may be transfused)

3.2.9 Pregnancy

There is information indicating a risk of fetal or teratogenic toxicity with this treatment. Fetal toxicities and teratogenic effects of Isotretinoin (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosome abnormalities, multiple anomalies, pancytopenia, and low birth weight.

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

3.2.10 Regulatory

3.2.10.1

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

3.2.10.2

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

4.0 TREATMENT PLAN

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

Overview of Treatment Plan

Following neurosurgical procedure and staging, patients will be randomized to receive either 36 Gy craniospinal irradiation with appropriate boost to the tumor bed or the same radiation regimen with addition of carboplatin as a radiosensitizing agent. All patients must begin therapy within 31 days of surgery. The dose of carboplatin will be 35 mg/m²/day for 30 doses over 6 ½ weeks based on the dose finding phase of COG 99701. All patients will receive vincristine 1.5 mg/m² once per week during radiation therapy for a total of 6 doses.

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

Patients will be randomized to receive either Isotretinoin during Maintenance or no additional drug. Patients randomized to Isotretinoin will receive 80 mg/m² twice daily on Day 1 and Days 16-28 in 28 day intervals during Maintenance and Days 15-28 during Continuation Therapy for a total of 12 cycles beginning concurrently with Maintenance chemotherapy and continuing for approximately six months after completion of chemotherapy.

Radiation Therapy

All patients will receive craniospinal radiation therapy (CSRT) to doses of:

36 Gy CSRT

55.8 Gy Posterior fossa (cumulative dose)

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

ALL PATIENTS WILL REQUIRE REVIEW OF RADIATION THERAPY TREATMENT PLAN. RADIATION TREATMENT PLAN MUST BE SUBMITTED TO QARC FOR QA REVIEW WITHIN 3 DAYS OF INITIATION OF RADIATION THERAPY (SECTION 18.9)

4.1 Regimen A and Regimen C Administration Schedule for Radiation Therapy

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

VinCRISTine: IV push over 1 minute (or infusion via minibag as per institution policy)
1.5 mg/m²/day (maximum single dose 2 mg) once weekly Weeks 1-6 during radiation for a total of 6 doses. Vincristine should be started within the first week of starting radiation therapy and given weekly thereafter. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg. Avoid extravasation; the use of a central line is suggested.

FATAL IF GIVEN INTRATHECALLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine.

Filgrastim: SubQ or IV IV (SubQ preferred)

5 micrograms/kg/day to be administered during Radiation Therapy as needed. CBCs will be obtained weekly. If ANC \geq 1500/ μ L, no GCSF is needed and weekly CBCs will continue. If ANC \leq 1500/ μ L at any point, then the following regimen should replace weekly CBCs. If ANC \leq 1500/ μ L on any Friday, Filgrastim will be administered subcutaneously or IV on Friday, Saturday, and Sunday. Filgrastim should not be given until after the radiation treatment on Friday has been delivered. If the ANC $>$ 1500/ μ L, no Filgrastim will be administered that weekend. On any Monday or Wednesday, if the ANC $<$ 1000/ μ L, Filgrastim will be administered on that day and the following day after the radiation treatment. If the ANC \geq 1000/ μ L on Monday or Wednesday, Filgrastim will not be administered (see Table below). Family members should be taught to administer Filgrastim. Filgrastim guidelines are tabulated below:

Guidelines for Filgrastim Administration During Radiotherapy

DAY	CBC with diff, plts	ANC 1000-1500	ANC $<$ 1000
Friday	x	5 micrograms/kg/day Fri., Sat., Sun.	5 micrograms/kg/day Fri., Sat., Sun.
Monday	x	No Filgrastim	5 micrograms/kg/day Mon., Tues.
Wednesday	x	No Filgrastim	5 micrograms/kg/day Wed., Thur.

There is to be no dose escalation of Filgrastim for neutropenia alone. In the event of a potentially life-threatening infection with neutropenia, Filgrastim may be increased to 10 micrograms/kg/day.

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

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

4.1.1 ACNS0332: Regimen A and Regimen C Radiation Therapy

Six weeks of radiation therapy (Weeks 1-6) and 6 weeks of rest (Weeks 7-12) will constitute one reporting period.

Patient name or initials

DOB

Radiation Therapy (See Section 18.0) must begin within 31 days of diagnostic surgery. Week 7 to 12 is a rest period (6 Week Rest Period), then proceed to Maintenance. The Therapy Delivery Map is on **one** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m ² (maximum dose 2 mg)	Administer once weekly Weeks 1-6 during radiation for a total of 6 doses	Vincristine should be started within the first week of starting radiation therapy and given weekly thereafter and can be administered any day during the week. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg.	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets *- If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M ₃). <i>See Section 7.1 for a complete list of observations.</i>
Filgrastim (G-CSF)	SubQ or IV (SubQ preferred)	5 micrograms/kg/day	See Administration Guidelines (Section 4.1)	Should be administered during Radiation Therapy as needed. See Administration Guidelines (Section 4.1).	OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Regimen _____ Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Week	Day	VCR _____ mg	G-CSF _____ mcg	Studies	Comments (Include any held doses, or dose modifications) Indicate days G-CSF given on each week
				Enter calculated dose above and actual dose administered below			
		1	1	_____ mg#	_____ mcg\$	a, f	
		2	8	_____ mg#		a, f	
		3	15	_____ mg#		a, f	
		4	22	_____ mg#		a, f	
		5	29	_____ mg#		a, f	
		6	36	_____ mg#		a, f	
		7	43			a, f	
		8				a, f	
		9				a, f	
		10				a, b%, c%, d%, e%, f	
		11				a, f	
		12				a, f	Indicate last day of G-CSF
				To begin Maintenance, the ANC must be ≥ 1000/μL, platelets ≥ 100,000/μL and the patient must have been off G-CSF for at least 24 hours. If ANC < 1000/μL or platelets < 100,000/μL then repeat CBC and differential at least twice a week until criteria are met.			

- Vincristine can be administered any day during the week.

\$ - Administer G-CSF as needed and according to table in Section 4.1.

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

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

4.2 Regimen B and Regimen D Administration Schedule for Radiation Therapy

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

VinCRISTine: IV push over 1 minute (or infusion via minibag as per institution policy)

1.5 mg/m²/day (maximum single dose 2 mg) once weekly Weeks 1-6 during radiation for a total of 6 doses. Vincristine should be started within the first week of starting radiation therapy and given weekly thereafter. Administer prior to CARBOplatin. The absolute dose of vincristine should be rounded down to the nearest 0.1 mg.

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

FATAL IF GIVEN INTRATHECALLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASStine.

CARBOplatin: IV over 15 minutes

35 mg/m²/day given daily during radiation therapy for a total of 30 doses. The first dose of CARBOplatin should be administered on the first day of radiation therapy. CARBOplatin will be over 15 minutes 1-4 hours prior to radiation therapy. This should be sufficient time for patients who may require sedation or who travel to another facility. **If a radiation treatment is not given, platin should be held as well. If a dose of CARBOplatin is given and radiation therapy is NOT administered due to sedation or technical issues, the CARBOplatin dose should not be made up (i.e. no more than 30 doses of CARBOplatin should be given). Since there are 31 fractions of radiation, the last radiation treatment will not be preceded by a dose of CARBOplatin.**

Avoid use of aluminum containing needles or administration sets.

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

Filgrastim: SubQ or IV (SubQ preferred)

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

Guidelines for Filgrastim Administration During Radiotherapy

DAY	CBC with diff, plts	ANC 1000-1500	ANC < 1000
Friday	x	5 micrograms/kg/day Fri., Sat., Sun.	5 micrograms/kg/day Fri., Sat., Sun.
Monday	x	No Filgrastim	5 micrograms/kg/day Mon., Tues.
Wednesday	x	No Filgrastim	5 micrograms/kg/day Wed., Thur.

There is to be no dose escalation of Filgrastim for neutropenia alone. In the event of a potentially life-threatening infection with neutropenia, Filgrastim may be increased to 10 micrograms/kg/day.

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

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

4.2.1 ACNS0332: Regimen B and Regimen D Radiation Therapy

Six weeks of radiation therapy (Weeks 1-6) and 6 weeks of rest (Weeks 7-12) will constitute one reporting period.

Patient name or initials

DOB

Radiation Therapy (See Section 18.0) must begin within 31 days of diagnostic surgery. Week 7 to 12 is a rest period (6 Week Rest Period), then proceed to Maintenance. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m ² (maximum dose 2 mg)	Administer once weekly Weeks 1-6 during radiation therapy prior to CARBOplatin dose that day for a total of 6 doses	VinCRISTine should be started within the first week of starting radiation therapy and given weekly thereafter and can be administered any day during the week. The absolute dose of vinCRISTine should be rounded down to the nearest 0.1 mg.	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus
CARBOplatin (CARBO)	IV over 15 minutes	35 mg/m ² /day	Daily During RT for a Total of 30 Doses	CARBOplatin and VinCRISTine will be given 1-4 hours prior to RT. See Administration Guidelines (Section 4.2).	*- If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M ₃).
Filgrastim (G-CSF)	SubQ or IV (SubQ preferred)	5 micrograms/kg /day		Should be administered during Radiation Therapy as needed. See Administration Guidelines (Section 4.2).	See Section 7.2 for a complete list of observations. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Regimen				Ht	cm	Wt	kg	BSA	m ²	
Date Due	Date Given	Week	Day	Time CARBO Finished	Time XRT Started	CARBO ____mg	VCR ____mg	G-CSF ____mcg	Studies	Comments (Include any held doses, or dose modifications) Indicate days G-CSF given on each week
						Enter calculated dose above and actual dose administered below				
		1	1			____mg	____mg#	____mcg\$	a ,f, g	
			2			____mg				
			3			____mg			f	
			4			____mg				
			5			____mg			f	
		2	8			____mg	____mg#		a,f	
			9			____mg				
			10			____mg			f	
			11			____mg				
			12			____mg			f	
		3	15			____mg			a ,f, g	
			16			____mg	____mg#			
			17			____mg			f	
			18			____mg				
			19			____mg			f	
		4	22			____mg	____mg#		a,f	
			23			____mg				
			24			____mg			f	
			25			____mg				
			26			____mg			f	
		5	29			____mg	____mg#		a,f, g	
			30			____mg				
			31			____mg			f	
			32			____mg				
			33			____mg			f	
		6	36			____mg	____mg#		a,f	
			37			____mg				
			38			____mg			f	
			39			____mg				
			40			____mg			f	
		7						▼	f&, g	
		8							f&	
		9							f&	
		10							b%,c%,d%,e%,f&	
		11							f	
		12							f	Indicate last day of G-CSF
					To begin Maintenance, the ANC must be ≥ 1000/μL, platelets ≥ 100,000/μL and the patient must have been off G-CSF for at least 24 hours. If ANC < 1000/μL or platelets < 100,000/μL, then repeat CBC and differential at least twice a week until criteria are met					

To begin Maintenance, the ANC must be ≥ 1000/μL, platelets ≥ 100,000/μL and the patient must have been off G-CSF for at least 24 hours. If ANC < 1000/μL or platelets < 100,000/μL then repeat CBC and differential at least twice a week until criteria are met.

- Vincristine can be administered any day during the week.

\$ - Administer G-CSF as needed and according to table in Section 4.2.

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

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

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

4.3 **Regimen A or Regimen B Maintenance (Without Isotretinoin)**

Begin each cycle of Maintenance on Day 29 and when ANC $\geq 1000/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$ and the patient must have been off G-CSF for at least 24 hours for a total of 6 Cycles.

CISplatin: IV over 6 hours

75 mg/m² on Day 1

Suggested hydration and supportive care: Prehydration should begin at least 2 hours prior to CISplatin infusion with normal saline and mannitol (7.5 g/l) at 125 ml/m²/hr. After the completion of the CISplatin infusion, begin D₅NS and mannitol (7.5 g/l) and 8 mEq MgSO₄/l at 125 ml/m²/hr x 8 hours. IV fluids should then be changed to D₅ 1/2 NS + 20 mEq KCl/l + 8 mEq MgSO₄/l at 125 ml/m²/hr to complete 24 hours of hydration (until first dose of cyclophosphamide). Urine output of at least 3 ml/kg/hr should be achieved prior to CISplatin infusion and maintained for at least 8 hours following completion of the infusion. Mannitol 0.5 g/kg may be used to maintain urine output. If a mannitol bolus fails to increase urine output over the ensuing hour, then furosemide 1 mg/kg IV should be given as a bolus. Four hour input and output totals should be maintained within 20% of each other.

Oral magnesium supplementation following CISplatin administration may be necessary. Electrolytes (i.e., Mg, Ca, PO₄, K) should be followed closely thereafter.

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

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

VinCRISTine: IV push over 1 minute (or infusion via minibag as per institution policy)

1.5 mg/m²/day (maximum single dose 2 mg) on Days 1 and 8. The absolute doses of vincristine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg.

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

FATAL IF GIVEN INTRATHECALLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine.

Cyclophosphamide: IV over 1 hour

1000mg/m² on Day 2 and Day 3. On Day 2, cyclophosphamide should be given at least 24 hours after CISplatin.

Suggested hydration and supportive care: Urine output should be maintained at a minimum of 3 ml/kg/hr. Hydration is continued with D₅ 1/2NS plus 20 mEq/L KCl at 100 mL/m² per hour. After second dose of cyclophosphamide, hydration should be continued for a minimum of 8 hours and until patient maintains

normal PO intake. Note: nausea and vomiting are likely and prolonged IV fluids may be necessary to prevent dehydration and maintain electrolyte balance.

Filgrastim (G-CSF): SubQ or IV (SubQ preferred)

5 micrograms/kg/day daily starting on Day 4 and continue for at least 10 days until post-nadir ANC > 1500 μ L. Filgrastim must be discontinued for a minimum of 24 hours prior to next chemotherapy cycle if counts have recovered.

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

4.3.1 ACNS0332: Regimen A and Regimen B Maintenance (Without Isotretinoin) Four consecutive weeks (28 days) will constitute one cycle. Use one copy of the TDM for each cycle (please note cycle number).	Patient name or initials	DOB
--	--------------------------	-----

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

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	75 mg/m ²	Day 1	See Administration Guidelines (Section 4.3)	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m ² (maximum dose 2 mg)	Days 1 and 8	The absolute doses of vincristine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg.	c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus h. SGOT, SGPT, Alkaline Phosphate, Bilirubin i. Creatinine Clearance or GFR j. Urinalysis k. Thyroid Function
Cyclophosphamide (CPM)	IV over 1 hour	1000 mg/m ²	Days 2 and 3	See Administration Guidelines (Section 4.3)	*- If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M ₃).
Filgrastim (G-CSF)	SubQ or IV (SubQ preferred)	5 micrograms /kg/day	Start on Day 4 and continue for at least 10 days until post-nadir ANC > 1500/μL.	Do not start the next cycle of chemotherapy until at least 24 hours after Filgrastim has been stopped. Filgrastim may be given concomitantly with vincristine.	See Section 7.3 for a complete list of observations. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Regimen		Cycle		Ht	cm	Wt		kg	BSA	m ²
Date Due	Date Given	Week	Day	CDDP ____mg	VCR ____mg	CPM ____mg	G-CSF ____mcg	Studies	Comments (Include any held doses, or dose modifications)	
				Enter calculated dose above and actual dose administered below						
		1	1	____mg	____mg			a, e, f, g, h, i%, j (b, c@)##,		
			2			____mg				
			3			____mg				
			4				____mcg			
		2	8		____mg			f+,g		
		3	15					f+,g		
		4	22					f+,g	Indicate last day of G-CSF	
			28					f+,g (a, b, c@, d#, e, f, g, h, k)&		
			29		To begin next cycle of Maintenance, the ANC must be ≥ 1000/μL, platelets ≥ 100,000/μL and the patient must have been off G-CSF for at least 24 hours. If ANC < 1000/μL or platelets < 100,000/μL then repeat CBC and differential at least twice a week until criteria are met. See Section 5.2.2.1					

+ If counts are low and while on Filgrastim, it is recommended that CBCs be performed twice weekly.

@ Spinal imaging is only necessary for patients with M₁ – M₃ disease.

Required only for patients who are positive at diagnosis.

% Obtain if creatinine is greater than normal for age (see Section 3.2.8.1)

& Obtain within 1 month of completing Maintenance.

Obtain prior to Cycle 4.

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

4.4 **Regimen C or Regimen D Maintenance (With Isotretinoin)**

Patients randomized to Isotretinoin will receive 80 mg/m² twice daily on Day 1 and Days 16-28 in 28 day intervals for a total of 12 cycles beginning concurrently with Maintenance chemotherapy and continuing for approximately six months after completion of chemotherapy.

Begin each subsequent cycle of Maintenance on Day 29 and when ANC \geq 1000/ μ L, platelets \geq 100,000/ μ L and the patient must have been off G-CSF for at least 24 hours, liver functions tests Grade 2 or less (SGPT $<$ 5 x upper limit of normal), calcium and uric acid normal, renal function with normal creatinine for age (see Section 3.2.8.1), skin toxicity no greater than Grade 1, serum triglycerides $<$ 300 mg/dL and no hematuria or proteinuria on urinalysis and off Filgrastim for 24 hours for a total of 6 Cycles.

Isotretinoin (Cis-Retinoic Acid): PO

80 mg/m²/dose twice daily for a total of 160 mg/m²/day on Day 1 and Days 16-28. Doses should be rounded down to the nearest 10 mg.

The dose of isotretinoin can be repeated if the child vomits within 30 minutes of taking the dose and the capsules can be seen in the vomitus. If the child takes the medicine in any other form except as a whole capsule(s), it should not be repeated.

To enhance absorption, administer capsules with high fat food (such as ice cream or peanut butter) or with milk. Isotretinoin capsules should be swallowed whole whenever possible. If not possible, for ease of swallowing, the capsules can be punctured and the contents squeezed into a high fat food immediately before administration or the capsules can be softened or punctured and chewed (best absorbed if chewed with high fat food). Isotretinoin should not be removed from the capsules for more than one hour prior to administering to the patient. See additional information in the drug monograph. Directions for accessing the drug monograph are available in Section 6.0.

MUST be prescribed under the Committed to Pregnancy Prevention Program (iPLEDGE) (see drug monograph). Pregnancy risk factor X. Pregnant women should not handle isotretinoin. Women of childbearing potential should wear gloves when handling isotretinoin capsules. Patients should be warned about photosensitivity; the use of sunscreen and avoiding exposure to direct sunlight should be recommended.

Patients with history of clinical depression prior to diagnosis or suicidal ideation should not receive Isotretinoin (Cis-retinoic acid).

Each cycle should begin on Day 29 and when the criteria below have been met.

Criteria to Begin Isotretinoin:

- a. SGPT (ALT) $<$ 5 X upper limit of normal
- b. Skin toxicity no greater than Grade 1
- c. Serum triglycerides $<$ 300 mg/dL
- d. No hematuria or proteinuria on urinalysis
- e. Serum creatinine within normal limits for age
- f. Normal calcium and uric acid

CISplatin: IV over 6 hours

75 mg/m² on Day 1 with normal saline and mannitol (7.5 g/l) at a rate of 125 ml/m²/hr.

Prehydration should begin at least 2 hours prior to CISplatin infusion with normal saline and mannitol (7.5 g/l) at 125 ml/m²/hr. After the completion of the CISplatin infusion, begin D₅NS and mannitol (7.5 g/l) and 8 mEq MgSO₄/l at 125 ml/m²/hr x 8 hours. IV fluids should then be changed to D5 1/2 NS + 20 mEq KCl/l + 8 mEq MgSO₄/l at 125 ml/m²/hr to complete 24 hours of hydration (until first dose of cyclophosphamide). Urine output of at least 3 ml/kg/hr should be achieved prior to CISplatin infusion and maintained for at least 8 hours following completion of the infusion. Mannitol 0.5 g/kg may be used to maintain urine output. If a mannitol bolus fails to increase urine output over the ensuing hour, then furosemide 1 mg/kg IV should be given as a bolus. Four hour input and output totals should be maintained within 20% of each other.

Oral magnesium supplementation following CISplatin administration may be necessary. Electrolytes (i.e., Mg, Ca, PO₄, K) should be followed closely thereafter.

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

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

VinCRISTine: IV push over 1 minute (or infusion via minibag as per institution policy) 1.5 mg/m²/day (maximum single dose 2 mg) on Days 1 and 8. The absolute doses of vincristine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg.

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

FATAL IF GIVEN INTRATHECALLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For intravenous use only."

Medication errors have occurred due to confusion between vinCRISTine and vinBLASTine.

Cyclophosphamide: IV over 1 hour

1000 mg/m² on Day 2 and Day 3. On Day 2, cyclophosphamide should be given at least 24 hours after CISplatin. Urine output should be maintained at a minimum of 3 ml/kg/hr. Hydration is continued with D5 1/2NS plus 20 mEq/L KCl at 100 mL/m² per hour. After second dose of cyclophosphamide, hydration should be continued for a minimum of 8 hours and until patient maintains normal PO intake. Note: nausea and vomiting are likely and prolonged IV fluids may be necessary to prevent dehydration and maintain electrolyte balance.

Filgrastim (G-CSF): SubQ or IV (SubQ preferred)

5 micrograms/kg/day daily starting on Day 4 and continue for at least 10 days until post-nadir ANC > 1500µL. Filgrastim must be discontinued for a minimum of 24 hours prior to next chemotherapy cycle if counts have recovered.

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

4.4.1 ACNS0332: Regimen C and Regimen D Maintenance (With Isotretinoin)

Four consecutive weeks (28 days) will constitute one cycle. Use one copy of the TDM for each cycle (please note cycle number).

Patient name or initials

DOB

Begin each subsequent cycle of Maintenance on Day 29 when ANC $\geq 1000/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$ and the patient must have been off G-CSF for at least 24 hours, liver functions tests Grade 2 or less (SGPT $< 5 \times$ normal), calcium and uric acid normal, renal function with normal creatinine for age (see Section 3.2.8.1), skin toxicity no greater than Grade 1, serum triglycerides $< 300 \text{ mg/dL}$ and no hematuria or proteinuria on urinalysis for a total of 6 Cycles. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Isotretinoin (Cis-Retinoic Acid) (ISOT)	PO	80 mg/m ² /dose twice daily	Day 1 and Days 16-28	Total Daily dose 160 mg/m ² /day. Doses should be rounded down to the nearest 10 mg. See Administration Guidelines (Section 4.4)	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus, h. SGOT, SGPT, Alkaline Phosphate, Bilirubin i. Creatinine Clearance or GFR j. Urinalysis k. Thyroid Function l. Total Protein, Albumin, Triglycerides, Uric Acid m. Pregnancy Test
CISplatin (CDDP)	IV over 6 hours	75 mg/m ²	Day 1	See Administration Guidelines (Section 4.4)	* If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M ₃). See Section 7.4 for a complete list of observations. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE
VinCRISTine (VCR)	IV Push over 1 minute or infusion via minibag as per institutional policy	1.5 mg/m ² (maximum dose 2 mg)	Days 1 and 8	The absolute doses of vinCRISTine to be delivered are a function of body surface area, rounded down to the nearest 0.1 mg.	
Cyclophosphamide (CPM)	IV over 1 hour	1000 mg/m ²	Days 2 and 3	See Administration Guidelines (Section 4.4)	
Filgrastim (G-CSF)	SubQ or IV (SubQ preferred)	5 micrograms/kg/day	Start on Day 4 and continue for at least 10 days until post-nadir ANC $> 1500/\mu\text{L}$. Filgrastim must be discontinued for a minimum of 24 hours prior to next chemotherapy cycle if counts have recovered.	Do not start the next cycle of chemotherapy until at least 24 hours after Filgrastim has been stopped. Filgrastim may be given concomitantly with vincristine.	

Regimen			Cycle		Ht		cm		Wt		kg		BSA		m ²			
Date Due	Date Given	Week	Day	ISOT ____mg		CDDP ____mg		VCR ____mg		CPM ____mg		G-CSF ____mcg		Studies		Comments (Include any held doses, or dose modifications)		
					Enter calculated dose above and actual dose administered below													
		1	1	____mg____mg		____mg		____mg						a, e, f, g, h, i%, j, l, m\$(b, c@, d#)##				
			2							mg								
			3							mg								
			4									mcg						
		2	8					mg						f+, g, h				
		3	15											f+, g, h				
			16	mg mg										j, (h, g, l)**				
			17	mg mg														
			18	mg mg														
			19	mg mg														
			20	mg mg														
			21	mg mg														
		4	22	mg mg										f+, g, h				
			23	mg mg														
			24	mg mg														
			25	mg mg														
			26	mg mg														
			27	mg mg														
			28	____mg____mg										f+, g, h (a, b, c@, d#, e, f, g, h, k)&				
			29					Begin Next Cycle of Maintenance on Day 29 and when criteria above have been met for a total of 6 cycles..										

+ If counts are low and while on Filgrastim, it is recommended that CBCs be performed twice weekly.

Indicate last day of G-CSF _____

@ Spinal imaging is only necessary for patients with M₁ – M₃ disease.

Required only for patients who are positive at diagnosis.

\$ Female patients must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription. See Section 6.5.

% Obtain if creatinine is greater than normal for age (see Section 3.2.8.1)

& Obtain within 1 month of completing Maintenance (Cycle 6).

Obtain prior to Cycle 4

** Obtain only SGPT, triglycerides, serum creatinine, calcium and uric acid.

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

4.5 **Regimen C or D Isotretinoin Continuation Therapy Cycles 7-12**

Patients randomized to Isotretinoin Continuation Therapy will receive 80 mg/m² twice daily on Days 15-28 in 28 day intervals for a total of 12 cycles beginning concurrently with Maintenance chemotherapy and continuing for approximately six months after completion of chemotherapy.

Begin each subsequent cycle of Continuation on Day 29 and when ANC \geq 1000/ μ L, platelets \geq 100,000/ μ L, liver functions tests Grade 2 or less (SGPT $<$ 5 x normal), calcium and uric acid normal, renal function with normal creatinine for age (see Section 3.2.8.1), skin toxicity no greater than Grade 1, serum triglycerides $<$ 300 mg/dL and no hematuria or proteinuria on urinalysis and off Filgrastim for 24 hours for a total of 6 Cycles.

Isotretinoin (13-Cis Retinoic Acid): PO

80 mg/m²/dose twice daily for a total of 160 mg/m²/day on Days 15-28. Doses should be rounded down to the nearest 10 mg.

The dose of isotretinoin can be repeated if the child vomits within 30 minutes of taking the dose and the capsules can be seen in the vomitus. If the child takes the medicine in any other form except as a whole capsule(s), it should not be repeated.

To enhance absorption, administer capsules with high fat food (such as ice cream or peanut butter) or with milk. Isotretinoin capsules should be swallowed whole whenever possible. If not possible, for ease of swallowing, the capsules can be punctured and the contents squeezed into a high fat food immediately before administration or the capsules can be softened or punctured and chewed (best absorbed if chewed with high fat food). Isotretinoin should not be removed from the capsules for more than one hour prior to administering to the patient. See additional information in the drug monograph. Directions for accessing the drug monograph is available in Section 6.0.

MUST be prescribed under the Committed to Pregnancy Prevention Program (iPLEDGE) (see drug monograph). Pregnancy risk factor X. Pregnant women should not handle isotretinoin. Women of childbearing potential should wear gloves when handling isotretinoin capsules. Patients should be warned about photosensitivity; the use of sunscreen and avoiding exposure to direct sunlight should be recommended.

Patients with history of clinical depression prior to diagnosis or suicidal ideation should not receive Isotretinoin (Cis-retinoic acid).

Each cycle should begin on Day 29 and when the criteria below have been met.

Criteria to Begin Isotretinoin:

- a. SGPT (ALT) $<$ 5 X upper limit of normal
- b. Skin toxicity no greater than Grade 1
- c. Serum triglycerides $<$ 300 mg/dL
- d. No hematuria or proteinuria on urinalysis
- e. Serum creatinine within normal limits for age
- f. Normal calcium and uric acid

4.5.1 ACNS0332: Regimen C and Regimen D Continuation (With Isotretinoin)

Four consecutive weeks (28 days) will constitute one cycle. Use a copy once for each cycle (please note cycle number).

Patient name or initials

DOB

Begin Next Cycle of Continuation on Day 29 and when ANC $\geq 1000/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$ (Section 5.2.2.1), liver functions tests Grade 2 or less (SGPT $< 5 \times$ normal), calcium and uric acid normal, renal function with normal creatinine for age (see Section 3.2.8.1), skin toxicity no greater than Grade 1, serum triglycerides $< 300 \text{ mg/dL}$ and no hematuria or proteinuria on urinalysis for a total of 6 Cycles. The Therapy Delivery Map is on **one page**.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Isotretinoin (Cis-Retinoic Acid) ISOT	PO	80 mg/m ² /dose twice daily (160 mg/m ² /day)	Days 15-28	Doses should be rounded down to the nearest 10 mg. See Administration Guidelines	a. Physical and Neurologic Exam, Weight b. MRI of Brain with and without Gadolinium c. MRI of Spine with Gadolinium d. Lumbar CSF Cytology* e. Audiogram f. CBC, Differential, Platelets g. Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus, h. SGOT, SGPT, Alkaline Phosphate, Bilirubin i. Creatinine Clearance or GFR j. Urinalysis k. Thyroid Function l. Total Protein, Albumin, Triglycerides, Uric Acid *- If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M ₃). See Section 7.4 for a complete list of observations. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Regimen				Cycle	Ht	cm	Wt	kg	BSA	m ²
Date Due	Date Given	Week	Day	ISOT mg		Studies		Comments (Include any held doses, or dose modifications)		
				Enter calculated dose above and actual dose administered below						
		1	1			a, e, f, g, h, l, j (b, c@)#				
		3	15	mg	mg	j, (h, g, l)**				
			16	mg	mg					
			17	mg	mg					
			18	mg	mg					
			19	mg	mg					
			20	mg	mg					
			21	mg	mg					
		4	22	mg	mg					
			23	mg	mg					
			24	mg	mg					
			25	mg	mg					
			26	mg	mg					
			27	mg	mg					
			28	mg	mg	(a, b, c\$, d@, e, f, g, h, l, j, k) &				
			29			Begin Next Cycle of Continuation on Day 29 and when criteria above have been met.				

Obtain prior to Cycle 10

\$ Spinal imaging is only necessary for patients with M₁ – M₃ disease.

@ Required only for patients who are positive at diagnosis

& Obtain within 1 month of completing Continuation Therapy (4 weeks after completing Cycle 12)

** Obtain only SGPT, triglycerides, serum creatinine, calcium and uric acid.

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

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Dose Modifications During Radiation Therapy

5.1.1 Vincristine

5.1.1.1 Neurotoxicity

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

5.1.1.2 Jaw Pain

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

5.1.1.3 Hepatotoxicity

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

5.1.2 Carboplatin (Regimen B and D)

5.1.2.1 Hematologic Toxicity

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

5.1.2.2 Nephrotoxicity

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

5.2 Dose Modifications during Maintenance Chemotherapy

5.2.1 Vincristine

5.2.1.1 Neurotoxicity

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

5.2.1.2 Jaw Pain

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

5.2.1.3 Hepatotoxicity

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

5.2.2 Cyclophosphamide

5.2.2.1 Hematological Toxicity

If chemotherapy is due and the absolute neutrophil count is below 750/ μ L or the platelet count is less than 75,000/ μ L, the next cycle of chemotherapy should be delayed. Repeat CBC and platelet count twice-weekly. The next cycle of therapy should be administered when the ANC >750 and the platelet count >75,000, but the dose of cyclophosphamide should be reduced by 25% to 750 mg/m²/dose (i.e. each daily dose should be reduced by 25%).

If the ANC is above 750/ μ L but below 1,000/ μ L or the platelet count is > 75,000/ μ L but below 100,000/ μ L, the next cycle of therapy should be administered, but the dose of cyclophosphamide should be reduced by 25% to 750 mg/m²/dose (i.e. each daily dose should be reduced by 25%).

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

5.2.2.2 Bladder Injury

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

5.2.2.3 Renal Dysfunction

If estimated creatinine clearance (by Schwartz formula for children or radioisotope GFR) is < 10 ml/min/1.73 m², reduce the dose of cyclophosphamide by 25% to 750 mg/m²/dose (i.e. administer 75% of the full dose.)

5.2.3 Cisplatin

5.2.3.1 Nephrotoxicity

If the creatinine clearance or GFR is < 60 ml/min/1.73 m², then the cisplatin should not be given. If the creatinine clearance or GFR improves to >60 ml/min/1.73 m², cisplatin should be reinstituted at 50% (37.5mg/m²/dose) dosage for the next two cycles of chemotherapy. After two cycles of therapy with stable creatinine clearance (>60 ml/min/1.73 m²), cisplatin should be given at full doses.

5.2.4 Ototoxicity

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

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

If there is a disparity between ears, the grading should reflect the better ear. For Grade 0 ototoxicity, no dose modification should be made. For Grade 1 ototoxicity (defined as a > 25 db loss at > 4 KHz, asymptomatic) a 25% reduction to 56 mg/m²/dose should be made in cisplatin dosage. For Grade 2 ototoxicity (defined as a > 25 db loss at 4 KHz, tinnitus) an additional 25% reduction (to 42 mg/m²/dose) in cisplatin should be made if previously reduced or a 50% reduction (to 37.5 mg/m²/dose) in cisplatin dose should be made. For Grade 3 and 4 ototoxicity (defined as a > 25 db loss at 2 KHz and ≥ 40 db loss at 2 KHz) cisplatin should be deleted and not restarted.

5.2.5 Hypomagnesemia

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

5.3 **Modifications for Toxicity for Isotretinoin (Regimen C and D)**

5.3.1 Hematologic and Non-Hematologic Toxicities

A dose reduction of 25% (60 mg/m²/dose or 120 mg/m²/day) for subsequent cycles should be made for the occurrence of any Grade 3 or 4 toxicities EXCLUDING: Grade 3 or 4 hematologic, Grade 3 alanine aminotransferase (ALT or SGPT) or aspartate aminotransferase (AST or SGOT), Grade 3 nausea, Grade 3 vomiting, or Grade 3 fever. If the same Grade 3 or 4 toxicity recurs at a 25% dose reduction, then decrease dose by another 20% (48 mg/m²/dose or 96 mg/m²/day). If the same Grade 3 or 4 toxicity recurs after two dose reductions, then discontinue Isotretinoin.

5.3.2 Timing of Next Cycle

If criteria to begin next cycle are not met by the date cycle is due to begin, delay cycle for one week. If criteria still not met, hold therapy until criteria are met, and treat at 25% (60 mg/m²/dose or 120 mg/m²/day) dose reduction. An additional dose reduction to 50 mg/m²/dose or 100 mg/m²/day should occur if criteria are not met within one week after due date for subsequent cycles.

5.3.3 Renal Function

If serum creatinine increases by > 50% in any cycle of therapy, creatinine clearance or GFR should be done prior to starting next cycle, and a urinalysis. If creatinine clearance and/or GFR are < 50 cc/min/1.73 m², hold Isotretinoin. Isotretinoin may be restarted in the next cycle if creatinine clearance and/or GFR are > 50 cc/min/1.73 m².

5.3.4 Hematuria, Proteinuria and/or Hypertension

If patient develops hematuria, proteinuria, and/or hypertension during any cycle of therapy, hold medication and restart in the next cycle. If these symptoms recur and pose risk to the patient, discontinue isotretinoin.

5.3.5 Cheilitis

For localized cheilitis, apply topical Vitamin E to lips for subsequent cycles. If this does not control symptoms sufficiently to allow sufficient oral intake, then decrease dose by 25% (60 mg/m²/dose or 120 mg/m²/day).

5.3.6 Serum Triglycerides (Hypertriglyceridemia)

If serum triglycerides are > 500 mg/dl when next cycle is due, start patient on medical therapy for serum triglyceride reduction and begin at the same dosage. If serum triglycerides are < 500 mg/dl by the time subsequent cycle is due, then continue at same dosage. If triglycerides are still > 500 mg/dl after one cycle on medical therapy, then reduce dose by 25% (60 mg/m²/dose or 120 mg/m²/day) for subsequent courses.

6.0 DRUG INFORMATION

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

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

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

7.1 Required Observations, Pre-Treatment and During Radiation Therapy for Regimens A & C

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

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

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

@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M₃).

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

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

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

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

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

@ Ventricular CSF (either pre-or post-op) may be used only if a post-operative spinal tap is contraindicated. If a spinal tap is contraindicated and there is no ventricular CSF available, then CSF cytology can be waived for patients with supratentorial tumors or if there is documentation of spinal subarachnoid metastases (M₃).

7.3 Required Observations During Maintenance Chemotherapy for Regimens A and B

Evaluation	Prior to Each Cycle		During Each Cycle	Prior to Cycle 4	1 Month After Cycle 6	Relapse/Disease Progression
Physical (Ht, Wt, BSA)/Neurologic exam	X				X	X
CBC with Diff, Platelets,	X		Weekly ⁺		X	X
Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus	X		Weekly		X	
SGOT, SGPT, Alkaline Phosphate, Bilirubin	X				X	
Creatinine Clearance or GFR	X##					
Urinalysis	X					
Audiogram (See Section 5.2.4 for Grading Scale)	X				X	
MRI of the head (T2-weighted imaging and T1-weighted imaging pre-and post- contrast) and spine with contrast				X*	X*	X
CSF cytology				X [#]	X [#]	X
Thyroid Function Evaluation (Free T ₄ and TSH)					X	

* Spinal imaging is only necessary for patients with M₁ – M₃ disease.

Required only for patients who are positive at diagnosis.

+ If counts are low and while on Filgrastim, it is recommended that CBCs be performed twice weekly.

Obtain if creatinine is > normal for age see Section 3.2.8.1.

7.4 Required Observations During Maintenance and Continuation Chemotherapy for Regimens C and D (With Isotretinoin)

Evaluation	Prior to Each Cycle	During Each Cycle	Prior to Cycle 4	1 Month After Cycle 6	Prior to Each Continuation Cycle (Cycles 7-12)	Prior to Starting Isotretinoin (Day 15 or 16)	1 Month After Continuation Therapy	Relapse/ Disease Progression
Physical (Ht, Wt, BSA)/Neurologic exam	X			X	X		X	X
CBC with Diff, Platelets	X	Weekly+		X	X		X	X
Electrolytes, Ca, Magnesium, Creatinine, BUN, Phosphorus	X	Weekly		X	X	X++	X	
SGOT, SGPT, Alkaline Phosphate, Bilirubin	X	Weekly		X	X	X++	X	
Total Protein, Albumin, Triglycerides, Uric Acid	X				X	X++	X	
Creatinine Clearance or GFR	X##							
Urinalysis	X				X	X	X	
Audiogram (See Section 5.2.4 for Grading Scale)	X			X			X	
MRI of the head (T2-weighted imaging and T1-weighted imaging pre-and post- contrast) and spine with contrast			X*	X*	X@,*		X*	X
CSF Cytology			X#	X#			X#	X
Thyroid Function Evaluation (Free T ₄ and TSH)				X			X	
Pregnancy Test	X**							

* Spinal imaging is only necessary for patients with M₁ – M₃ disease.

Required only for patients who are positive at diagnosis.

+ If counts are low and while on Filgrastim, it is recommended that CBCs be performed twice weekly.

& Obtain within 4 weeks of completing Cycle 12

@ Obtain prior to Cycle 10.

Obtain only if creatinine is > normal for age see Section 3.2.8.1.

** Female patients must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane prescription

% Obtain within 2 weeks of starting Maintenance

++ Obtain only SGPT, triglycerides, serum creatinine, calcium and uric acid.

7.5 Required Observations Following Therapy

Evaluation	3 mos	4 mos	6 mos	8 mos	9 mos	12 mos	15 mos	16 mos	18 mos	20 mos	21 mos	2.0 yrs	2.5 yrs	3.0 yrs	3.5 yrs	4.0 yrs	Annually	At Relapse Disease Progression
History, Physical with Neurologic Exam	X		X		X	X	X		X		X	X	X	X	X	X	X	X
Liver Function, BUN, Creatinine, Electrolytes (Ca, Mg), CBC	X		X		X	X	X		X		X	X	X	X	X	X	X	
MRI of head (with contrast)	X		X		X	X	X		X		X	X	X	X	X	X	X	X
Spinal MRI (with contrast)*	X\$		X\$		X\$	X\$	X\$		X\$		X\$	X\$	X\$	X\$	X\$	X\$	X\$	X
Lumbar CSF Cytology		X\$		X\$		X\$		X\$		X\$		X\$	X\$	X\$		X\$	X\$	X
Audiogram			X			X			X			X		X		X	X	
Thyroid Function Evaluation (Free T ₄ and TSH)			X			X						X		X		X	X	
LH, FSH, estradiol or testosterone						X						X		X		X	X	
Serial Measurment of Height (Stature)%			X			X						X		X		X	X	

* Spinal MRI should include complete spine (cervical, thoracic, lumbar and sacral)

% Refer to endocrinologist if a growth below the 3rd percentile, drop in height percentile on growth grid, growth velocity <4-5cm/yr in childhood or lack of pubertal growth spurt

\$ Obtain if initially positive. Patients with M1-M3 disease require the more frequent scans.

7.6 Optional Studies

7.3.1 Neuropsychologic Evaluations

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

8.0 SUPPORTIVE CARE GUIDELINES

These are provided for institutional consideration. Investigator discretion should be used, and individual considerations made for specific patient situations and institutional practices. Patients may receive supportive care as clinically indicated. Supportive care for any reason, including care of complications arising from the cancer, adverse reactions, or other underlying diseases, must be recorded through resolution of the event. The Study Chair may be called with any questions or problems. Please also see the COG Supportive Care Guidelines at:

https://members.childrensoncologygroup.org/prot/reference_materials.asp and the *Supportive Care of Children with Cancer, 2004 ed., Arthur R. Altman, M.D.*

8.1 Venous Access

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

8.2 Antiemetics

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

Dexamethasone may be used for delayed nausea and vomiting.

8.3 Fever and Neutropenia

Patients who develop a fever greater than 38.5°C should be evaluated for neutropenia and infection. Blood cultures should be drawn and antibiotics should be administered per institutional policy. Aminoglycosides should be avoided if possible to decrease the chance of ototoxicity.

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

8.4 Prophylactic Antibiotics

Patients who receive chemotherapy should be started on trimethoprim/sulfamethoxazole (TMP/SMZ) at trimethoprim 2.5mg/kg/dose twice daily on 2 or 3 sequential days per week or per primary care institution's protocol for *Pneumocystis carinii* prophylaxis. TMP/SMZ can be discontinued 3 months after chemotherapy has been discontinued. Patients with TMP/SMZ allergy should be treated with

dapsone or pentamidine. Additional treatments and information can be found in the COG Supportive Care Guidelines (see above).

8.5 **Azole Anti-fungal Agents**

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

8.6 **Blood Products**

8.6.1 Irradiation

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

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

8.6.2 Platelets

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

8.6.3 Red Blood Cells

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

8.7 **Nutritional Support**

Any patient with greater than 10% weight loss should begin megestrol (Megace) at 5 mg/kg/dose twice daily or nutritional support either enterally or via a central venous catheter with parenteral hyperalimentation. Patients should have their magnesium checked frequently and be supported with magnesium supplementation if necessary.

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

9.1 **Criteria for Removal from Protocol Therapy**

- a) Progressive disease.
- b) Refusal of further protocol therapy by patient/parent/guardian.
- c) Completion of planned therapy.
- d) Physician determines it is in patient's best interest.
- e) Development of a second malignant neoplasm (SMN)

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

9.2 Off Study Criteria

- a) Death.
- b) Lost to follow-up.
- c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g. at recurrence)
- d) Withdrawal of consent for any further data submission.
- e) Tenth anniversary of study entry.

10.0 STATISTICAL CONSIDERATIONS

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

10.1 Design Considerations

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

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

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

10.2 Patient Accrual

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

10.3 Study Duration

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

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

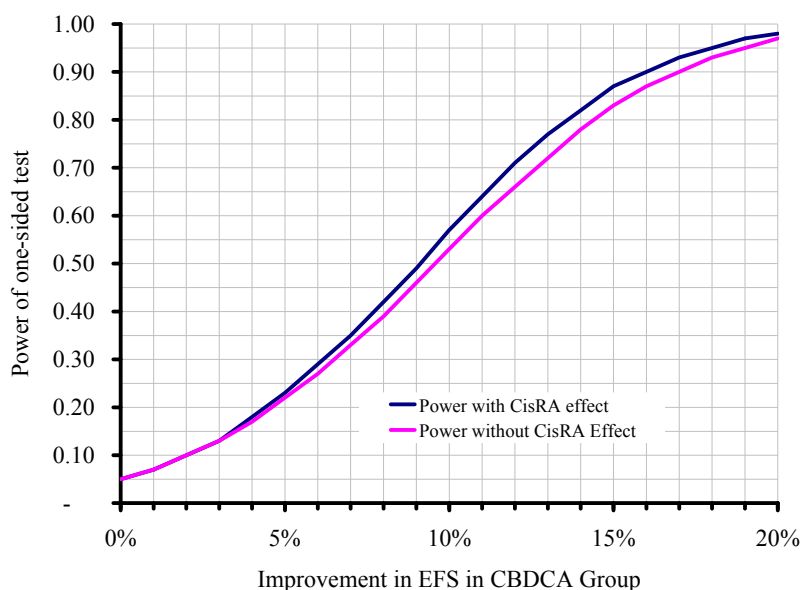
10.4 Study Endpoints For Analysis Of Treatment Efficacy

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

10.5 Statistical Analysis Of Difference In Long-Term EFS Rate

The main study analysis will be based a stratified logrank test,⁴⁰ with stratification on all randomization stratifiers (below) as well as on the factorial treatment group not the subject of the analysis. Good approximation to the power of these test are obtained using the methods of Sposto and Sather.⁴¹

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



10.6 Interim Monitoring

Monitoring for differences in long-term EFS will be based on the same one-sided likelihood ratio test as described above. Interim monitoring rules will be devised according to the methods of Lan-Demets.⁴² To detect substantial *increases* in efficacy due to the addition of either CBDCA or Isotretinoin, the 5% Type I error will be spent at a rate of αt^2 , where t is the appropriate information-time scale. To detect substantial *decreases* in efficacy due to either of these additions, a 20% Type I error rate will be used, with error spent at a rate of αt . Interim monitoring analyses are planned at least after 2, 3, 4, and 5 years of the study. Monitoring after 5 years is not planned, because all patients on the trial will have completed treatment.

Previous studies that utilized full dose craniospinal irradiation followed by cisplatin-based maintenance therapy showed approximate 25% to 30% grade 3 and 10% grade 4 ototoxicity (personal communication with Dr. Roger Packer). The occurrence of excessive grade 4 ototoxicity rates at any time during therapy will constitute a primary endpoint for safety monitoring. A grade 4 ototoxicity rate that exceeds $p_0=15\%$ will be considered unacceptable. A Bayesian monitoring rule with prior density Beta (2,12) on the probability p of ototoxicity rate will be used as a trigger for careful assessment of excess hearing loss. The prior has median $p=0.125$ and mean $p=0.14$, with approximately 95% of support less than $p=0.32$. A posterior probability $P(p > p_0 | \text{data}) > 85\%$ will satisfy the monitoring criterion. This represents 85% certainty that the ototoxicity rate exceeds p_0 given the data and the assumed prior density. Ototoxicity rates will be monitored separately in each of the two chemotherapy induction groups. Operationally, the monitoring criterion will be satisfied if 4 patients developing grade 4 ototoxicity in the first 10 patients, or $\geq 6/20$, $\geq 8/30$, etc. If the monitoring criterion is satisfied, an immediate clinical review of the cause and timing of the hearing loss will be undertaken. In frequentist viewpoint, this criterion will be satisfied 9% of time if $p=11\%$ and 94% of time if $p=20\%$ assuming we have $n=150$ patients.

10.7 Statistical Analysis of the Post-RT Response

In CCG-99701, 50/146 patients (34%) had residual tumor measuring at least 1.5 cm^2 . These are the patients who will be evaluable for post-RT response assessment. Hence, approximately 100 patients in the current study, 50 each receiving XRT alone or XRT+CBDCA, will be evaluable for this endpoint. Using a two-sided test of proportions with Type I error 5%, this sample size will provide at least 80% power to detect a 30%

difference in post-RT response rate between the two treatment groups. There will be no interim monitoring based on this endpoint.

10.8 Stratification

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

10.9 Neuropsychological and Quality of Life

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

Descriptive statistics, including means, standard errors, medians, inter-quartile ranges, proportions, will be used to characterize the overall QOL and NP outcome for patients. Descriptions at baseline will estimate the acute effects of the tumor before the onset of treatment effects, and descriptions at follow up periods will estimate the long-term effects of the tumor and its treatment. The raw scores obtained in this study population, for example, the Processing Speed Indices from the WISC-IV or WAIS-III, will be compared with established population test norms provided in the scoring tables of the manuals. Test variables of the instruments, for example, nonverbal skills and processing speed, will be compared on the basis of intercorrelations. Using two-sample t tests for continuous variables and Pearson's χ^2 test for categorical variables, the intervention and the control arms will be compared in terms of clinical characteristics at the time of randomization, and in terms of baseline QOL and NP scores. Data-reduction strategy, such as factor analysis can be used to reduce the overall number of statistical comparisons and thus minimize inferential errors associated with multiple univariate tests of dependent variables.

For patients who have baseline and at least two follow up evaluations, a growth curve model, which is a particular variant of random-effects models, will be utilized. This approach treats data from different patients as statistically independent and data from the same patient as correlated. Growth curve models emphasize the explanation of within-person variation over time by a natural developmental process. The growth curve model allows an estimation of the average rate of change (or slope) over time for patients within the total group, as well as an estimation of the differences in the slopes between subgroups. Growth curves for patients will be averaged, and comparisons will be made between those who receive intervention and those who do not, controlling for variables such as age at diagnosis, sex, race/ethnicity and treatment related factors.

10.9.1 Sample Size Calculation

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

10.9.2 Subject Attrition and Missing Data

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

10.10 **Laboratory Correlates**

Please refer to Section 16 for statistical considerations related to Biology Aims 1-4.

10.11 **Gender and Ethnicity Considerations**

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

Expected Accrual by Sex and Race/Ethnicity

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	12	18	30
Not Hispanic or Latino	110	160	270
Ethnic Category: Total of all subjects	122	178	300
Racial Category			
American Indian or Alaskan Native	1	2	3
Asian	4	6	10
Black or African American	7	11	18
Native Hawaiian or other Pacific Islander	1	1	2
White	109	158	267
Racial Category: Total of all subjects	122	178	300

11.0 EVALUATION CRITERIA

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

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

11.2 Methodology to Determine Tumor Measurement

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

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

(See drawing below for illustration)

1. Longest diameter of target lesion(s) should be selected in the axial plane only for CT. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) – tumor extent in the plane perpendicular to the selected plane)

Figure 11.1: COG Guidelines for Measurement of Tumor Size

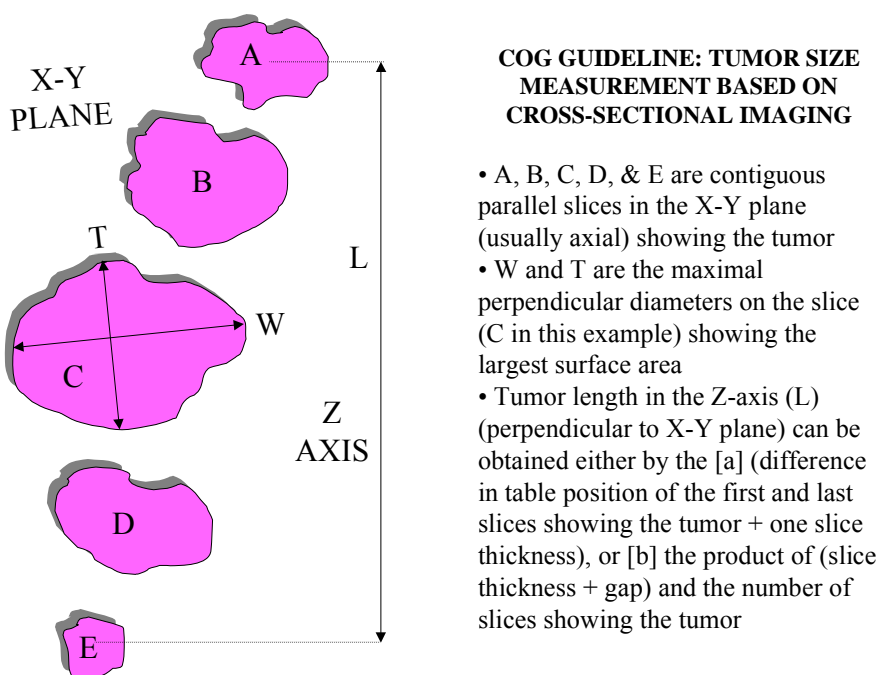


Table 11.1: RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")
(Modified from Appendix II, Table 2, JNCI 92:213, 2000)

Response	Diameter, 2R	Product, (2R)²	Volume, 4/3pR³
	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%
Disease Progression	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

4. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be "measurable".

Options:

- if the cyst/necrosis is eccentric, the W, T and L of the solid portion should be measured, the cyst/necrosis excluded from measurement
 - if the cyst/necrosis is central but represents a small portion of the tumor (<25%), disregard and measure the whole lesion
 - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured
5. Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted, change in extent/thickness assessed on follow up studies.
6. Overall Response Assessment

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

Table 11.2 Overall Response Assessment

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

CR – Complete Response

PR – Partial Response

SD – Stable Disease

PD – Progressive Disease

IR – Incomplete Response

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

11.3 Selection of Target and Non-Target Lesions

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

11.4 Response Criteria for Target Lesions

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

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

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

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

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

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

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

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

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

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

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

11.5 Response Criteria for Non-target Lesions

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

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

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

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

12.2 Determination of Reporting Requirements

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

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

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

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

12.3 Reporting of Adverse Events for Commercial Agents - AdEERS abbreviated Pathway

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the Drug Information Section of this protocol.

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

Table B

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

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days¹

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS
¹ This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is <u>not</u> due to cancer recurrence must be reported via AdEERS.			

12.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for AdEERS reporting.

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

13.0 RECORDS AND REPORTING

13.1 Categories of Research Records

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

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

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

13.2 CDUS

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

14.0 SURGICAL GUIDELINES

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

14.1 Neurosurgical Procedure

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

14.1.1 Types of Surgery

A craniotomy is necessary to remove the bulk of the tumor, to re-establish CSF flow through the fourth ventricle, and to establish a tissue diagnosis. When feasible, an attempt will be made to perform a gross total tumor removal; if not feasible, an attempt will be made to remove as much tumor as possible without jeopardizing the patient. Eligible patients are strongly encouraged to undergo resection of residual tumor prior to radiation therapy. Biopsies alone, with no attempt at resection, may be associated with statistically worse survival and should not be done. No patient will be eligible for this study without a pathologic diagnosis. The surgical procedure may be carried out in any position in which the neurosurgeon feels comfortable; i.e. sitting, prone, or park bench.

14.1.2 Opening the Dura

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

14.1.3 Leptomeningeal Examination

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

14.1.4 Hemostatic Agents in the Intra-operative Field

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

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

14.1.5 Pathology Studies

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

14.1.6 Biology Studies

Please note that the biology studies in this protocol request approximately 2 grams (2 cc) of tissue, divided into fixed, snap frozen, and fresh tissue shipped in tissue culture media. Because the fresh tissue must remain sterile, please coordinate tissue handling with the pathology service and refer to tissue submission guidelines in Section 16.1. In many institutions, the responsibility for obtaining consent for biology studies (ACNS02B3 consent) will be the responsibility of the surgeons because it is necessary to obtain consent prior to surgery.

14.1.7 Ancillary Neurosurgical Procedures

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

14.2 **Shunts**

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

14.3 **Assessment of Residual Tumor**

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

14.3.1 Size of Post-Surgical Residual Tumor

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

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

14.4 **Extent of Tumor Resection**

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

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

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

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

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

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

14.5 Imaging Confirmation of Extent of Resection

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

14.6 Peri-operative Corticosteroids

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

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

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

15.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

15.1 Neuropathology Goals

Precise histopathological diagnosis of tumors of primitive neuroepithelium.

15.2 Requirements for Handling Biopsy or Surgical Resection Tissue

15.2.1 Light Microscopy

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

15.2.2 Biology Studies

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

15.2.3 Autopsy Tissue

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

A complete autopsy report along with representative sections of residual tumor and/or metastases should be sent to the primary review pathologist. If available, snap frozen and fixed specimens of non-neoplastic cerebellum, cerebral cortex (frontal, parietal, occipital), basal ganglia, and pons should be sent to the Biopathology Center using guidelines in ACNS02B3. These tissues are valuable controls for biology studies

15.3 Pathology Review Materials

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

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

Required materials for continued inclusion in this study:

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

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

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

- Institutional pathology report
- Operative report
- Electron Microscopy Report, if available.
- Photographs of representative gross lesions, if available
- Specimen transmittal form (with each shipment).

*Paraffin blocks will be retained at the Biopathology Center unless the institution requests their return. For cases requiring urgent return of paraffin blocks to the primary institution, the referring institution should contact the Biopathology Center to request that initiation of the review process be expedited or blocks be returned immediately after completion of central review.

15.4 Central Review Process

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

Shipping

Send all materials for pathology review to:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, WA1340*
Columbus, Ohio 43205
Phone: (614) 722-2894
Fax: (614) 722-2897

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

16.0 SPECIMEN REQUIREMENTS FOR BIOLOGY STUDIES

16.1 Optional Biology Studies

Institutions are encouraged to enroll and submit specimens for ACNS02B3. If enough material is available to meet the biology requirements of this protocol and still have enough material left to meet minimal banking requirement for ACNS02B3, then the patient could receive credit for both this therapeutic trial and ACNS02B3. The minimum submission requirements for ACNS02B3 are tumor tissue (50 mg snap frozen or 50 mg fresh or OCT embedded) plus either a block or slides (2 H&E stained and 20 unstained).

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

16.1.1 Materials for Submission:

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

Snap Frozen Tissue: Submit as many 100-mg pieces of tumor tissue as possible. Wrap each piece of tissue in sterile foil and snap freeze in liquid nitrogen within 10 minutes of removal. A minimum of > 0.5 cm² is preferred. Label with the BPC Number, collection date and specimen type.

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

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

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

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

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

16.1.2 Shipment Of Fixed and Frozen Specimens

Biological specimens (other than fresh tissue which is sent to Dr. Olson) can be shipped to the BPC in a Specimen Procurement Kit. Specimen procurement kits must be shipped to the BPC, Monday through Thursday for delivery Tuesday through Friday since Saturday delivery is only available for fresh blood or bone marrow. The specimen procurement kit is constructed to allow shipment of frozen (**on dry ice**) and ambient temperature tissues in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both.** This kit contains most of the supplies necessary for shipping specimens to the BPC. Please call the BPC at 800-347-2486 in order to request specifically a Specimen Procurement Kit.

Before specimens are placed into the Specimen Procurement Kit, they need to be placed in several layers of packaging. Package the frozen and room temperature specimens separately so that they can be placed into separate compartments of the kit for shipping. First place specimens into a clear plastic secondary biohazard envelope with absorbent material. Next, place the secondary biohazard envelope into the white Tyvek pressure-proof secondary envelope.

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

Formalin fixed tissue is shipped at room temperature in the second compartment of the kit. Place the formalin fixed tissue (already packaged in the biohazard and Tyvek envelopes) into the kit compartment and then set the Styrofoam insert on top to secure specimens during shipment.

Include the specimen transmittal form and pathology report with the shipment. Put these forms in the plastic bag that contained the kit instructions and place the bag in the space between the Styrofoam container and the cardboard shipping box.

Close the outer lid of the Specimen Procurement Kit and seal the kit **securely** with filament or other durable sealing tape. Complete the pre-printed Federal Express air bill, insert into the plastic pouch and attach the pouch to the top of the kit. Complete the dry ice label (UN 1845). Stick the dry ice and Exempt Human Specimen labels to the side of the box.

Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, be sure to give the account number (1290 2562 0) on the pre-printed air-bill, but **stress** that pick-up is at your institutional address.

Send the Specimens to:

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

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

16.1.3 Shipment Of Fresh Specimens

Complete the Specimen Transmittal Form on the RDE and print a copy to send with the specimen. Label specimens with COG patient identification and the BPC Number (if available). Fax a copy of the transmittal form to Dr. James Olson at (206) 667-2917. Transport of fresh primary brain tumors should abide by the following guidelines to maximize the viability after transport. First, all fresh tumors should be sent **ON ICE OR ICE PACKS**. Also, while RPMI media is acceptable, DMEM-F12 with 10% FBS and Antibiotics and Antimycotics is far preferable. Please contact the Olson Lab at Brainumor@fhcrc.org to obtain frozen aliquots of this media. Also, please notify us (at the above address) as soon as a tumor is resected or ready for shipment; this allows us time to make the necessary preparations for specimen processing. Any further questions should be addressed to Brainumor@fhcrc.org.

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

James Olson, M.D., Ph.D.
Fred Hutchinson Cancer Research Center, Floor D4-275
1100 Fairview Avenue North
Seattle, WA 98109
Phone: (206) 667-4033 (request COG brain tumor technician)

Arrange for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355. Use the COG FedEx account Number (2504-6481-9).

16.2 Specific Aims

Biology studies are critical to the development of more effective and less toxic therapies and for the purpose of stratifying patients to the most appropriate treatment regimens. The biology study accompanying this trial aims to test candidate biomarkers of retinoid response prospectively to further

define mechanisms of retinoid resistance. In parallel with other COG medulloblastoma studies, the role of molecular markers for prediction of outcome will be assessed. Finally *ex vivo* cultures of fresh surgical specimens will be used to assess pre-clinical efficacy of new candidate therapeutics providing data for future clinical trial development.

The specific aims of the biology studies are:

1. To identify *ex vivo* prognostic indicators of therapy failure in high-risk medulloblastomas/SPNETs
2. To predict medulloblastoma outcome with molecular markers
3. To prioritize targeted therapies for future clinical trials
4. Tissue banking

16.3 **Aim 1. To identify *ex vivo* prognostic indicators of therapy failure in high-risk medulloblastomas/SPNETs**

The hypothesis being tested in Aim 1 is that tumors with cell autonomous resistance to carboplatin, cisplatin, and Isotretinoin are unlikely to respond to these agents *in vivo*.

Fresh tumor specimens are sent on the day of surgery by first a.m. express delivery to Dr. Olson's laboratory. Upon receipt, the tumor is mechanically dispersed into near single cell suspension. Medulloblastoma/PNET cells are separated from non-neoplastic (e.g., endothelial & blood cells) by magnetic beads coated with antibody against CD56 (nerve cell adhesion molecule). In this process, 20 μ L of anti-CD56-coated beads are mixed with 10^7 positive cells in 80 μ L media and incubated for 15 minutes. The magnetic beads with cells attached are sorted in a Miltenyi Biotec MACS MS column. Previous flow cytometry experiments show that this process yields a single population of cells that are uniform with regard to size and side scatter. Viability is assessed by trypan blue exclusion. Specimens with < 75% viability after sorting are excluded from further study because previous studies have shown that > 75% viability is necessary in order to clearly delineate active from inactive compounds. When cells are received within 24 hours of surgery and shipped properly, > 95% of cases meet these quality assurance parameters. When samples are delayed or shipped improperly, personal phone calls are made to the responsible colleague to prevent similar problems in future cases.

Cells are plated into 96 well plates that contain vehicle control, or the agents described below. Total vehicle is kept constant for each condition with the final concentration of DMSO of 1 part in 1000, a level that does not induce cell death or differentiation in our experiments. Two sets of vehicle (negative) control wells are included in every microassay plate. A mixture of etoposide (10 μ M), cisplatin (10 μ M), and cyclosporine A (25 μ M) is used for positive controls to ensure that endpoint assays are working. Relative viability compared to controls is assayed at 2 days using a highly sensitive ATP-luciferase assay that we have validated and now utilize routinely (ViaLight, Cambrex BioScience). Ongoing quality assurance tests include independent measures of cell death are obtained using Annexin V and propidium iodide staining as previously described.¹³ For statistical analysis, each specimen will be scored as "Responsive" or "Non-responsive" to the drug in the well. Based on preliminary data, tumor specimens will be classified as "responsive" if apoptosis in the presence of drug exceeds apoptosis in vehicle by at least 25% at 48 hours.

16.3.1 Correlation of Ex Vivo Resistance with Clinical Outcome

Using the *ex vivo* assay described above, triplicates of carboplatin (20 μ M- concentration), cisplatin (20 μ M), and Isotretinoin (5 μ M) will be compared to DMSO controls. Each specimen will be classified as responsive or non-responsive to each agent using criteria described above. The primary goal is to determine if *ex vivo* resistance to cisplatin, carboplatin and Isotretinoin correlates with treatment failure in

ACNS0332. This will be assessed by determining whether specimens that are resistant to all three agents *ex vivo* are disproportionately represented in the cohort of patients that show progressive or recurrent disease. Secondary analyses will focus on whether retinoid resistance *ex vivo* correlates with treatment failure among retinoid-treated patients and whether carboplatin resistance correlates with treatment failure among carboplatin-treated patients.

Statistical considerations

For the primary goal of determining whether *ex vivo* resistance to cisplatin, carboplatin and Isotretinoin correlates with treatment failure in ACNS0332: The following power calculations assume the analysis at the same time the analysis for the primary therapeutic study that includes 5 years of accrual and 1 year of additional follow-up. In addition, it is assumed that the reference group (no carboplatin, no 13-cis-RA) is best represented by a PCM with long-term (5 year rate) EFS rate of 55%.

The table below shows the increased 5-year EFS in patients with responsive tumors compared to those with non-responsive tumors that would be detectable with at least 80% power, using a two-sided score based on the Cox proportional hazards model with 5% Type I error rate. The table entries are EFS_{Res} / EFS_{NonRes} (diff), where ' EFS_{Res} ' is the 5-year EFS in patients with responsive tumors, ' EFS_{NonRes} ' the same for non-responsive tumors, and 'diff' is the difference between the two. Entries are provided for 20%, 50%, and 80% of tumors being responsive, as well as for 100, 150, or 200 of the 300 study patients having available tissue.

The rate of submission of adequate tissue specimens and the rate of successful testing for the various biological aims will be provided to the Study Committee and to the DSMC at regular intervals.

The table gives power for simplified two sample problem, and assumes no treatment effect for experimental arms. However, they are a reasonable approximation for the power for the Cox proportional hazards model adjusting for treatment factors in this case. Power was also calculated under the assumption one of the factors was positive in the primary therapeutic study. Power for each of the differences was reduced by approximately 2-5%.

**Detectable Differences with 80% power, two-sided 5% logrank test
As a function of % responsive tumors and sample size**

	20% Responsive	50% Responsive	80% Responsive
N=100	90.0% / 45.5% (45.5%)*	73% / 40.2% (32.8%)	67% / 28.7% (38.3%)
N=150	86% / 48.1% (39.7%)**	70% / 43.0% (27.0%)	64% / 33.1% (30.9%)
N=200	83% / 49.3% (33.7%)	68% / 44.6% (23.4%)	63% / 35.9% (27.1%)

*65% power.

**75% power

Secondary analyses compare carboplatin or Isotretinoin resistance *ex vivo* to patient outcome. Assuming 75 study patients having available tissue, we will have 80% power to detect a 37% increase in long-term EFS (41% to 87%) assuming 50% of tumors being responsive, and a 42% (35% to 77%) increase assuming 80% response rate, based on a two-sided logrank test with 5% Type I error rate.

16.3.2 Correlation of Ex Vivo Resistance with Neuropathologic Classification

If neuropathologic features correlate highly with *ex vivo* drug resistance to certain agents, then neuropathologic assessment could be substituted for *ex vivo* analyses in future clinical trials that involve those drugs. For example, if our preliminary data showing that anaplastic medulloblastomas are resistant to retinoids is confirmed in this larger study, and patients with anaplastic medulloblastomas show equal EFS in the presence or absence of Isotretinoin-containing maintenance therapy, then patients with

anaplastic disease should not be exposed to Isotretinoin in future trials. Drs. Peter Burger and Charles Eberhart will classify each medulloblastoma case as classic, nodular/desmoplastic or anaplastic using established criteria. They will also characterize the extent of nodularity/desmoplasia and anaplasia (i.e., focal or diffuse). Finally, in anaplastic tumors they will note if any “Large Cell” features are present.

Identification of molecular markers of *ex vivo* drug resistance

We hypothesize that molecular identifiers of *ex vivo* response to therapeutic agents can be identified in these molecular signatures. For this comparison, *ex vivo* response data will be treated in a manner analogous to clinical outcome data for identification of molecular determinants of *ex vivo* drug response. A training set of microarray profiles (from Aim 2) will be utilized to identify markers of drug resistance for each compound tested. Then, an independent test set will be utilized to prospectively determine whether the putative determinants predict *ex vivo* resistance.

For the purpose of future patient stratification, successful identification of molecular predictors of *ex vivo* response could be substituted for *ex vivo* experiments if certain drugs are to be avoided in patients that are unlikely to respond to them. In addition, the nature of the molecular predictors has potential to influence future mechanistic experiments related to drug resistance.

Statistical considerations

The statistical analysis of these data will be similar to the statistical analysis of microarray data with regard to clinical outcome as described in Aim 2. The primary differences are that 1) we anticipate using 50 cases for the training set and 100 for the test set and 2) *ex vivo* drug response will be substituted for EFS as the primary endpoint for analysis. The reduced sample size compared to Aim 1B will alter precision as follows: We assume there will be 100 specimens available for this analysis (150 less the 50 specimens used in the training set). Assume that 20% of these specimens (20 specimens) will respond *ex vivo*, and are relevant to the estimation of FPF, and 80% (80 specimens) will not respond, and are relevant to estimation of FNF. For observed FNF of 10%, the 95% confidence interval (CI) for this quantity will be approximately (5%, 18%). For observed FPF of 10% the 95% CI will be (1% to 30%). For FNF and FPF of approximately 50%, the 95% CIs will be (39%, 61%) and (27%, 73%), respectively. Assume that 50% of these specimens (50 specimens) will respond, and are relevant to the estimation of FPF, and 50% (50 specimens) will not respond, and are relevant to estimation of FNF. For observed FNF (or FPF) of 10%, the 95% confidence interval (CI) for this quantity will be approximately (3%, 21%). For FNF (or FPF) of approximately 50%, the 95% CI will be (37%, 63%).

16.3.3 To Test Whether Retinoid Resistance is Related to Transcriptional Induction of BMP2 or Suppression of OTX2

Data from the Olson laboratory shows that Isotretinoin induces apoptosis by transcriptional activation of BMP2, which in turn, induces phosphorylation of p38 MAPK leading to apoptosis. We hypothesize that retinoid resistance will correlate with an inability of Isotretinoin to transcriptionally induce BMP2 mRNA. In contrast to our finding, Dr. Hai Yan at Duke University recently published data suggesting that anaplastic large cell medulloblastomas were *more likely* to be retinoid sensitive than other types by virtue of the fact that the oncogene, OTX2, is amplified or overexpressed in most anaplastic medulloblastomas, that OTX2 reduction causes apoptosis and that all-trans RA causes downregulation of OTX2. Dr. Yan and our group will collaborate to resolve whether anaplastic medulloblastomas are retinoid sensitive or resistant *ex vivo* and whether this relates to transcriptional regulation of BMP2 or OTX2.

In parallel to the drug efficacy studies described above, wells of CD56-sorted medulloblastoma/PNET cells will be treated with Isotretinoin (5 μ M) or DMSO vehicle for 48 hours. Cells will be harvested, RNA isolated and cDNA generated. BMP2 levels will be assessed by quantitative RT-PCR using the

primers ATGTGGACGCTCTTTCAATGG (forward) and ACGCTAGAAGACAGCGGGTC (reverse) as previously published. BMP2 levels will be compared in Isotretinoin-treated and control cells. Tumors that undergo a greater than 2-fold induction in BMP2 expression with Isotretinoin treatment as compared to vehicle will be classified as responsive, those with a less than 2-fold induction as resistant. OTX2 mRNA levels will be measured in Isotretinoin-treated and DMSO control cells using the same approach described for BMP2. The forward primer will be AGCGCCGGGAGAGGACGAC and the reverse will be CTGTTGTTGGCGGCACTTAGC. These studies will be complemented by studies that assess whether BMP2 or retinoid receptor promoters are methylated in frozen tissue samples using a genome-wide denaturation analysis of methylation differences technique.

Twelve unstained slides from patients enrolled in ACNS0332 will be sent to Dr. Yan's laboratory at Duke for the analysis of OTX2 amplification by FISH and expression by immunohistochemical staining. Dr. Yan's group has identified a working OTX2 FISH probe from the human BAC clones containing the OTX2 genomic locus. To further evaluate the role of OTX2 amplification in medulloblastomas, he will analyze OTX2 gene copy number by using dual-color interphase FISH. Tumor sections will be cohybridized with an OTX2 genomic probe and a centromeric chromosome 14 probe, each covalently linked to different fluorophores, followed by counterstaining with DAPI. Monoclonal and polyclonal antibodies reacting against human OTX2 protein (R&D System) are commercially available. Optimization of OTX2 immunohistochemistry on paraffin-embedded tissue slides has been performed by using positive controls of medulloblastoma cases which express OTX2 mRNA evaluated by Q-PCR and OTX2 protein by Western blotting. Primary antibodies to OTX2 and a species- and isotype-specific negative control antibody will be run at the same concentration and under the same conditions on tissue sections.

Statistical Considerations

We assume that this section will utilize specimens from approximately 100 patients with high risk medulloblastoma/SPNET given this aim has lower priority than aim 1a and 1b and potentially fewer samples will be available. In determining the power of this study to address the major study questions, it is assumed that comparisons will be made between patients with indicator positive vs. indicator negative. We hypothesize that BMP2 induction or OTX2 suppression, are summarized as 0/1 indicator variables, with frequency of positivity (=1) of either 50%, to indicate a common attribute, or 10%, to indicate a rare attribute.

With 50% frequency of positivity, for two-sided tests at 0.05 significance, the table below shows the magnitude of difference (in the proportion with *ex vivo* response to retinoids) that would be detectable with power of 0.80. "Group 1" indicates the group with indicator positive and "Group 2" is the group with indicator negative.

Proportion with drug response

Group 1	Group 2
0.2	0.48
0.4	0.70
0.5	0.79

Similar assumptions are made for the power calculations with respect to EFS and survival comparisons (this is, two-sided 0.05 tests, two-way comparison with equally sized groups, 100 cases). Based on data from a similar cohort of patients, a 5 year EFS of about 0.55 can be anticipated for EFS. We will achieve 80% power if the two groups differed in their event-free survival plateau by 0.33 (0.40 vs. 0.73), this

corresponds to a hazard ratio of 2.91. The analysis will use the Cox model allowing for adjustment of treatment differences.

16.4 **Aim II. Predicting Medulloblastoma Outcome with Molecular Markers**

In the past decade, several developmentally regulated genes have been identified as markers that are highly and independently associated with medulloblastoma outcome. Initially, expression of the neurotrophin-3 receptor, *TrkC*, was found to be associated with favorable clinical outcome.⁴³⁻⁴⁵ Subsequently, increased expression levels of the neuregulin receptors *erbB2* and *erbB4* and of the immediate early gene *cMyc* were found to be highly correlated with poor outcome.⁴⁶⁻⁴⁹ Pomeroy et al.⁵⁰ recently extended these findings by demonstrating that predictors based on microarray gene expression profiles can predict clinical outcome with high statistical significance. Using oligonucleotide microarray-based gene expression profiling to monitor the expression of over 6800 genes in the tumors of 60 children with medulloblastomas, 5 – 20 marker gene predictors were found to be the most accurate outcome predictors to date, performing significantly better than clinical staging.

16.4.1 Optimizing and Validating Outcome Predictors

The basic strategy of developing an outcome predictor requires a “training set” of tumor samples that is used to define the expression levels of marker genes that are characteristic of each outcome (alive versus dead). The training set will be collected in the initial phase of this study. A validation step on a “test set” of tumor samples is then needed to show that the predictor developed with the training set accurately assigns unknown samples to the correct outcome class.⁵⁰ Validation of the predictors will be performed using the test set of samples collected during the second phase. Note that although the training and validation samples will be collected and assayed, the development of the classification rule and the validation of the rule will be performed after sufficient follow-up is available to provide the necessary precision for these analyses. From a practical standpoint, the collection of samples and their biological analysis will be performed on an ongoing basis during the time period of this clinical study. The results from the first 75 to 100 samples (the training set) will be used to establish the outcome predictor model and subsequent samples (the test set) will be used to validate these observations. The process can be summarized as follows:

- a) Collect tumor samples suitable for gene expression analysis from a cohort of children with medulloblastoma;
- b) Identify “marker” genes that are associated with outcome class (tumor progression/recurrence-free at three years, or not), by measuring the expression levels of “marker” genes (ie. *TrkC*, *cMyc*, *erbB2/erbB4*) in all patients and comparing the range, mean/median, and variance of expression levels associated with each outcome. For microarray-based datasets, marker genes are selected using a class separation statistic such as the signal-to-noise ratio^{50,51} or the logrank statistic.⁵² Microarray based markers are tested by applying a permutation test to the top ranked genes to assess their class-correlation statistical significance;
- c) Build a classifier in cross-validation (leave-one-out) by removing one sample from the dataset and then use the remaining samples as a training set;
- d) Build several models using different numbers of marker genes in microarray datasets, or for single gene classifiers using different levels of expression, and choose a best model based on a minimum weighted total error in cross-validation (see Statistical Considerations);
- e) Validate optimal predictor selected from cross-validation analysis in the separate “test” cohort of patients.

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

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

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

16.4.3 Gene Expression Profiling (Pomeroy)

Sample requirements: 10 µg total RNA. RNA integrity will be assessed either by northern blotting or by gel electrophoresis. Reverse transcriptase generated biotinylated antisense RNAs will be hybridized overnight to Affymetrix (Santa Clara, CA) Human Genome U133 (HG-U133) microarrays.⁵⁰ Arrays will be scanned on Affymetrix scanners and the expression value for each gene calculated using Affymetrix GENECHIP software. Minor differences in microarray intensity will be corrected using a linear scaling method.⁵⁰ Scans will be rejected if the scaling factor exceeds 3, fewer than 1000 genes received 'Present' calls, or microarray artifacts are visible.

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

During the optimization phase of the study, decision boundaries between the alive versus dead classes will be determined using the *k-Nearest Neighbors* (k-NN) algorithm,⁵³ *Weighted Voting*,^{51,54} *Support Vector Machines*,^{54,55} and *SPLASH*.⁵⁶ The predictors will be optimized by calculating error rates on datasets of increasing size, observing as the error rates asymptotically approach a minimum.

16.4.4 Selecting an Outcome Predictor for Future Clinical Trials

The optimal predictors determined by each of the three groups in cross-validation analysis of the training set will then be applied to the test dataset in the second phase of the study. Relative accuracy of each of the predictors will be compared, and the most accurate predictor will be selected. Moreover, during the final year of the study, it will be necessary for each of the groups to demonstrate on a cohort of at least 25 patients that their test can be completed within 2 weeks of receiving the sample. Proving the ability for "real time" analysis will be mandatory for selection of a lab to perform tumor stratification analysis in future clinical trials. Internal cross-validation procedures, such as the leave-one-out method,⁵⁰ will be utilized in the training set to provide less-biased estimates of correct classification rates. However, the test data set will provide the best estimate of the correct classification rates associated with these

classification rules. It may be possible, in the analysis, also to include clinical measures of disease progression probability, such as metastasis stage and amount of post-surgical residual, to improve the classification rules developed from gene expression data.

16.4.5 Genome-wide Genetic Testing

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

16.4.6 Nuclear β -catenin Immunoreactivity

It was recently shown that nuclear beta-catenin immunoreactivity correlated with favorable outcome in medulloblastoma patients (Ellison et al., JCO23:7951, 2005). Two of the unstained slides from patients enrolled in ACNS0332 will be forwarded to the COG Brain Tumor Resource Laboratory for beta-catenin immunostaining. Staining and analysis will be conducted by Dr. Alex Judkins in collaboration with Dr. Jackie Biegel. The same reagents and scoring criteria used for the CCSG study will be applied to these specimens. Scoring will be done by individuals that do not have access to clinical outcome data. Assuming nuclear beta-catenin immunoreactivity will be detected in 25% of the 300 enrolled patients, we will have 80% power to detect a 23% increase in 5 year EFS (41% to 64%), based on a two-sided logrank test with 5% Type I error rate.

16.4.7 Statistical Considerations for Biology Aim 2

The statistical analysis of these data will comprise several distinct components. The first is to identify, in the training set, the "marker" genes that are most associated with three-year progression-free survival, and to use these to develop 'optimal' classification rules to predict which patients will or will not survive progression-free to three years. The second is to investigate in a subsequent, independent test set whether the resulting classification rules retain the correct-classification rates that were estimated in the initial development of the rules. The methods used by Golub and colleagues⁵¹ and Pomeroy and colleagues,²⁹ as well as standard statistical techniques such as Cox regression analysis,³⁴ will be used in these analyses. Internal cross-validation procedures, such as the leave-one-out method,²⁹ will be utilized in the training set to provide less-biased estimates of correct classification rates. However, the test data set will provide the best estimate of the correct classification rates associated with these classification rules. It may be possible, in the analysis, also to include clinical measures of disease progression probability, such as metastasis stage and amount of post-surgical residual, to improve the classification rules developed from gene expression data.

Definition of Optimality

In this study, different predictors will be developed and investigated for a spectrum of optimality criteria based on weighted total cross-validation error, which is defined as:

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

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

Study Cohort

The patient cohort for this biology study will comprise patients treated on COG studies for average (Trial ACNS0331) and poor risk medulloblastoma (Trial ACNS0332), in infants (age < 3 years, P9934 and ACNS0334) and older children (ages 3 to 21 years). Because this biological study will incorporate patients enrolled in several clinical studies, it is difficult to predict the precise composition of patients that will be represented in the biological cohort. Patients available to this study can be conservatively estimated from the performance of COG institutions in several past studies. COG A9961 enrolled ~400 average risk medulloblastoma patients in 4 years. CCG-9921 enrolled 92 infants with medulloblastoma in 5 years, which would represent approximately 150 infants in 5 years in COG overall. CCG-9931 enrolled 85 patients with disseminated or unresected medulloblastoma in 3 years, which would correspond to 135 patients in COG overall. Hence, 175 patients per year (57% average risk age >3 years; 26% other > 3 years; 17% infant) are expected from these patient groups combined, with 3-years progression-free survival of 60 to 65% in aggregate. Very conservatively, if only 60% of patients enrolled on these studies have adequate tissue for this biological study, the minimum target accrual of 400 patients can be achieved in 4 years. This biological study will continue to accrue sample through the duration of these next-generation COG therapeutic studies, so that the sample size is expected to exceed 400 patients.

Precision

The elemental parameters that will best reflect the value of the classification rules will be the false positive fraction (FPF) and false negative fraction (FNF) of the resulting rules estimated from the test sample. A minimum of 225 patients will be available for this analysis (300 less the 75 patients used in the training set). 90 of these patients will be 3-year progressors, and are relevant to the estimation of FNF, and 135 will not have progressed, and are relevant to estimation of FPF. For observed FNF of 10%, the 95% confidence interval (CI) for this quantity will be approximately (5%, 18%). For observed FPF of 10% the 95% CI will be (6% to 16%). For FNF and FPF of approximately 50%, the 95% CIs will be (50%, 60%) and (42%, 58%), respectively.

16.5 Aim III To Prioritize Targeted Therapies for Future Clinical Trials

The provision of fresh surgical specimens offers an unprecedented opportunity to prioritize candidate therapies for future medulloblastoma/PNET clinical trials. There are approximately 150 compounds in or near Phase I or II clinical trials for cancer. Because of the limited number of medulloblastoma/PNET patients, only a small fraction of these compounds can be tested in human clinical trials. The *ex vivo* platform was established in 1999 in Dr. Olson's laboratory. This platform has been utilized to demonstrate the efficacy of sonic hedgehog antagonists, retinoid agonists, notch pathway inhibitors and histone

deacetylase (HDAC) inhibitors in *ex vivo* patient samples (Science 297:1559, 2002; Nature Medicine 9:1033, 2003; Cancer Research 64:7794, 2004). Each of these compounds was subsequently shown to have activity in mouse models of medulloblastoma and two are advancing toward human clinical trial, including this phase III study of retinoid activity. This has been modified to 96 well format so that the efficacy of dozens of compounds, alone or in combination, can be compared in each patient's medulloblastoma/PNET specimen. This approach is not used to predict whether an individual patient will respond to a drug, but simply to prioritize compounds for phase I and II trials in children with medulloblastoma.

16.5.1 To Prioritize shh, notch, and HDAC Inhibitors as Single Agents

Through Material Transfer Agreements and commercial sources, we have 7 hedgehog pathway inhibitors, 5 notch pathway inhibitors, 4 HDAC inhibitors and 1 Wnt pathway inhibitor. The first objective is to eliminate the least active compounds in each class so that combinatorial studies can be conducted on a reasonable number of compounds. Compounds are tested in *ex vivo* medulloblastoma/PNET samples as described in Aim 1 at concentrations of 1 – 10 micromolar. Agents that lack efficacy in this concentration range are eliminated (de-selected) for further consideration. Criteria for de-selection is ≥ 8 non-responsive specimens out of the first 10. Beyond this, experience and judgement are used regarding selection of compounds to bring forward for IC₅₀ determination.

Because fresh tumor tissue quantity is limited, the IC₅₀ and maximal effect will be determined for typically 1-3 compounds per pathway. Concentrations ranging from 1 nM to 10 μ M will be tested in triplicate and dose response curves will be established. Each drug will be tested in at least three specimens, more if the IC₅₀ varies by more than one log between the initial three tumors.

The IC₅₀ concentration and a concentration 2 logs higher than the IC₅₀ of each drug will be tested (limited by maximum solubility) in a large series of medulloblastoma/PNET specimens from ACNS0332 and ACNS02B1. The rationale for testing the IC₅₀ concentration is that it will provide the most sensitive means of comparing drugs in the absence of full dose response curves on each. The rationale for testing the 2 log higher than IC₅₀ is that we cannot assume that the IC₅₀ will be similar across tumors even if it consistent among tumors tested in Aim 2B. Therefore, the higher concentration will ensure that we do not miss active agents.

16.5.2 To Explore Potential Synergistic Activity Among wnt, shh, notch, HDAC Inhibitors and Retinoids

In this Aim, we extend our pilot studies to identify combinations of targeted therapies that induce near complete cell kill in *ex vivo* medulloblastoma/PNET specimens in a relatively large cohort of patient specimens. The results of these studies will be used to prioritize drug combinations for evaluation in the medulloblastoma mouse models and to provide information that will help prioritize combination therapies for future clinical trials.

One agent from each of 5 pathways will be tested in pairwise combinations and, when sufficient wells are available, three-way combinations. The concentration of compound for combination studies will be one log lower than the IC₅₀. At this concentration, single agents are expected to typically have approximately 10% of maximum activity. Drug combinations will be scored as potentially synergistic or additive if apoptosis in the presence of the combination exceeds apoptosis in wells that contain single agent at the same concentration by at least 25% at 48 hours. The absolute extent of cell death will be recorded for each combination and the data set will be provided to the COG CNS Tumor Committee for reference as new therapeutic protocols are considered.

Statistical Considerations

Accrual

We have demonstrated that 100 mg of fresh tissue from each patient is sufficient to accomplish both Aim1 and Aim3, provided that it is shipped properly. In cases where tissue quantity limits the number of wells for *ex vivo* analysis, Aim 1 will take priority over Aim 3. The reason for this priority is that specimens from ACNS02B1 (the ongoing biology study) will also be available along with those of ACNS0332 for Aim 3. The accrual goal for ACNS0332 is 300 high risk medulloblastoma/PNET patients. Allowing for consent, specimen quantity and technical and logistical issues, we expect that quality specimens for this study will be submitted on at minimum 100 patients. Based on current accrual in ACNS02B1, we anticipate that nearly 100 medulloblastoma/PNET specimens will be available for Aim 2 from standard risk medulloblastoma/PNET patients that are not enrolled in ACNS0332. Thus we anticipate a minimum of 200 specimens will be available for investigation in Aim 3. Furthermore, the work on Aim 3 has already begun and can continue after the completion of ACNS0332, whereas Aim 1 is directly linked to the patients enrolled in ACNS0332.

Compound Prioritization

Compound prioritization will occur twice each year. This will allow drug plates to be prepared and frozen in advance so that all experiments conducted during the subsequent 6 months are identical in all regards except pipetting error (which is addressed through replicates). There will be separate plates for Aims 2A, 2B, 2C, and 2D. Aim 2C has the highest priority, but can only be done after Aims 2A and 2B. Therefore, current samples in ACNS02B1 and initial samples from ACNS0332 will be used to eliminate the least active compounds from each pathway and identify the IC_{50} for the most active compounds. After that, priority will be given to Aim 2C then 2D. As new drugs become available, the IC_{50} will be determined in cases where there are gram quantities of tissue. Within a given signal transduction pathway, compounds that have Phase I trials in adults will have priority over lead compounds that are not yet in clinical trial provided that the IC_{50} of the drug given priority is in the nanomolar rather than micromolar range.

Statistical Considerations

For statistical analysis, each specimen will be scored as "Responsive" or "Non-responsive" if apoptosis in the presence of drug exceeds apoptosis in vehicle by at least 25% at 48 hours as described in Aim 1a. The primary statistical analysis will be a test of difference in the proportion of samples that are responsive, as a function of the particular agent used, vehicle as negative control. Since each tumor specimen is treated with vehicle as well as all drugs, the inherent differences in sensitivity of the individual tumor to these agents will result in a vector of correlated Bernoulli observations. A valid approach for testing the null hypothesis of no difference in the probability of tumor response among treatment groups is to use a Cochran-Mantel-Haenszel (CMH) chi-square statistic³⁸ with stratification by patient. Using a sample size of 100, the power of this test was calculated where the probability of response was 0.05 for vehicle. A correlation of .2 was assumed between the vehicle and each drug. The table below shows the power of this test as function of the response probability to this last drug. If a two-sided critical region with Type I error 5% is used.

Response Probability	0.05	0.20	0.30	0.40
Power	0.025	0.94	>0.99	>0.99

This test will have 94% power to detect an increase from 0.05 response rate in control to 0.20 response rate. It is also possible that, based on current accrual in ACNS02B1, we anticipate that approximately 100 medulloblastoma/PNET specimens will be available for Aim2 from standard risk medulloblastoma/PNET

patients that are not enrolled in ACNS0332. Thus we anticipate more than 100 specimens will be available for investigation in Aim 2. If accrual exceeds the above targets, the study would have more power to detect correspondingly smaller differences in response rate between groups.

We acknowledge that there will be a substantial number of tests performed to investigate pair-wise combinations of drugs. Therefore, care must be taken in interpreting results. However, if large differences are present, they will be able to be confirmed.

Hence, this study will have adequate power to meaningful increases in response rate due to drug treatment. Estimates of effects will also be estimable. Additional analyses will be performed to estimate the proportion of medulloblastomas that are “responsive” to each agent. We will use conditional logistic regression analysis to investigate which drug or combination of drugs is most strongly correlated with the probability of responsiveness.

We also plan secondary analyses will also include the analysis of absolute viability using Analysis of Variance (ANOVA) (blocking/matching on patient sample) Ranking the drug effects components in the blocked ANOVA model may provide alternative powerful method for selecting best combinations. Note, this application in much larger scale parallels the idea of selection designs used in some randomized Phase II clinical trials (Liu, PY. Phase II Selection Designs. In Handbook of Statistics in Clinical Oncology, Marcel Dekker, New York. 2001. Ed John Crowley.).

16.6 Aim IV. Tissue Banking

Snap frozen and fixed tissue specimens that are not used for the experiments described above will be banked through the Cog Biopathology Center as described in protocol ACNS02B3. In addition, primary cultures of enriched medulloblastoma cells derived from patients in this study will be cryopreserved and stored for future use. Medulloblastoma cultures can be difficult to establish. Many cases do not survive in culture long enough to expand and cryopreserve the specimens. Whenever possible, cases will be cryopreserved so that a potentially viable tumor sample is available for each patient enrolled on study for whom fresh tissue is submitted. When possible, several vials will be cryopreserved. Samples will be stored in a -135C freezer with liquid nitrogen and emergency electric generator backup. Due to limited resources, these cultures will not undergo extensive characterization (e.g., cytogenetics, growth parameters, media optimization). The frozen vials will belong to COG and will be managed in an identical fashion as COG/CHTN snap frozen and fixed tumor specimens.

17.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

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

17.1 Whole Brain MRI With and Without Contrast

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

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

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

Required sequences:

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

Optional sequences

Precontrast :

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

Post contrast :

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

Notes:

1. DO NOT INTERLEAVE T1 weighted sequences

2. Flow compensation should not be used (or at least not on all T1 enhanced sequences)
3. Fat Saturation not necessary

17.2 MR Spine With and Without Contrast

Spinal MRI (T-1 weighted imaging with and without gadolinium) is required within 28 days of surgery if done post-operatively and within 10 days of surgery if done pre-operatively. If an MRI scan is performed within 10 days prior to surgery, then only a post-contrast examination is necessary. For posterior fossa tumors, pre-operative MRI scans are preferred because surgically-induced inflammation/blood can be difficult to distinguish from tumor.

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

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

Technical notes:

- Phase direction AP, frequency direction SI
- Acquire 2 separate acquisitions (one cervical and upper thoracic, the second lower thoracic and lumbosacral) to optimize placement of presaturation pulse.
- Place anterior saturation pulse close to the anterior margin of the spinal column - to minimize motion artifacts from chest/abdomen.
- Pixel size 1 mm² or less (example: for 26 cm FOV, use 256 x 256 matrix)
- Keep TE to minimum (<15 msec)
- Do not use fat saturation

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

Technical notes:

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

For primary tumors of the spinal cord, add:

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

Technical notes:

- Can keep Phase direction AP, frequency direction SI, with anterior saturation pulses; or switch phase direction SI, frequency direction AP, with inferior and superior saturation pulses if that produces better images (less CSF pulsation artefacts)
- Pixel size 1 mm² or less (example: for 26 cm FOV, use 256 x 256 matrix)

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

NOTE:

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

1. High quality T1 images are essential - without artifacts from physiologic motion (cardiac, respiratory) or from CSF pulsation.
2. T2 weighted sequences (sagittal or axial) are not needed. They are optional.

17.3 Central Review

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

- Pre-operative Cranial MRI with and without contrast
- Post-operative Cranial MRI with and without contrast
- Pre OR Post-operative Spinal MRI with contrast

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

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

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

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

18.0 RADIATION THERAPY GUIDELINES

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

18.0.1 General Guidelines

Radiation therapy for patients on COG protocols can only be delivered at approved COG RT facilities (see Administrative Policy 3.9). Contact QARC for questions or further information.

Three-dimensional image-based radiation therapy treatment planning and computer-controlled delivery systems (*conformal radiation therapy*) should improve disease control and functional outcome for infants with brain tumors. The tools necessary to perform conformal radiation therapy have become widely available, thus sufficient experience has been gained to develop guidelines for use by investigators who treat these patients. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons or proton beam therapy and electronic data submission is required.

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

18.0.2 Required Benchmark and Questionnaires

Radiation therapy will be administered using protons or photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT), intensity modulated radiation therapy (IMRT) and craniospinal

radiation therapy. Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom and those using protons must complete the proton benchmark and questionnaire. All centers must complete the QARC craniospinal radiation therapy benchmark. All centers participating in this protocol must complete the QARC CT/MR image fusion benchmark. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. For information regarding the IMRT phantoms, please contact the RPC (<http://rpc.mdanderson.org/rpc>).

18.0.3 Guidelines and Requirements for the Use of IMRT

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

18.0.4 Guidelines and Requirements for the Use of Proton Beam Therapy

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

18.1 **Timing of Radiation Therapy**

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

18.2 **Equipment**

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

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

18.2.1 Modality

X-rays with a nominal energy ≥ 4 MV. Craniospinal axis irradiation is best done with x-rays between 4-6 MV. The boost volume may be treated with a nominal energy ≥ 4 MV, as long as dosimetric constraints are accomplished. Electron beams of suitable energy to treat the spinal cord may be allowed if prior documentation has been reviewed and approved by QARC. Proton beams may be used by credentialed centers and will require digital submission of treatment planning data to QARC for QA review.

18.2.2 Calibration

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

18.2.3 Equipment

Patients enrolled on this study must be treated using conformal radiation therapy treatment planning and delivery techniques at a minimum for the primary. IMRT or Proton Therapy will be allowed if

appropriate benchmarks have been submitted and approved by QARC. All patients must be treated on isocentric machines. All machines must have a minimum source-to-axis distance (SAD) of 80 cm. Treatments may be given with fixed SSD techniques. If proton beams are used, prior approval from the study radiation therapy coordinator is necessary. For treatment to be conformal the following criteria must be met:

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

18.3 3-D Target Volume and Organ At Risk Definitions

The definitions for the target volumes and treatment dosimetry will adhere as closely as possible to the ICRU Report 62 definitions whenever possible.

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

18.3.1 Gross Tumor Volume (GTV)

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

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

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

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

The Clinical Target Volume₁ (CTV₁) is the entire craniospinal axis. The craniospinal axis Planning Target Volume (PTV₁) is institution-defined according to immobilization techniques and their inherent setup uncertainties. The margin defining the PTV may range from 0.3 cm to 1.0 cm. For the Craniospinal volume, a larger PTV₁ margin should be considered due to inexactness of repositioning for the spinal fields.

Although conventional simulation will be allowed for the craniospinal axis PTV₁ treatments, it should be noted that CT based or 3D treatment planning for craniospinal axis irradiation may offer advantages over conventional simulation methods. (Reference Mah Int J Radiat Oncol Biol Phys 2000). A better appreciation of the cribriform plate and middle cranial fossa can be gained with a CT simulation. In most circumstances, the same CT simulation data used for planning the craniospinal axis RT can be used to plan the 3-D conformal boost.

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

Whole Brain (CTV₁): The whole-brain field shall extend anteriorly to include the entire frontal lobe and cribriform plate region. Coverage of the CTV takes precedence over protection of the lenses or eyes. Inferiorly, the CTV₁ shall be at least 0.5 cm below the base of the skull at the foramen magnum. PTV₁ should be defined to account for setup error. The radiation fields to cover this target volume should follow established guidelines for cranial irradiation in medulloblastoma. There will be a junction with the spinal field.

Spine (CTV₁): The spinal target volume will be the entire thecal sac. The field to cover this volume should extend laterally on both sides to cover the recesses of the entire vertebral bodies, with at least a 1 cm margin on either side. The superior border will be the junction with the whole brain field. The inferior border of the treatment volume will be placed after review of the spinal MRI. The border will be 2 cm below the termination of the subdural space. This will extend at least to the inferior border of the second sacral segment (S2-S3 interspace), but may be as low as the inferior border of S4. If this cannot be accomplished in a single field, there will be a junction between the two spinal fields. PTV₁ should be defined to account for setup error.

For proton therapy, the spinal target volume will include the vertebral bodies for skeletally immature patients to minimize the risk of unequal vertebral growth. Skeletal maturity can be estimated with a wrist x-ray to determine bone age. Dose to the thyroid gland can be attenuated by allowing incomplete coverage of the lower cervical vertebra. The spinal target volume in skeletally mature patients will include the spinal subarachnoid space with a margin of 3-5 mm into the vertebral body to allow for inter-fraction set up variation.

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

Posterior Fossa Boost (CTV_{PF}): This volume refers to patients with posterior fossa primaries. 3D-based treatment planning is mandatory for these volumes. IMRT is allowed for the PTV_{PF}. The CTV_{PF} should encompass the entire posterior fossa. The posterior fossa must be defined on the planning CT scan. It is strongly recommended that a sagittal and/or coronal MRI be used to assist in identification of the position of the tentorium. The CTV_{PF} extends inferiorly from C1 vertebral canal through the foramen magnum, laterally to the bony walls of the occiput and temporal bones and superiorly to the tentorium cerebelli. Generally, the sigmoid sinuses define the lateral-superior extent of the bony confines of the posterior

fossa that attach contiguously to the tentorium above. The folia of the cerebellum and the anterior border of the brainstem and midbrain bound the CNS contents of the posterior fossa. The Planning Target Volume (PTV_{PF}) is a 0.3cm to 0.5cm margin around the CTV to account for day-to-day setup variation. The PTV_{PF} should not extend beyond the external bony confines of the skull except at the foramen magnum to C1-C2. The PTV_{PF} should extend anteriorly to the posterior clinoids (the pituitary is not included) and inferiorly to the C1-C2 junction. In treatment planning, shielding of critical structures should be attempted. At least 95% of the prescription study dose of 55.8 Gy must encompass at least 95% of the PTV_{PF} (the posterior fossa) as shown by DVH. No part of the PTV_{PF} should receive less than 50 Gy. Treatment techniques for the PTV_{PF} may include parallel opposed laterals or other 3D CRT methods to limit dose to the supratentorial brain, hypothalamus, pituitary or middle ear.

Supratentorial Boost (CTV_{ST})

This volume refers to children with supratentorial primaries (ST-PNET). The CTV_{ST} for a supratentorial boost will be defined using a 1 cm margin around the presurgical MRI defined tumor volume. In the event of proximity to normal tissue structures, this margin may be reduced to 0.5 cm to allow for sparing of critical structures. As the total dose to the optic chiasm and both optic nerves should not exceed 50.4 Gy, these structures should be excluded accordingly. The Planning Target Volume (PTV_{ST}) is a 0.3cm to 0.5cm margin around the CTV_{ST} to account for day-to-day setup variation.

Metastasis Site Boost (CTV_M):

Patients with M1 disease will receive no additional boost.

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

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

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

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

18.3.2.1 Proton Definitions for GTV, CTV and PTV

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

18.3.3 Organs at Risk (OAR)

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

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

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

A Web based atlas with normal organ contours will be made available.

18.4 Dosimetry

18.4.1 Prescription Point

The prescription point for the neuroaxis (PTV₁, whole brain and spine) is at or near the center of the targets. For the brain this may be a point other than the central axis. Consideration should be made to using a point midway of the biparietal diameter. The spinal axis dose should be prescribed to the anterior aspect of the spinal canal. In many cases, the depth of the anterior spinal canal will vary by vertebral level. An average depth may be used that keeps the dose uniformity within the constraints defined below. For the posterior fossa and limited target boost volumes, the doses shall be prescribed in order to have at least 95% of the 55.8 Gy isodose covers at least 95% of the respective planning target volumes. The minimum dose to the PTV_{PF}, PTV_{ST} or PTV_{boost} shall not be < 50 Gy.

18.4.2 Dose Definition

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

18.4.3 Prescribed Dose and Fractionation

36.0 Gy CSRT (PTV₁)

55.8 Gy Posterior fossa boost, **cumulative dose** (PTV_{PF} or PTV_{ST})

Patients with M1 disease will receive no additional boost.

Patients with M2 disease (intracranial subarachnoid disease) will receive boosts to areas of supratentorial or posterior fossa metastatic disease. (Table 18.4)

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

Table (18.4) Radiation Dose for Craniospinal Axis Radiation Therapy

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

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

18.4.4 Dose Fractionation

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

18.4.5 Dose Uniformity

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

At least 95% of the PTV_{PF}, PTV_{ST} or PTV_{boost} should be encompassed within 95% of the 55.8 Gy isodose surface and no more than 5% of the PTV should receive greater than 110% of the prescription dose as evaluated by DVH. These targets should not receive less than 50 Gy. Treatment should be planned to spare the spinal cord, brainstem, optic chiasm and optic nerves from the highest doses resulting from dose inhomogeneity. An effort should be made to spare the cochlea and middle ear contents.

18.4.5.1 Proton Dose Uniformity

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

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

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

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

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

†The proton distal range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns.

‡The uncertainty of distal margin has been estimated to be as large as 4mm.

18.4.6 Treatment Interruptions

Treatment will not be interrupted for anemia, leukopenia, or thrombocytopenia unless life threatening. Blood product support should be instituted according to institutional/protocol guidelines. For interruptions of more than 2 treatment days, please notify Dr. Jeff Michalski.

18.5 **Treatment Technique**

18.5.1 Craniospinal Axis Irradiation

18.5.1.1 Patient Position

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

18.5.1.2 Whole Brain Irradiation

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

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

If symmetric collimator jaws are used:

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

If asymmetric collimator jaws are used:

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

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

18.5.1.3 Spine Irradiation

Preferably, the spinal volume should be treated with a single posterior field. An extended SSD is preferable to the use of adjacent ports. If adjacent ports are necessary, the 50% decrement should cross at the posterior margins of the vertebral body. It is preferable that the match line be placed inferior to the spinal cord (below L2) and should be moved every 900 cGy. Custom blocking may be required at the inferior border of the spine.

18.5.1.4 Abutting Fields

With the use of collimator rotation and an independent jaw technique, the cranial and spinal fields may be directly abutted (light fields). Many radiation oncologists, though, are more comfortable with a gap between the cranial and spinal light fields. A gap of 0.5 cm is allowed on this protocol. The match line should be moved at least twice during treatment of the cranio-spinal axis (e.g. after each 9Gy). Also, a penumbra broadening “match line wedge” or a dynamic wedge may be used. The match line should never overlap the posterior fossa boost. Therefore, it is recommended that the first match line lie just above the shoulder, and the last 2 cm higher. Alternatively, the first match point could begin at the superior point and end at the inferior point.

18.5.1.5 Conformal Boost Treatment

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

18.5.1.6 Selection of Proton Beam Arrangements

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

18.5.1.7 Field Shaping

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

18.5.1.8 Example Cases

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

18.5.1.9 Imaging

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

18.6 Normal Tissue Sparing

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

18.6.1 Spinal Cord

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

18.6.2

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

18.7 Dose Calculations and Reporting

18.7.1

Institutions using conventional 3D treatment planning must have a 3-dimensional Benchmark on file at QARC. If IMRT or Protons are to be used, then the benchmark specific to IMRT or Protons must be submitted. Patients will be considered unevaluable if benchmarks are not approved. Centers treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) Contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms.

18.7.2 Prescribed Dose

For standard or 3D conformal techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the "RT-1 Dosimetry Summary" or Proton Reporting Form. A separate form shall be submitted for each of the planning target volumes.

For IMRT techniques: The monitor units required to deliver the prescribed dose shall be calculated and submitted using the IMRT Dosimetry Summary Form. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

18.7.3 Isodose Distributions

Color hard copies of the isodose distributions must be submitted for each of the treatment sites including the craniospinal axis (CSA) and primary site boost at the start of radiation therapy and a composite isodose distribution will be required at the completion of radiation therapy, whenever it is technically possible. The isodose distributions will display the actual dose to be delivered for a particular phase of treatment (e.g., CSA isodose distributions will show 36 Gy, primary site boost isodose distributions will show 19.8 Gy). The cumulative dose (55.8 Gy) will be displayed on the composite isodose distribution.

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

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

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

18.7.4 Dose Volume Histograms

Dose volume histograms will be calculated and submitted for organs at risk (Section 18.3.3) including

right and left optic nerves, optic chiasm, right and left cochlea, pituitary/hypothalamus, supratentorial brain, and spinal cord (foramen magnum to C2). Dose volume histograms will be calculated and submitted for the GTV, CTV and PTV of each volume treated. Dose volume histograms will be calculated and submitted in composite form whenever technically possible.

18.8 Quality Assurance Documentation

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

Institutions are required to submit the treatment plan in digital format. An institution's treatment planning system must have the capability of exporting data in 1 of 2 formats:

- RTOG Data Exchange Format, Version 3.20 or later (specifications at http://itc.wustl.edu/exchange_files/tapeexch400.htm); or
- DICOM 3.0 in compliance with the Advanced Technology Consortium's (ATC) DICOM 3.0 Conformance Statement. A list of commercial systems that are known to have this capability are listed on the ATC Website (http://atc.wustl.edu/credentialing/atc_compliant_tps.html).
- The data may be submitted on a CD or sent electronically via ftp to QARC. Instructions for digital submissions may be found on the QARC Website - www.qarc.org, under Digital Data, RT Treatment Planning.

Data to be Submitted:

External beam Treatment Planning System

- Digitally reconstructed radiographs (DRR) or simulator films for each treatment field and orthogonal (anterior/posterior and lateral) images for isocenter localization for each group of concurrently treated beams. When using IMRT, orthogonal isocenter images are sufficient.
- Isodose distributions for the composite treatment plan in the axial, sagittal and coronal planes at the center of the treatment or planning target volume. The planning target volume, isocenter and the normalization method must be clearly indicated.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in Section 18.3.3. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Beams-eye-view (BEV) of portals showing collimator, beam aperture, target volume and critical structures are required when not using IMRT.

Digital Data

- Submission of the treatment plan in digital format is required. Please refer to www.QARC.org and click on "Digital Data" for guidelines regarding digital submission. All submissions, including those that are digital, require hard copy submission of the other items included in this list. If there are any problems with digital data submission, please contact QARC.

Supportive Data

- Copies of all diagnostic materials and surgical reports used in defining the target volume including (i) preoperative MRI and postoperative cranial MRI with and without contrast; (ii) pre or postoperative spinal MRI with and without contrast; sagittal imaging should be included for both brain and spine; (iii) copies of the all op reports, pathology reports, and copies of the results for the Lumbar CSF cytology examination must also be submitted.
- Prescription Sheet for Entire Treatment
- Documentation of an independent check of the calculated dose when IMRT is used.
- For protons, a description of the rationale for the PTV margins.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.

Forms

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

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

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

The data should be sent to:

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

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

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

18.9 Definitions of Deviation in Protocol Performance

18.9.1 Prescription Dose

Minor Deviation

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

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

Major Deviation

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

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

18.9.2 Dose Uniformity

Minor Deviation

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

Major Deviation

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

18.9.3 Volume

Minor Deviation

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

Major Deviation

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

19.0 QUALITY OF LIFE AND NEUROPSYCHOMETRIC GUIDELINES

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

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

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

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

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

APPENDIX III: YOUTH INFORMATION SHEETS

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

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

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

2. We are asking you to take part in a research study because you have a type of brain cancer called high risk medulloblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat the type of brain cancer that you have. We want to find out if adding 1 or 2 drugs to the usual therapy can improve the treatment for the type of brain cancer that you have. The drugs we are testing are carboplatin (the ‘C’ drug) and isotretinoin (the ‘I’ drug.) We will do this by comparing 4 ways to treat the cancer. We don’t know which way is better. That is why we are doing this study.

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

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

- * The usual therapy.
- * The usual therapy plus the ‘C’ drug.
- * The usual therapy plus the ‘I’ drug.
- * The usual therapy plus both the ‘C’ drug and the ‘I’ drug.

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

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

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

8. We would also like to do research to see if there are ways to tell how the cancer will respond to treatment. We hope to find that out by doing tests on samples of tumor tissue. You have already had surgery. We would use a sample of the tumor that was removed during that surgery for tests. No extra procedures will be done to remove tissue for these research tests. You can choose to be on the study but not to allow us to use extra tumor cells for research.

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

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

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

2. We are asking you to take part in a research study because you have high risk medulloblastoma. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to find out if adding 1 or 2 chemotherapy drugs to the standard therapy will improve the treatment for young people with high risk medulloblastoma.

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

This study deals with treatment after surgery. The standard treatment for high risk medulloblastoma after surgery is chemoradiotherapy followed by “Maintenance” chemotherapy. In this study, we want to find out if adding a drug called cisplatin to the chemoradiotherapy can improve the outcome of patients. We also want to find out if adding a drug called isotretinoin to the standard Maintenance chemotherapy and including a stage of “Continuation” therapy with isotretinoin, can improve the outcome of patients.

3. Children and teens who are part of this study will all be treated with the standard therapy for high risk medulloblastoma but some patients will have 1 or 2 drugs added to that therapy. This means that you will be treated in 1 of 4 ways:

- * Standard therapy (chemoradiotherapy followed by Maintenance chemotherapy)
- * Standard therapy with the addition of carboplatin during chemoradiotherapy
- * Standard therapy with the addition of isotretinoin during Maintenance therapy. This is followed by Continuation therapy with isotretinoin.
- * Standard therapy with the addition both carboplatin and isotretinoin.

If you are assigned to receive isotretinoin, Continuation therapy will extend the treatment time by around 6 months.

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

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called “risks.” The risks to you from this study are that if you receive carboplatin or

isotretinoin then you may have more side effects than you would on standard therapy. Other things may happen to you that we don’t yet know about.

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

7. Another part of the study is to see if there are ways to tell how the cancer will respond to treatment. We hope to find that out by doing tests on samples of tumor tissue. You have already had surgery. We would use a sample of the tumor that was removed during that surgery for tests. No extra procedures will be done to remove tissue for these research tests. If there are any leftover samples from these tests, we would like your permission to store them for use in future research. This is called banking. This part of the study is optional.

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

REFERENCES

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

19. Patton TF, Himmelstein KJ, Belt R, et al: Plasma levels and urinary excretion of filterable platinum species following bolus injection and IV infusion of cis-diachlorodiammineplatinum in man. *Cancer Treat Rep* 62:1359, 1978
20. Alberts DS, Mason-Liddil N: Carboplatin in the treatment of ovarian cancer. *Semin Oncol* 16:19-26, 1989
21. Patel M, Godwin K, McCully C, et al: Plasma and cerebrospinal fluid pharmacokinetics of carboplatin and cisplatin. *ProcAACR* 37:403-404, 1996
22. Alverez MV, Cobreros G, Heras A, et al: Studies of cisdiachlorodiammineplatinum (II) as a radiosensitizer. *Br J Cancer* 3 (S3):68-72, 1978
23. Dritschilo A, Piro AJ, Kelman AD: The effect of cis-platinum on the repair of radiation damage in plateau phase Chinese hamster cells. *Int J Radiat Oncol Biol Phys* 5:1345-1349, 1979
24. Stewart DJ, Leavens M, Maor M, et al: Human central nervous system distribution of cisdiamminedichloroplatinum and use as a radiosensitizer in malignant brain tumors. *Can Res* 42:2474-2479, 1982
25. Hallahan AR, Pritchard JI, Chandraratna RA, et al: BMP-2 mediates retinoid-induced apoptosis in medulloblastoma cells through a paracrine effect. *Nat Med* 9(8):1033-8, 2003
26. Gumireddy K, et al: All-trans-retinoic acid-induced apoptosis in human medulloblastoma: activation of caspase-3/poly(ADP-ribose) polymerase 1 pathway. *Clin Cancer Res* 9(11):4052-9, 2003
27. Di C LS, Adamson DC, Parrett TJ, et al: Identification of OTX2 as a Medulloblastoma Oncogene Whose Product can be Targeted by All-Trans Retinoic Acid. *Cancer Res* 65(3):919-24, 2005
28. Khan AA, Villablanca JG, Reynolds CP, et al: Pharmacokinetic studies of 13-cis-retinoic acid in pediatric patients with neuroblastoma following bone marrow transplantation. *Cancer Chemother Pharmacol* 39(1-2):34-41, 1996
29. Formelli F, Cavadini E, Mascheroni L, et al: Pharmacokinetics and effects on plasma retinal concentrations of 13-cis-retinoic acid in melanoma patients. *Br J Cancer* 76:1655-60, 1997
30. LeDoze F, Debruyne D, Albessard F, et al: Pharmacokinetics of all-trans retinoic acid, 13-cis-retinoic acid, and fenretinide in plasma and brain of Rat. *Drug Metab Dispos* 28:205-208, 2000
31. Matthay KK, Villablanca JG, Seeger RC, et al: Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *Children's Cancer Group. N Engl J Med* 341:1165-1173, 1999
32. Villablanca JG, Khan AA, Avramis VI, et al: Phase I trial of 13-cis-retinoic acid following bone marrow transplantation. *J Clin Oncol* 13:894-901, 1995
33. Liu J, Guo L, Luo Y, et al: All trans-retinoic acid suppresses in vitro growth and down-regulates LIF gene expression as well as telomerase activity of human medulloblastoma cells. *Anticancer Res* 20:2659-2664, 2000
34. Shin DM, et al: Phase II and biologic study of interferon alpha, retinoic acid, and cisplatin in advanced squamous skin cancer. *J. Clin. Oncol.* 20 (2):364-370, 2002
35. Shalinsky DR, et al: Enhanced antitumor efficacy of cisplatin in combination with ALRT1057 (9-cis retinoic acid) in human oral squamous carcinoma xenografts in nude mice. *Clin Cancer Res* 2:511-520, 1996
36. Aebi S, et al: all-trans retinoic acid enhances cisplatin-induced apoptosis in human ovarian adenocarcinoma and in squamous head and neck cancer cells, *Clin. Cancer Res.* 3:2033-2038, 1997
37. Formelli F, Cleris L: Therapeutic effects of the combination of fenretinide and all-trans-retinoic acid and of the two retinoids with cisplatin in a human ovarian carcinoma xenograft and in a cisplatin-resistant subline . 2000
38. Recchia F, Lalli A, Lombardo M, et al: Ifosfamide, cisplatin, and 13-Cis retinoic acid for patients with advanced or recurrent squamous cell carcinoma of the head and neck: a phase I-II study. *Cancer* 92:814-21, 2001

39. Yung WK, Kyritsis P, Gleason MJ, et al: Treatment of recurrent malignant Gliomas with High Dose 13-cis Retinoic Acid. *Clin Cancer Res* 2:1931-35, 1996
40. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*, 2nd Edition. New York: Wiley. 36:2411-2419, 2002
41. Sposto R, Sather HN: Determining the duration of comparative clinical trials while allowing for cure. *Journal of Chronic Diseases* 38(8):683-90, 1985
42. DeMets DL, Lan KKG: "Interim analysis: The alpha spending function approach". *Statistics in Medicine* 13:1341-1352, 1994
43. Grotzer MA, Janss AJ, Fung KM, et al: TrkC expression predicts good clinical outcome in primitive neuroectodermal brain tumors. *J CO* 18:1027-35, 2000
44. Kim JYH, Sutton ME, Lu DJ, et al: Activation of neurotrophin-3 receptor TrkC induces apoptosis in medulloblastomas. *Cancer Research* 59:711-19, 1999
45. Segal RA, Goumnerova LC, Kwon YK, et al: Expression of the neurotrophin receptor TRKC is linked to a favorable outcome in medulloblastoma. *Proc. Natl. Acad. Sci. (USA)* 91:12867-71, 1994
46. Gilbertson RJ, Perry RH, Kelly PJ, et al: Prognostic significance of HER2 and HER4 co-expression in childhood medulloblastoma. *Cancer Research* 57:3272-80, 1997
47. Grotzer MA, et al: MYC messenger RNA expression predicts survival outcome in childhood primitive neuroectodermal tumor/medulloblastoma. *Clin Cancer Res* 7:2425-33, 2001
48. Herms J, Neit I, Bernhard L, et al: C-MYC expression in medulloblastoma and its prognostic value. *Int J. Cancer* 89:395-402, 2000
49. Herms JW, et al: Potential prognostic value of C-erbB-2 expression in medulloblastomas in very young children. *J. Pediatr. Hematol. Oncol.* 19:510-5, 1997
50. Pomeroy SL, Tamayo P, Gaasenbeek M, et al: Prediction of central nervous system embryonal tumour outcome based on gene expression. *Nature* 415:436-442, 2000
51. Golub TR, et al: Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring. *Science* 286:531-537, 1999
52. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*. John Wiley and Sons, New York, 1980
53. Dasarathy VB e: *Nearest Neighbor (NN) Norms: NN Pattern Classification Techniques*. IEEE computer society press, Los Alamitos, Calif: 0818689307. ISBN, 1991
54. Brown MPS, et al: Knowledge-based analysis of microarray gene expression data by using support vector machines. *Proc. Natl. Acad. Sci. (USA)* 97:262-67, 2000
55. Mukherjee S, et al: Support vector machine classification of microarray data. CBCL Paper #182/AI Memo #1676, Massachusetts Institute of Technology, Cambridge, MA, December., 1999
56. Califano, et al: Analysis of Gene Expression Microarrays for Phenotype Classification. *Proceedings of the Eighth International Conference on Intelligent Systems for Molecular Biology*, San Diego, California, August 19-23.:75-85, 1999

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

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM

ACNS0332: Efficacy of Carboplatin Administered Concomitantly With Radiation and Isotretinoin as a Pro-Apoptotic Agent in Other Than Average Risk Medulloblastoma/PNET Patients

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

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to take part in this research study because you have been diagnosed with a type of cancer called medulloblastoma, a type of brain tumor. This study is for patients with high risk medulloblastoma. The term, risk, refers to the chance of the cancer coming back after treatment.

One or more of the following factors make the cancer more likely to return after treatment:

- The tumor is not at the very back of the brain
- Some of the tumor was not removed by surgery
- The cancer has spread to more than one site

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for medulloblastoma and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

Standard therapy for medulloblastoma may include surgery, radiation therapy to the brain and spinal cord, and chemotherapy. Radiation therapy is the use of high-energy x-rays to kill cancer cells. Chemotherapy means treatment with “cancer killing” drugs.

WHY IS THIS STUDY BEING DONE?

The overall goal of this study is to compare the effects, good and/or bad, of the chemotherapy drugs carboplatin and isotretinoin on subjects with high risk medulloblastoma and to find out if one or both are better than standard therapy alone.

In this study you will get either standard therapy alone, standard therapy plus one of the chemotherapy drugs added to the regimen, or standard therapy plus both of the chemotherapy drugs.

Carboplatin

Both radiation therapy and the drug carboplatin have an anti-cancer effect when given alone. However, studies have shown that when carboplatin is given along with radiation therapy a greater effect is produced than when either is given alone. In this study we will look at whether giving radiation therapy and carboplatin together can improve the rate of survival of subjects with high risk medulloblastoma.

Isotretinoin

The drug isotretinoin has been shown to cause the death of medulloblastoma cancer cells in the laboratory. Isotretinoin has not been tested in children with medulloblastoma but it has been effective in clinical trials for subjects with a type of cancer called neuroblastoma. Neuroblastoma is a different kind of tumor that develops in some kinds of nerve cells but not in the brain. We do not know if this drug will be effective in medulloblastoma. This study will look at whether adding isotretinoin to the standard chemotherapy drugs can improve the rate of survival of children with high risk medulloblastoma.

Because of isotretinoin's ability to cause severe birth defects in infants born to women who are taking the drug, it is available only under a special distribution program approved by the U.S Food and Drug Administration. This program is called iPledge. If you are randomized to Arm C or D containing isotretinoin, you will be required to register in the iPledge program and sign a separate patient information/informed consent for the program. If you are a female of child-bearing potential, you will also be required to sign a second consent, get pregnancy tests, and agree to use 2 forms of birth control or practice abstinence. And you will be required to answer questions in the iPledge program about the program and preventing pregnancy each month while you are taking the isotretinoin.

The main aims of this study are:

- **To find out if giving the drug carboplatin along with radiation therapy is more effective than giving radiation therapy alone.**

- **To find out if the drug isotretinoin can improve the survival of subjects with high risk medulloblastoma.**

Other aims of this study are:

- To measure any effects that the different types of treatment have on the subject's quality of life (general well-being).
- To measure the brain function of subjects (measuring intelligence, memory, language, nonverbal skills, attention, and academic achievement) and to examine the relationship between the subject's level of brain function and their quality of life.

An additional research aim for which participation is optional is:

- To identify markers in the DNA of tumor tissue that will help us know how best to treat patients in the future and to pick the most promising new therapies for future studies.

All of the drugs used on this study are FDA approved for various kinds of cancers and commercially available, but using them together with radiation therapy in this way is experimental treatment.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of people enrolled on this study is expected to be 300.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Random Assignment

Subjects (people participating in the study) will receive 1 of 4 different treatment plans. The treatment plan they receive is decided by a process called randomization. Randomization means that the treatment is assigned based on chance. It is a lot like flipping a coin, except that it is done by computer to make sure that there are about the same number of people on each treatment plan of the study. The randomization process is described in your Family Handbook for Children with Cancer. Subjects who have had clinical depression or an allergy to parabens or soybeans will be randomized to Regimen A or Regimen B and will not receive isotretinoin.

Treatment Plan

The treatment plan will begin within 31 days after your surgery (to remove the tumor) and will involve a combination of radiation therapy and chemotherapy. The treatment on this clinical trial takes either 9 or 15 months (depending on the treatment arm you are randomized to) and is divided into 2 or 3 stages (also depending on the treatment arm you are randomized to).

The first stage of therapy is called chemoradiotherapy. All subjects will receive a combination of radiation therapy and chemotherapy to kill the cancer cells that are left over after surgery. This stage of therapy will take 6 weeks. Some subjects will have an extra chemotherapy drug, carboplatin, added to this treatment phase.

In the second stage of therapy, called Maintenance, all subjects will receive a combination of chemotherapy drugs (see Attachment #1 for a list of drugs used). Maintenance therapy will last 6 months. The goal of maintenance therapy is to kill any remaining cancer cells that are left over from chemoradiotherapy. Some subjects will have an extra chemotherapy drug, isotretinoin, added to their regimen of chemotherapy drugs during this stage.

Only some subjects will go onto a third stage of therapy, called Continuation. Continuation therapy will consist of 6 more months of therapy with the drug isotretinoin.

The stages of therapy and chemotherapy drugs that you receive will depend upon which treatment arm you are assigned to. You will be "randomized" into one of the study groups described below.

All subjects will receive the standard therapy for medulloblastoma, but some subjects will receive additional drugs during their course of therapy.

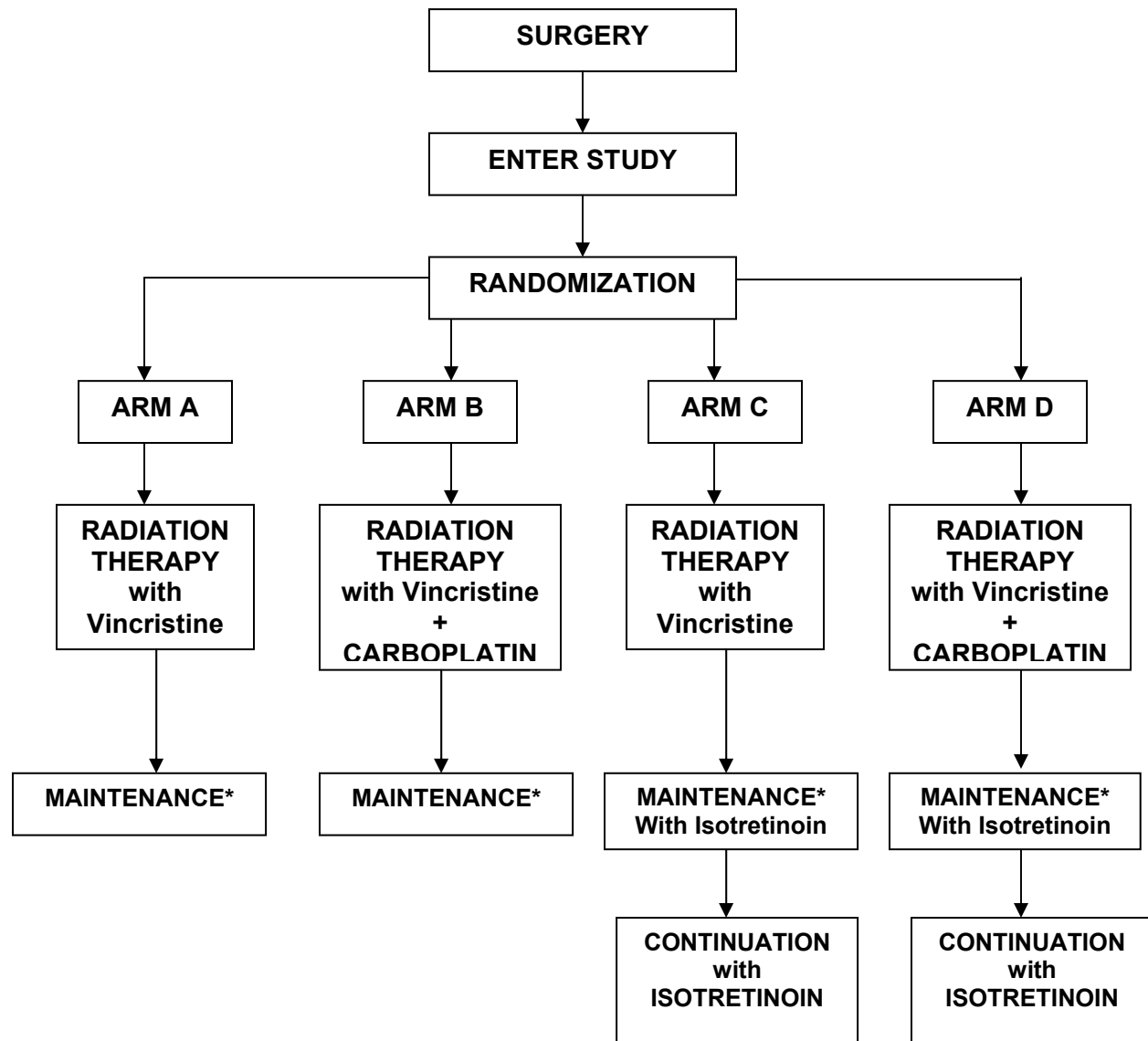
The four treatment arms are as follows:

- **Arm A:** will receive standard chemoradiotherapy (radiation therapy and the drug vincristine). Subjects will then receive standard Maintenance chemotherapy.
- **Arm B:** will receive chemoradiotherapy plus the experimental drug **carboplatin**. Subjects will then receive standard Maintenance chemotherapy.
- **Arm C:** will receive standard chemoradiotherapy. Subjects will then receive Maintenance therapy with the addition of the drug **isotretinoin** and Continuation therapy with **isotretinoin**.
- **Arm D:** will receive chemoradiotherapy plus the experimental drug **carboplatin**. Subjects will then receive Maintenance therapy with the addition of the drug **isotretinoin** and Continuation therapy with **isotretinoin**.

If you are randomized to Arm C or Arm D to receive isotretinoin, you will be required to complete the attached Patient Drug Diary (see Attachments #4 and #5).

Diagram of Treatment

A diagram of treatment can be seen below.



* Maintenance therapy will use the drugs cisplatin, vincristine and cyclophosphamide

Treatment Plan Tables

Treatment that is standard for medulloblastoma is described in Attachment #1. The following drug therapies relate to the experimental comparison of the treatment groups in this study.

The following methods will be used to give the two investigational drugs in this study:

- PO - Drug is given by tablet or liquid swallowed through the mouth (PO). This applies to the isotretinoin.
- IV - Drug is given using a needle or tubing inserted into a vein. It can be given by IV push over several minutes or by infusion over minutes or hours. This applies to the carboplatin.

Chemoradiotherapy

All subjects will be given radiation therapy 5 days a week for 6 weeks. In addition to the radiation therapy all subjects will receive the drug vincristine on one day each week. This is standard chemoradiotherapy.

Treatment for subjects on Treatment Arm B and D

Carboplatin will be given to subjects in Arm B and D on the same days that radiation therapy is given (5 days of each week for 6 weeks).

Drug	How the drug will be given	Days
carboplatin	IV	5 days each week for 6 weeks

Subjects in treatment Arm A and Arm C will not receive carboplatin during chemoradiotherapy.

When the 6 weeks of chemoradiotherapy treatment is over all subjects will have a 6 week rest period with no treatment.

Maintenance chemotherapy

When the rest period is over, all patients will move on to maintenance therapy. Maintenance therapy is part of standard care and all patients will get a combination of standard chemotherapy drugs for this stage. Maintenance therapy will consist of 6 cycles of chemotherapy that each last 28 days (for all Treatment Arms). See Attachment #1 for a description of the drugs and other details of standard maintenance therapy.

Treatment for subjects on Treatment Arm C and D

Arm C and D will have an extra chemotherapy drug, isotretinoin, added to the maintenance therapy regimen.

Drug	How the drug will be given	Days (for 1 cycle)
Isotretinoin	PO twice a day	Day 1, and Days 16-28

Treatment Arm A and B will not receive isotretinoin as part of maintenance therapy. Subjects in Treatment Arm A and B will have completed study treatment after maintenance therapy and will only have follow-up testing from that point on unless the tumor grows back.

Continuation Therapy

If you are in Arm C or D you will have 6 more cycles of therapy with isotretinoin.

Treatment for participants who are on treatment plan Arm C and D

Drug	How the drug will be given	Days (for one cycle)
Isotretinoin	PO twice a day	Days 15-28

Subjects in Arm A and B will have no continuation therapy (their treatment is completed after maintenance therapy).

Research study tests and procedures

The following tests will be done as part of this study.

Although the following tests are part of standard care, they may be done more often if you are on this study:

- Hearing tests
- Blood Tests

Optional Neuropsychological Tests

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

Review of Diagnosis

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

Follow-Up Tests

You will need to have a number of tests and procedures done as part of your follow-up to treatment. We will use these tests to follow your progress, monitor side effects and look for any signs that the disease has returned.

In addition to those tests done to evaluate the cancer, there will be other tests to monitor the effects of the treatment in your body. Some tests, like the brain function tests and hearing tests, will need to be done more frequently than usual because you are in this study.

- An MRI of your head
 - will be done every 3 months from the time of diagnosis until 2 years after treatment is finished, then every 6 months for years 3 and 4. An MRI will also be done if the disease gets worse or comes back after therapy.
- An MRI of your spine
 - will be done at the same time points described above for your head if your initial spine MRI showed disease.
- A lumbar puncture
 - will be done at the time of diagnosis. If it shows disease at the time of diagnosis, the test will be repeated every 3 months for the first year, then every 6 months for years 2 and 3, then once a year for years 4 and 5. A lumbar puncture will also be done if the disease gets worse or comes back after therapy.
- A hearing test
 - will be performed before each cycle that contains cisplatin, then every 6 months for 2 years, and then once a year.
- A test to measure your thyroid function
 - will be performed every 6 months for the first year after treatment, and then once a year.
- A test to measure your growth
 - will be performed every 6 months for the first year after treatment, and then once a year.

Optional Biology Test

In addition to the required tests described above, we would like to use information collected on this study to answer some research questions that might benefit future patients. We would like to do some extra tests on your tumor tissue. We are requesting a sample of your tumor that was removed during surgery and left over after diagnostic tests were completed. Taking part in these extra tests will not require that you undergo any additional procedures.

The result of these tests will not affect your treatment. These tests are voluntary and if you say “no” your treatment will not be changed in any way.

You will not have to pay for these tests to be done, and you will not be paid for the use of your tissue for research purposes.

The reason for the optional research studies is that we hope to develop markers from the tumor that can predict (a) how a subject will respond to treatment, and (b) which drugs will be useful for future patients. This information will help us to target more effective therapies against medulloblastoma in the future

It is very unlikely that the research testing might uncover important information about your current or future health. If this unlikely event occurs, the researchers may contact your doctor through COG's Data Center about what the research tests might mean. Only the doctor will be notified and the information will not become part of your medical record. It will remain confidential. Your doctor may discuss this unexpected finding with you. Your doctor may recommend consultation with a genetic counselor or repeat testing in a clinical (not research) laboratory if needed. It is possible that your doctor may recommend that no additional action is necessary.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to receive treatment on this study for 9 months (if you are on Arm A or B) or 15 months (if you are on Arm C or D). After treatment, subjects will have follow-up examinations and medical tests for 4 years. We would like to continue to find out about your health for about 10 years after you start this study. Keeping in touch with you and checking on how your health is every year for a while after you have finished the study helps us understand the long-term effects of the study.

Your doctor or the study doctor may decide to take someone off this study under the following circumstances:

- if he/she believes that it is in the person's best interest
- if the person's disease comes back during treatment
- if the person experiences side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for the person

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

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks

All people who receive cancer treatment are at risks of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications.

Common side effects include nausea, vomiting, hair loss, and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. Some chemotherapy may lead to sterility. Sterility is the inability to have children. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy. The risks of the individual drugs given as standard treatment and risks of radiation therapy are listed on the tables in **Attachment #2**. Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in your Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not get rid of the cancer or that the cancer can go away after the treatment and then come back at a later date.

Because the drugs and/or radiation therapy used in this study can affect a developing fetus (unborn baby in the womb), you should not become pregnant or father a baby while on this study. Ask about counseling and more information about preventing pregnancy. The

administration of chemotherapy and radiation described may cause infertility (being less able to produce a viable egg or sperm) or sterility (being unable able to produce a viable egg or sperm). We will talk to males who have reached puberty about sperm banking.

Risks of Study

The use of carboplatin and/or isotretinoin may cause more complications than standard therapy alone.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

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

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> • Nausea and vomiting • Fewer red blood cells and white blood cells and platelets in the blood <ul style="list-style-type: none"> ○ a low number of red blood cells can make you feel tired and weak ○ a low number of white blood cells can make it easier to get infections ○ a low number of platelets causes you to bruise and bleed more easily • Abnormal levels of certain salts in the body like sodium and potassium 	<ul style="list-style-type: none"> • Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure) • Rash • Metallic taste • Numbness and tingling in the fingers and toes • Hair loss • Constipation or diarrhea • Pain in your abdomen • Temporary changes in vision • Damage to the ear causing hearing and balance problems • A feeling of weakness and/or tiredness • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores) 	<ul style="list-style-type: none"> • Damage to the liver • Damage to the kidney • Leukemia later in life

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

Likely	Less Likely	Rare but serious
<ul style="list-style-type: none"> • Dryness of your skin and mucous membranes • Dry, cracked and bleeding lips • An increased tendency to sun burn • Bloody nose from dry membranes of the nose • Aches and pains in the joints • Back pain • Elevation of the fats in your blood • Increase in calcium in your blood which may require decreasing the 	<ul style="list-style-type: none"> • Rash and itching • Headache • Increase in cholesterol and a decrease in the good fat in the blood • Red eyes • Elevation in the blood of certain enzymes found in the liver which may mean liver irritation or damage • Fewer red blood cells and white blood cells and platelets in the blood <ul style="list-style-type: none"> ○ a low number of red blood cells can make you feel 	<ul style="list-style-type: none"> • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Irritation of the small airways in your lungs that can make you cough and wheeze • An allergic reaction in the blood vessels of the skin which turn the skin red, inflamed and bumpy and which may

<p>dose</p> <ul style="list-style-type: none"> • An increase in a laboratory test on your blood that may measure some non specified inflammation which may or may not be of any importance 	<p>tired and weak</p> <ul style="list-style-type: none"> ○ a low number of white blood cells can make it easier to get infections ○ a low number of platelets causes you to bruise and bleed more easily <ul style="list-style-type: none"> • Too many platelets in the blood • Loss or thinning of hair • Appetite disturbances causing you not to feel hungry or to feel unusually hungry • Weight loss • Increase in blood sugar levels • A darkening or lightening of your skin • Finger and toe nail changes including breaking or splitting more easily • The sudden appearance of little yellow raised bumps on the skin usually because the cholesterol in the blood is too high (xanthomas) • Dizziness • Difficulty falling asleep or staying asleep and strange dreams • A feeling of tiredness or not feeling well • Nervousness • Numbness and tingling in the fingers and toes • Difficulty hearing clearly or a ringing in the ears • Changes in vision including more difficulty seeing at night, blurred vision, changes in color vision, pain or squinting in bright light, and cataract formation • Fluid retention • Chest pain • Inflammation of the 	<p>lead to skin breakdown</p> <ul style="list-style-type: none"> • A severe lowering of the white blood count which can make you very susceptible to infections which could be life threatening • Convulsions • Brain swelling that can give you symptoms of severe headache, nausea and vomiting, and changes to your vision including blurriness and pressure behind the eyes • Life threatening or fatal changes in moods have occurred including severe depression or feelings of suicide and feelings of aggressiveness and violent behavior • Thinning of the bone (osteoporosis) which could lead to weakness of the bone, bone fractures or delay in healing of fractures • Inflammation of the pancreas which can lead to severe abdominal pain and in some very rare cases can be fatal • Damage to the muscle which can release a protein that can cause severe damage to the kidneys • Inflammation of the intestinal tract which can result in diarrhea and bleeding • This drug can cause severe birth defects in a developing fetus, if you are capable of becoming pregnant or of child bearing age, you must practice 2 forms of reliable birth control, sign the Patient Information/Informed
---	---	--

	<p>gums</p> <ul style="list-style-type: none"> • A dry throat which could lead to a change in your voice and more throat infections • Slowed growth • Irregular periods • Mild kidney damage which could lead to blood or protein in the urine or renal stones • Extra bone growth along the spine and a tendency for calcium deposits in the tendons and ligaments where they attach to the bone which can lead to pain or stiffness and arthritis of the back and tendonitis 	<p>Consent form(s), have regular pregnancy tests, be able to keep appointments and agree to follow the iPLEDGE program steps (a special program required by the manufacturers and approved by the Food and Drug Administration (FDA) which your doctor will explain to you).</p>
--	--	---

Reproductive Risks

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. While doctors hope that treatment that includes the drugs carboplatin and/or isotretinoin will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about using carboplatin and isotretinoin as a treatment for this type of cancer.

If you are randomized to receive carboplatin during the period of chemoradiation you may benefit from this study if carboplatin does improve the effectiveness of the radiation and/or make the cancer less likely to return.

If you are randomized to receive isotretinoin during the maintenance phase of therapy you may benefit from this study if the addition of isotretinoin does make the cancer less likely to return.

The potential benefits of participation in this study could include better chance of getting rid of cancer for subjects with high risk medulloblastoma. We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

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

- **Current standard therapy even if you do not take part in the study. Standard therapy is described on page 3 and Attachment #1. It is Arm A of this study.**
- **Taking part in another study**

Please talk to your doctor about these and other options.

WHAT ABOUT PRIVACY?

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

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is attached at end of this consent (Attachment #3).

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

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

WHAT ARE THE COSTS?

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

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

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

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

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

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

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

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at (XXXX

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at XXXX

WHERE CAN I GET MORE INFORMATION?

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

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

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

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. The form includes five (5) attachments.

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

I agree to take part in this study.

Participant _____ Date _____

Parent/Guardian _____ Date _____

Parent/Guardian _____ Date _____

Physician/PNP obtaining consent _____ Date _____

IRB#

IRB Approved:

Attachment #1 **Treatment and Procedures Common to all Patients with Medulloblastoma**

Central Line

For drugs to be given by vein, your doctor will likely recommend that you (your child has) have a central venous line placed. A description of the types of central lines is in your Oncology Family Notebook.

Methods for Giving Drugs

Various methods will be used to give drugs to patients. Some drugs will be given by tablet or liquid swallowed through the mouth (**PO**). Other drugs are given by inserting a needle into the tissue just under the skin. This method is called a subcutaneous (**SubQ**) injection. Most drugs on this study will be given using a needle or tubing inserted into a vein (**IV**).

Therapy for patient on all treatment plans:

Chemoradiotherapy

In the first stage of treatment all patients receive chemoradiotherapy. The purpose of the chemoradiotherapy phase of therapy is to kill as many of the cancer cells left over from your surgery as possible so the disease goes into remission.

Radiation Therapy

Radiation therapy will begin about 4 weeks after surgery.

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

Chemotherapy

V = Vincristine will be given directly into a vein (for less than 60 seconds) once a week for 6 weeks. The dose will be 1.5 mg/m².

Surgery	Rest		Chemoradiotherapy						Rest
	4 weeks		Radiation Therapy						6 weeks
		Week	1	2	3	4	5	6	
		Days	1-5	8-12	15-19	22-26	29-33	36-40	
			Chemotherapy						
			V	V	V	V	V	V	
		Day	1	8	15	22	29	36	

Maintenance Chemotherapy

Maintenance chemotherapy would be the second stage of treatment for standard therapy. Maintenance therapy is used in this study but with the addition of isotretinoin for some treatment arms. Below is a description of Maintenance chemotherapy as it is being used in this study for all subjects.

Maintenance chemotherapy begins 6 weeks after the completion of chemoradiotherapy. Maintenance chemotherapy will consist of 6 cycles of chemotherapy that each last 28 days.

Maintenance chemotherapy will include the following drugs:

- Cisplatin, given directly into a vein over 6 hours on Day 1 of each cycle. The dose will be 75 mg/m².
- Vincristine, given directly into a vein over one minute or using a minibag over several minutes by some institutions on Days 1 and 8 of each cycle. The dose will be 1.5 mg/m².
- Cyclophosphamide, given into a vein over 1 hour on Days 2 and 3 of each cycle. The dose will be 1 g/m².

Other drugs will be given to all subjects to help with the side effects of the study drugs. These drugs include:

- Filgrastim (also called G-CSF) to help your child's blood counts recover after chemotherapy given directly into a vein or by inserting a needle into the tissue just under the skin.

Standard tests and procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study.

- Frequent labs to monitor blood counts and blood chemistries
- Urine tests to measure how the kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins. If you are randomized to Arm C or D a pregnancy test will also be obtained before the start of Maintenance.
- X-rays and scans to monitor the patient's response to treatment.
- Physical exam
- Liver function tests
- Brain function tests
- MRI (Magnetic Resonance Imaging) of brain and spine. MRI uses magnetic waves to look at soft tissue of the body.
- Evaluation of cerebral spinal fluid (CSF) obtained by lumbar puncture. A small needle will be inserted into the spinal fluid, and a few teaspoons of spinal fluid will be collected. The test is painful and has a small risk of infection or bleeding. The pain usually is brief but may linger. Lumbar punctures may cause headache. In most cases, you will get medications to numb the pain and blur the memory.
- Thyroid function tests.
- Growth tests

Attachment #2
Risks of Chemotherapy Drugs and Radiation Used to Treat

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

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

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

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

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

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

The drug below will be given to help with the side effects of the study drugs.

Risks and side effects related to Filgrastim (G-CSF) include those which are:

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

Radiation Risks – CNS radiation

Radiation therapy may produce the following side effects: nausea, vomiting, diarrhea, generalized redness or dryness of the skin, bone marrow failure (absent blood counts resulting in increased risk of infection, weakness and bleeding), loss of hair (which may take 6 months or more for full re-growth), parotitis (swelling of salivary glands) causing jaw pain and swelling, damage to major body organs which may include the brain, eyes, heart, lung, liver and kidneys, and reddening of the skin. There is also the risk of temporary worsening of neurological symptoms such as weakness or loss of sensation. Some children experience a week or two of low grade temperature and extreme sleepiness six to eight weeks after radiation therapy has been completed.

Possible late effects may include: shortened height (growth retardation), back bone change of shape (vertebral deformities), difficulty with vision (cataracts), changes in endocrine function (low hormones), inability to have children (sterility), learning disabilities or brain damage, and increased risk of developing another cancer.

Attachment #3
Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

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

Attachment #4
ACNS0332 ISOTRETINOIN MAINTENANCE PATIENT DIARY

Patient Name: _____

Drug: Isotretinoin

Daily Dose (divided bid): _____ mgs.

A.M.	Take _____	10 mg capsule(s)
	Take _____	20 mg capsule(s)
	Take _____	30 mg capsule(s)
	Take _____	40 mg capsule(s)

P.M.	Take _____	10 mg capsule(s)
	Take _____	20 mg capsule(s)
	Take _____	30 mg capsule(s)
	Take _____	40 mg capsule(s)

CYCLE _____

	Date	Time	Number of Capsules Taken				Problems
			10mg	20mg	30mg	40mg	
Day 1	AM						
	PM						
Day 16	AM						
	PM						
Day 17	AM						
	PM						
Day 18	AM						
	PM						
Day 19	AM						
	PM						
Day 20	AM						
	PM						
Day 21	AM						
	PM						
Day 22	AM						
	PM						
Day 23	AM						
	PM						
Day 24	AM						
	PM						
Day 25	AM						
	PM						
Day 26	AM						
	PM						
Day 27	AM						
	PM						
Day 28	AM						
	PM						

Attachment #5
ACNS0332 ISOTRETINOIN CONTINUATION PATIENT DIARY

Patient Name: _____

Drug: Isotretinoin

Daily Dose (divided bid): _____ mgs.

A.M.	Take _____	10 mg capsule(s)
	Take _____	20 mg capsule(s)
	Take _____	30 mg capsule(s)
	Take _____	40 mg capsule(s)

P.M.	Take _____	10 mg capsule(s)
	Take _____	20 mg capsule(s)
	Take _____	30 mg capsule(s)
	Take _____	40 mg capsule(s)

CYCLE _____

	Date	Time	Number of Capsules Taken				Problems
			10mg	20mg	30mg	40mg	
Day 15	AM						
	PM						
Day 16	AM						
	PM						
Day 17	AM						
	PM						
Day 18	AM						
	PM						
Day 19	AM						
	PM						
Day 20	AM						
	PM						
Day 21	AM						
	PM						
Day 22	AM						
	PM						
Day 23	AM						
	PM						
Day 24	AM						
	PM						
Day 25	AM						
	PM						
Day 26	AM						
	PM						
Day 27	AM						
	PM						
Day 28	AM						
	PM						