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The world's childhood cancer experts

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June 23, 2014

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Dear Ms. Kruhm,

Attached is Amendment #4 to **ACNS0821**, *Temozolomide with Irinotecan versus Temozolomide, Irinotecan plus Bevacizumab (NSC# 704865, BB-IND# 7921) for Recurrent/Refractory Medulloblastoma/CNS PNET of Childhood, A COG Randomized Phase II Screening Trial*.

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The amendment is being submitted in response to an RA from Dr. Helen Chen (helen.chen@nih.gov) dated May 9, 2014. The bevacizumab monograph has been modified to reflect the incorporation of the revised Comprehensive Adverse Events and Potential Risks (CAEPR) list for bevacizumab provided by the NCI. The changes made due to this request are detailed below.

In addition, the eligibility criteria have been revised regarding measurable disease. Liberalizing the eligibility requirement will allow the study to enroll more patients with recurrent/refractory disease and will offer these patients the opportunity for study participation when other therapeutic options are quite limited.

The primary objective of the study is to compare the overall survival (OS) of subjects receiving the combination of temozolomide and irinotecan with that of subjects receiving temozolomide, irinotecan and bevacizumab for recurrent medulloblastoma (MB)/PNET of childhood. Measurable disease is a vital eligibility criterion only if the primary objective is tumor response and EFS. However, with OS as the primary outcome of the study, it is not imperative that patients have measurable disease at the time of enrollment. Patients with leptomeningeal disease or patients with clear residual disease following resection of recurrence will be enrolled and still be assessable for OS. The Study committee will stratify patients for randomization to each treatment arm according to whether or not they have measurable disease. Thus, exposure to each treatment arm will be similar for an equal number of patients that have no measurable disease at the time of enrollment. While power may be limited, the investigators will test for a differential effect on outcome based on whether or not measurable disease was present at enrollment.

In addition, administrative changes have also been included.

Specific changes are detailed below.

## SUMMARY OF CHANGES: PROTOCOL DOCUMENT

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | Title Page | 1 | The version date and amendment number have been updated. |
| 2. | Table of Contents | 2-3 | The table of contents has been updated since the protocol has been repaginated. |
| 3. | Study Committee | 4-5 | The contact information for Drs.Krailo and Chris Williams-hughes have been updated. Dr. Jakacki has been replaced by Dr. Chi as the Vice-chair. Dr. Turner and Ingrid Shieh have been removed and Sung Tse has been added. |
| 4. | Abstract | 6 | The last paragraph has been revised to include evaluable disease. |
| 5. | 1.2.1 | 8 | The objective has been revised as below.<br><br>To assess the response rate for each treatment arm **amongst patients who are enrolled with measurable disease**. |
| 6. | 3.1.5 | 14 | The following statement has been added.<br><br>**Patients will be stratified for randomization to each treatment arm according to whether or not they have measurable disease.** |
| 7. | 3.2.2.3 | 14 | The section has been revised as below.<br><br>**Patients must have clear residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI OR diffuse leptomeningeal disease OR clear MRI evidence of disease that may not be measurable in two perpendicular diameters.**<br>~~Patients must have measurable residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI. Diffuse leptomeningeal disease is not considered measurable.~~ |
| 8. | 6.0 | 31 | The following statement was added, "**Please see Appendix VIII for drug interactions associated with the drugs used in this study**". |
| 9. | 6.1 | 31-38 | The Bevacizumab monograph has been updated as requested by the RA to include the updated CAEPR (Version 2.3).<br><br>• Added New Risk:<br>  • Less Likely: Dehydration; Wound complication<br>  • Rare But Serious: Infections and infestations |

| | | | |
|---|---|---|---|
| | | | – Other (necrotizing fasciitis)<br>• Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (tympanic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyramidal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular pucker); Eye disorders – Other (transient increased IOP > or = 30 mm Hg); Eye disorders – Other (vitreous hemorrhage); Eye pain; Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperthyroidism; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; |

| | | | |
|---|---|---|---|
| | | | Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor pain; Typhlitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain<br><br>• Increase in Risk Attribution:<br>  • Changed to Likely from Less Likely: Neutrophil count decreased<br>  • Changed to Less Likely from Reported But Undetermined: Platelet count decreased<br><br>• Decrease in Risk Attribution:<br>  • Changed to Reported But Undetermined from Less Likely: Vertigo<br><br>• Provided Further Clarification:<br>  • Supraventricular tachycardia is now reported |

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| | | | as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, "Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter."<br>• Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the following footnote (#10) was added, "Anastomotic leak may include Gastrointestinal anastomotic leak; Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak."<br><br>• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:<br>• Added: Dehydration; Platelet count decreased; Wound complication<br><br>• Deleted Risk:<br>• Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothorax<br><br>In addition, the version date and agent ordering information have been updated. |
| 10. | 9.2 | 45 | The following statement was added.<br>**Patients will be stratified for randomization to each treatment arm according to whether or not they have measurable disease**. |
| 11. | 9.3.3 | 47 | The following statement has been added.<br><br>**Only patients who are enrolled with measurable disease will be considered in the evaluation of response rate.** |
| 12. | 9.5 | 48 | The section title has been revised. |
| 13. | 10.2 | 49-52 | The section has been revised and separated into sections 10.2.1, 10.2.2 and 10.2.3. The title of Table 10.2 has been revised and Table 10.2b has been added. |
| 14. | 10.4 | 53 | Item 5 was added for patients with measurable disease. |
| 15. | 10.5 | 53 | The following statement was added.<br>**Non-target lesions will only be evaluated in patients with measurable disease.** |
| 16. | 11.0 | 55-62 | The AE Reporting guidelines have been updated using the new CTEP AERS Reporting. |

| | | | |
|---|---|---|---|
| 17. | Appendix VIII | 77-78 | The Appendix was added to include possible drug interactions for each agent used in the study. |

**SUMMARY OF CHANGES: INFORMED CONSENT DOCUMENT**

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

| # | Section | Page(s) | Change |
|---|---|---|---|
| 1. | WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT? | 7-8 | The side effects of bevacizumab have been updated using the COG format.<br><br>The bevacizumab monograph has also been revised to include the following changes according to the Request for Amendment for bevacizumab from CTEP.<br><br>• Added New Risk:<br>  • **Occasional: Dehydration; Delay in healing of wounds or spontaneous opening of wounds**<br>  • **Rare: Flesh-eating bacteria syndrome, an infection in the deep layers of skin**<br><br>• Decrease in Risk Attribution:<br>  • Changed to Reported But Undetermined from Less Likely (i.e., removed from the Risk Profile): Feeling of spinning or whirling<br><br>The condensed risk profile has been modified to include the following.<br>Added to to "Common"<br>• **Low white cell count that may increase the risk of infection**<br>• **Absence of menstrual cycles (periods) and damage to the ovaries that may decrease the ability to have children in the future**<br><br>Added to "Occasional"<br>• **Abnormal bone changes which may interfere with growth**<br>• **Increased blood level of liver tests which may mean there has been damage to the liver**<br><br>In addition, the following statement was added.<br>**Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription drugs, over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.** |

| | | | |
|---|---|---|---|
| 2. | WHAT ARE THE COSTS? | | The fourth paragraph has been revised. |
| 3. | WHAT ARE MY RIGHTS AS A PARTICIPANT? | 11 | The fourth paragraph has been updated and revised regarding follow-up visits. |
| 4. | Attachment #2 | 14-15 | The possible side effects of irinotecan have been updated using the COG format. In addition, the drug interactions for temozolomide have been removed and included in Appendix VIII. |

Please let me know if we can offer further information.

Sincerely,

Chris Williams-Hughes, Protocol Coordinator (for)
Adam Levy, MD, MS, Study Chair, ACNS0821
Peter Adamson, MD, Group Chair, Children's Oncology Group

Activated: November 22, 2010
Closed:
Version Date: 6/23/14
Amendment # 4

**CHILDREN'S ONCOLOGY GROUP**

**ACNS0821**

# Temozolomide with Irinotecan versus Temozolomide, Irinotecan plus Bevacizumab (NSC# 704865, BB-IND# 7921) for Recurrent/Refractory Medulloblastoma/CNS PNET of Childhood, A COG Randomized Phase II Screening Trial

**A Groupwide Phase II Study**

***NCI Supplied Agent: Bevacizumab (IND# 7921, NSC#704865)***



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**AGENT NSC# AND IND#'s**

Bevacizumab (Supplied by the NCI) NSC# 704865 IND# 7921
Irinotecan NSC #616348
Temozolomide NSC# 362856

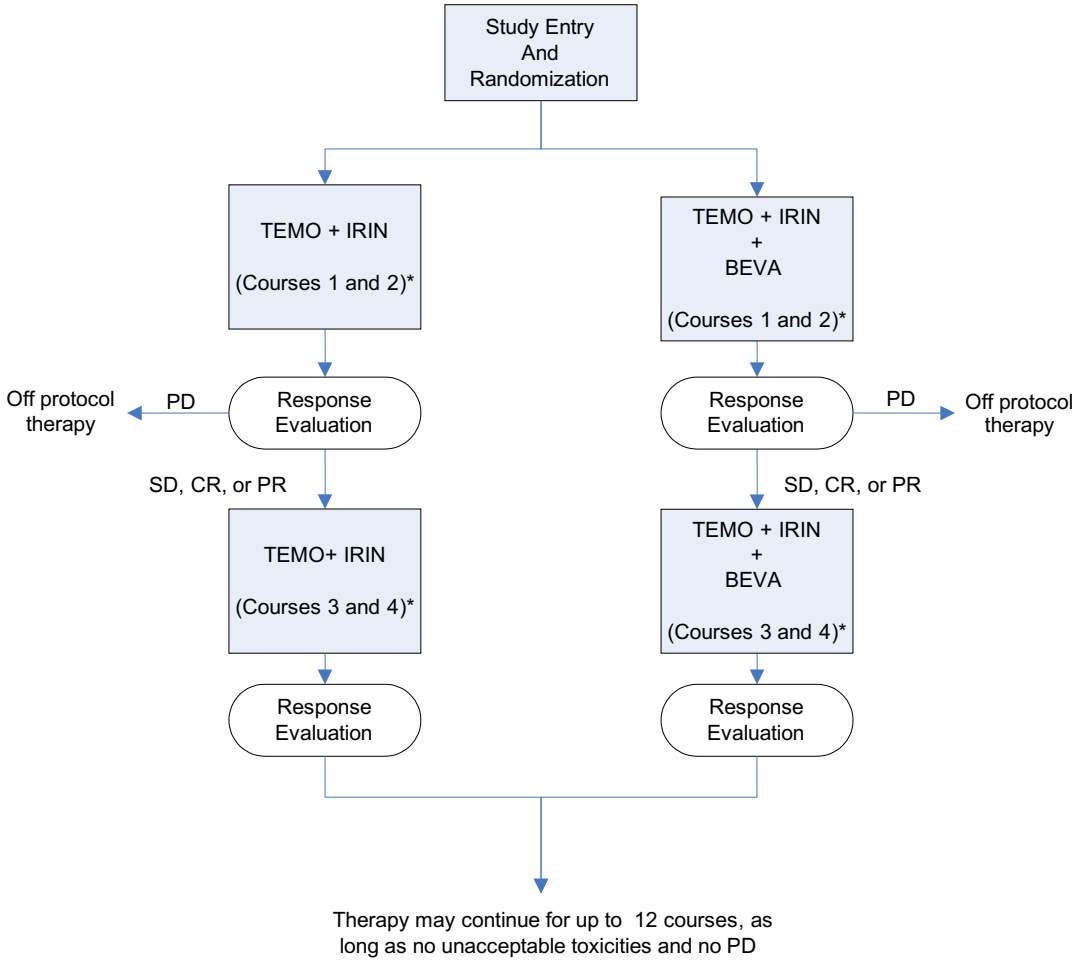
## ABSTRACT

Temozolomide is an orally administered alkylating agent of the imidazotetrazine derivatives with excellent CNS penetration. Phase II studies have shown variable response rates of 16-47% in children and adolescents with recurrent medulloblastomas/PNET. Irinotecan is a water-soluble campothecin derivative that inhibits topoisomerase I (topo I), an enzyme involved in DNA repair, transcription and replication.[1-3] Irinotecan has been shown to have single agent activity against recurrent medulloblastomas.[4] A British study found a 40% objective response rate to the combination of irinotecan and temozolomide in patients with recurrent MB/PNET. Bevacizumab is a humanized monoclonal neutralizing antibody binding all five isoforms of human vascular endothelial growth factor (VEGF). CNS tumors are potentially excellent targets for anti-angiogenic therapy given the presence of tumor neo-vascularization and high concentrations of pro-angiogenic factors.[5-7]

Both irinotecan and temozolomide have activity against recurrent MB/PNET and the combination has been well tolerated in heavily pre-treated patients.[8] The addition of bevacizumab theoretically may increase the efficacy of chemotherapy. Therefore, a phase II trial evaluating the addition of bevacizumab to the combination of irinotecan and temozolomide in MB/PNET of childhood will be performed.

This study will use a randomized phase II screening design[4,9] to compare temozolomide (150 mg/m$^2$ PO for 5 days) with irinotecan (50 mg/m$^2$ IV for 5 days) to temozolomide, irinotecan plus bevacizumab (10 mg/kg IV on Days 1 and 15), in children with recurrent MB/PNET. Patients must have measurable or evaluable disease. Response will be evaluated prior to every other course. Therapy can be continued for up to 12 courses in the absence of disease progression or unacceptable side effects.

## EXPERIMENTAL DESIGN SCHEMA




* Each course is 28 days

TEMO = Temozolomide 150 mg/m$^2$/day PO on Days 1-5
IRIN = Irinotecan 50 mg/m$^2$/day IV on Days 1-5
BEVA = Bevacizumab 10 mg/kg IV on Days 1 and 15
PD = Progressive Disease
SD = Stable disease
PR = Partial Response
CR = Complete Response

## 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

### 1.1 Primary Objective

To compare the overall survival (OS) of subjects receiving the combination of temozolomide and irinotecan with that of subjects receiving temozolomide, irinotecan and bevacizumab for recurrent medulloblastoma (MB)/PNET of childhood.

### 1.2 Secondary Objectives

1.2.1 To assess the response rate for each treatment arm amongst patients who are enrolled with measurable disease.

.

1.2.2 To determine event-free survival (EFS) for each patient compared across regimens.

## 2.0 BACKGROUND

2.1 Redacted

2.2 Redacted

Redacted

2.3 **Temozolomide**

Temozolomide is an orally administered alkylating agent of the imidazotetrazine derivatives with excellent CNS penetration. It is the prodrug of the cytotoxic triazine, monomethyl triazenoimidazole carboxamide (MTIC), which is the active metabolite of dacarbazine (DTIC).[20] Temozolomide is currently FDA approved for the treatment of recurrent anaplastic astrocytomas and newly diagnosed glioblastoma multiforme. The Children's Cancer Group (CCG) conducted a phase I study of temozolomide in children and adolescents with recurrent solid tumors. In this study, responses were seen in medulloblastomas and supratentorial PNETs.[21] A complete response to temozolomide has also been reported in a patient with leptomeningeal recurrence of a medulloblastoma.[22] An Italian multicenter study of temozolomide in patients with recurrent or refractory MB/PNET following craniospinal radiation therapy and multiple chemotherapy regimens found an objective response rate of 47%, including 6 of 34 patients with a complete response.[23] A COG phase 2 study of temozolomide in children and adolescents with recurrent CNS tumors found temozolomide to be modestly active as a single agent for recurrent MB/PNET with an overall response rate of 16%. Of 29 patients with MB/PNET, 25 were evaluable with 1 CR (4%) and 3 PR (12%).[1] Thus, temozolomide appears to be active as a single agent for recurrent medulloblastoma although the reported response rates are highly variable.

2.4 **Irinotecan**

Irinotecan is a water-soluble campothecin derivative that inhibits topoisomerase I (topo I), an enzyme involved in DNA repair, transcription and replication.[2,3,24] In xenograft models of childhood tumors including neuroblastoma, sarcomas and brain tumors, single agent irinotecan has demonstrated anti-tumor activity.[25-27] Irinotecan demonstrated potent therapeutic activity in medulloblastoma xenografts in nude mice.[28] Irinotecan is a prodrug that is metabolized by carboxylesterase enzymes to form SN-38 which is 100-1000 times more potent as a topo I inhibitor than irinotecan.[29-33] Major common toxicities include diarrhea, altered liver function, and myelosuppression when given in combination with other chemotherapeutic agents. IRIN activity is schedule-dependent in mouse xenograft models,and a low-dose protracted schedule administered daily x 5 for 2 consecutive weeks in preclinical studies was most efficacious and demonstrated less hematological toxicity than higher-dose bolus regimens.

Many doses and schedules of irinotecan have been studied. A phase I pediatric study of irinotecan given as a 2-hour infusion once every 3 weeks reported 1 partial response, 1 minor response, and 2 patients with stable disease out of the 19 previously treated medulloblastoma patients.[34] A COG phase II trial evaluated irinotecan 50 mg/m$^2$/day for 5 days every 21 days in children with refractory tumors.[4] Irinotecan on this schedule was generally well tolerated. The best response rate was seen in the recurrent medulloblastoma stratum (16%). In a separate pediatric phase II study of irinotecan dosed at 125 mg/m$^2$ per week given IV for four weeks followed by a two week rest, two of three patients with MB/PNET had stable disease for 9 and 13 months.[35] Based on the preclinical experience suggesting enhanced irinotecan activity when given on a protracted daily schedule and the responses seen in the phase II COG study, the current study will utilize daily irinotecan given on the first 5 days of each course.

### 2.5 Combination of Temozolomide and Irinotecan

The combination of temozolomide with irinotecan was studied in xenograft models of neuroblastoma, rhabdomyosarcoma and glioblastoma.[36] The activity of the combination suggested schedule-dependent synergistic efficacy, and pharmacokinetic studies demonstrated no interactions between the agents. To the contrary, administration of irinotecan with temozolomide appeared to reduce temozolomide toxicity in this mouse model. The combination of temozolomide with irinotecan has been evaluated in adult solid tumors using a variety of schedules. Jones et al.[37] reported partial responses in patients with GBM, head and neck carcinoma and colorectal carcinoma in a phase I trial utilizing three different dosing schedules. A total of 49 patients were enrolled and the ideal dosing schedule could not be determined. Another study for patients with recurrent malignant glioma combined temozolomide 200 mg/m$^2$ daily for 5 days and irinotecan given at different doses and schedules.[38] Limited accrual precluded determining an advantage of one schedule over the other. Toxicity was mild, and only rare Grade 4 leukopenia and thrombocytopenia were noted. A phase I trial for adults with recurrent malignant glioma determined an MTD of temozolomide 200 mg/m$^2$/day on Days 1-5 plus intravenous IRIN 125 mg/m$^2$ (325 mg/m$^2$ for patients receiving enzyme-inducing antiepileptic drugs) administered Weeks 1, 2, 4, and 5 of each 6-week cycle. The DLTs were hematologic, gastrointestinal, and hepatic.[39]

Pooled data from children with Ewing sarcoma treated according to a phase I trial schedule using temozolomide 100 mg/m$^2$/day on Days 1-5 and intravenous irinotecan 10-20 mg/m$^2$/day on Days 1-5 and 8-12 every 21-28 days reported the combination to be generally well tolerated with minimal myelosuppression in heavily pre-treated patients. Grade 3-4 diarrhea was seen in 11% of courses.[40] The MTD in a pediatric phase I trial of temozolomide and irinotecan using a protracted daily irinotecan schedule was temozolomide 100 mg/m$^2$/day for five days combined with 10 mg/m$^2$/day irinotecan IV daily for 5 days for 2 consecutive weeks. Temozolomide was not dose-escalated beyond 100 mg/m$^2$/day. No pharmacokinetic interactions were seen between the agents, and myelosuppression was minimal and noncumulative.[41] Patients who had previously received craniospinal radiation were not eligible. Using a simpler schedule, Kushner et al. published results in children with refractory or relapsed neuroblastoma using 150 mg/m$^2$/day of temozolomide in combination with intravenous irinotecan 50 mg/m$^2$/day for 5 consecutive days every 3-4 weeks.[8] Hematologic and GI toxicities were easily manageable and no cumulative toxicities were seen. Responses and prolonged stable disease were seen in this heavily pre-treated group of patients with poor bone marrow reserve.

The preliminary results of an ongoing phase 2 open label study of irinotecan and temozolomide in children with recurrent or refractory medulloblastoma were presented at the International Society of Pediatric Neuro-Oncology meeting in early July 2008. The study utilizes temozolomide 100 mg/m$^2$/day on days 1-5 and intravenous irinotecan 10 mg/m$^2$/day on days 1-5 and 8-12 every 3 weeks with planned escalation of temozolomide to 125 mg/m$^2$/day for patients that tolerate the initial dosing. There were 6 reported responses within the first 15 enrolled patients, with central review ongoing.[42] The proposed COG study utilizes the doses and schedule of temozolomide and irinotecan administered by Kushner et al[8] and found to be tolerable in heavily pre-treated patients.

In summary, considering the single-agent activity of both agents in recurrent MB, the non-overlapping toxicity profiles for temozolomide and irinotecan, and the proven feasibility of using this regimen in heavily pre-treated patients, further evaluation of this combination in a phase II study is warranted. Preclinical data suggests that a protracted schedule of irinotecan enhances efficacy but this has not been borne out at least in patients with recurrent rhabdomyosarcomas where similar efficacy was seen in patients randomized to the 5 day regimen as compared to the 5 days x 2.[43] The current study will utilize 150 mg/m$^2$/day of temozolomide with intravenous irinotecan 50 mg/m$^2$/day for 5 consecutive days every 28 days.

2.6 Redacted

# 3.0 ENROLLMENT PROCEDURES AND ELIGIBILITY CRITERIA

## 3.1 Study Enrollment

### 3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the 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.

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.

### 3.1.2 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 on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

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

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, 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.

### 3.1.3 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 RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

### 3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will not be entered on study**.

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

If a patient will have a port placed, the patient should be enrolled a few days after placement (see Section 3.2.5.3).

3.1.5 Randomization

Randomization will take place at the time a patient is entered On Study via RDE. Patients will be assigned to receive one of two regimens with equal probability: temozolomide with irinotecan (TEMO+IRIN), or temozolomide with irinotecan plus bevacizumab (TEMO+IRIN+BEVA). Patients will be stratified for randomization to each treatment arm according to whether or not they have measurable disease.

## 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.**

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

INCLUSION CRITERIA

3.2.1 Age

Patients must be no greater than 21 years of age at the time of study enrollment.

3.2.2 Diagnosis

3.2.2.1

Medulloblastoma (CTEP SDC=10027107) or PNET of childhood (CTEP SDC=10056672) that has relapsed or become refractory to standard chemotherapy. Patients with pineoblastoma are eligible.

3.2.2.2

Patients must have had histologic verification of the malignancy at original diagnosis or at the time of recurrence.

3.2.2.3

Patients must have clear residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI OR diffuse leptomeningeal disease OR clear MRI evidence of disease that may not be measurable in two perpendicular diameters.

3.2.2.4 Brain and Spine MRI

To document the degree of residual tumor, the following must be obtained (see Section 13.0 for complete details):

All patients must have a brain MRI with and without gadolinium and a spine MRI with gadolinium performed within 2 weeks prior to study enrollment.

3.2.3 Performance Level

Patients must have a Lansky or Karnofsky performance status score of ≥ 50%, corresponding to ECOG
categories of 0, 1 or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age. For Performance Status Scoring see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

3.2.4 Life Expectancy

Patients must have a life expectancy of ≥ 8 weeks.

3.2.5 Prior Therapy

3.2.5.1

Patients must have experienced at least one and at most two relapses prior to study enrollment. Patients with primary refractory disease are eligible.

3.2.5.2

Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

a. Myelosuppressive chemotherapy: Must not have received within 3 weeks of entry onto this study (6 weeks if prior nitrosourea).
b. Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent; at least 3 weeks for biologic agents with a long half life, such as antibodies.
c. XRT: Must not have received craniospinal radiotherapy within 24 weeks prior to study entry. The tumor designated as "measurable" for protocol purposes must not have received radiation within 12 weeks prior to study entry); focal radiation to areas of symptomatic metastatic disease must not be given within 14 days of study entry.
d. Stem Cell Transplant (SCT): For autologous SCT, ≥ 3 months must have elapsed prior to study entry.
e. Study specific limitations on prior therapy:
   1) Patients must not have previously received bevacizumab, irinotecan, temozolomide or other anti-VEGF inhibitor.
   2) Patients must not be taking enzyme-inducing antiepileptic medicines within 1 week of study entry.

3.2.5.3

Patients must have recovered from any surgical procedure before enrolling on this study (see Table below for examples of major, intermediate, and minor surgical procedures):

a) Patients with a major surgical procedure within 28 days prior to enrollment should be excluded.
b) Patients with an intermediate surgical procedure within 14 days prior to enrollment should be excluded.

c) For minor surgical procedures (including Broviac line or infusaport placement), patients should not receive the first planned dose of bevacizumab until the wound is healed and at least 7 days have elapsed.

d) There should be no anticipation of need for major surgical procedures during the course of the study.

Examples of Major, Intermediate, or Minor Surgical Procedures

| Major Procedures | Intermediate Procedures | Minor Procedures |
|---|---|---|
| Major craniotomy for tumor resection | VP-shunt placement | Incision and drainage of superficial skin abscesses |
| Organ resection | Stereotactic brain biopsy | Punch biopsy of skin lesions |
| Bowel wall anastomosis | | Superficial skin wound suturing |
| Arteriovenous grafts | | Bone marrow aspirate and/or biopsy |
| Exploratory Laparotomy | | Fine needle aspirations |
| Thoracotomy | | Broviac line or infusaport placement |
| | | Paracentesis or thoracocentesis |

Please note: Lumbar punctures or placement of PICC lines are not considered minor procedures and may occur at any time prior to or during therapy.

3.2.6 Cardiac Disease or Hypertension

a. Hypertension must be well controlled (≤ 95$^{th}$ percentile for age and height if patient is ≤ 17 years) on stable doses of medication. (See Appendices I and II for tables of blood pressure based on age and gender.)

Please see exclusion criteria in 3.2.15 – 3.2.16.

3.2.7 Concomitant Medications Restrictions

(Please see Section 4.2 for the concomitant therapy restrictions for patients while on study.)

a. Growth factor(s): Must not have received within 7 days of entry onto this study.

b. Steroids: Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 7 days.

c. Study Specific: Patients must not be currently taking NSAIDs, clopidrogel, dipyridamole or aspirin therapy > 81 mg/day.

3.2.8 Organ Function Requirements
All patients must have:

3.2.8.1 Adequate Bone Marrow Function (including status post SCT) Defined As

- Peripheral absolute neutrophil count (ANC) ≥ 1000/μL (must not have received G-CSF within the prior 7 days)
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 gm/dL (may receive PRBC transfusions)

3.2.8.2 Adequate Renal Function Defined As

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

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

3.2.8.3 Urine protein should be screened by dipstick analysis. If protein ≥ 2+ on dipstick, then Urine Protein Creatinine (UPC) ratio should be calculated. If UPC ratio > 0.5, 24-hour urine protein should be obtained and the level should be < 1000 mg/24 hours for patient enrollment.

Note: UPC ratio of spot urine is an estimation of the 24 urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulae:

- [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.2.8.4 Adequate Liver Function Defined As

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age,
- SGPT (ALT) ≤ 3 x upper limit of normal (ULN) for age,

3.2.8.5 Central Nervous System Function Defined As

- Patients with a seizure disorder may be enrolled if well-controlled and on non-enzyme inducing anticonvulsants.

3.2.8.6 Adequate Coagulation Defined As

- INR/PT ≤ 1.5 x upper limit of normal

Please see coagulation exclusion criteria in 3.2.11 – 3.2.12.

EXCLUSION CRITERIA

3.2.9
Patients with a serious or non-healing wound, ulcer, or bone fracture are not eligible for this study.

3.2.10
Patients must not have a history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to study entry.

3.2.11
Patients must not have a known bleeding diathesis or coagulopathy.

3.2.12
Patients must not have had significant vascular disease (eg, aortic aneurysm requiring surgical repair, deep venous or arterial thrombosis) within the last 6 months prior to study entry.

3.2.13
Patients must not have a known thrombophilic condition (i.e. protein S, protein C or antithrombin III deficiency, Factor V Leiden, Factor II G20210A mutation, homocysteinemia or antiphospholipid antibody syndrome). Testing is not required in patients without thrombophilic history.

3.2.14
Patients must not have evidence of new CNS hemorrhage on baseline MRI obtained within 14 days prior to study enrollment.

3.2.15

Patients with a history of stroke, myocardial infarction, transient ischemic attack (TIA), severe or unstable angina, peripheral vascular disease, or grade II or greater congestive heart failure within the past 6 months are not eligible.

3.2.16
Patients must not have serious and inadequately controlled cardiac arrhythmia.

3.2.17
Female patients who are pregnant are not eligible for this study.

3.2.18
Female patients who are breastfeeding are not eligible for this study unless they agree not to breastfeed.

3.2.19
Female patients of childbearing potential must have a negative pregnancy test.

3.2.20
Sexually active patients of childbearing potential must agree to use an effective method of contraception during the study and for at least 6 months after the completion of bevacizumab therapy.

3.2.21
Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

REGULATORY

3.2.22
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.23
All institutional, FDA, and NCI requirements for human studies must be met.

## 4.0 TREATMENT PROGRAM

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

### 4.1 Overview of Treatment Plan

Patients will be randomized at enrollment to one of two study arms: temozolomide with irinotecan (TEMO+IRIN) or temozolomide with irinotecan plus bevacizumab (TEMO+IRIN+BEVA). The primary study endpoint is overall survival. Therapy may continue for a maximum of 12 courses, in the absence of disease progression (see Section 10.4. for definition) if off protocol criteria have not yet been satisfied (see Section 8.1).

Each course of therapy will last 28 days. The temozolomide dose will be 150 mg/m$^2$/day by mouth daily for the first 5 days of each course. Irinotecan 50 mg/m$^2$/day will be given intravenously for the first 5 days of each course. For patients receiving bevacizumab, the dose will be 10 mg/kg intravenously on Days 1 and 15 of each course.

Disease status will be assessed prior to the initiation of therapy and at the end of every other course of treatment. In the absence of disease progression (see definition in Section 10.4) and unacceptable toxicities, patients can begin subsequent courses of therapy once the following criteria have been met:

- ANC ≥ 1,000/μL
- Platelets ≥ 100,000/μL (transfusion independent)

Following completion of a course, the next course begins on Day 29 or when blood count parameters are met (whichever occurs later).

**See Section 7.1 for required observations prior to starting protocol therapy.**

## 4.2 Concomitant therapy restrictions

4.2.1
No other cancer chemotherapy or immunomodulating agents are permitted. The use of alternative or complementary therapies is discouraged.

4.2.2
Radiotherapy is not permitted.

4.2.3
Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary.

4.2.4
Corticosteroid therapy is permissible only for treatment of increased intracranial pressure or for hormonal replacement and should not be used as a prophylactic antiemetic.

4.2.5
Irinotecan is a substrate for CYP3A4 (major) and CYP2B6 (major). CYP3A4 and CYP2B6 inhibitors may increase the level/effects of irinotecan and inducers may decrease the level/effect of irinotecan. Strong inhibitors of cytochrome CYP3A4, include azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's Wort. Additional drugs and inducers or inhibitors of CYP3A4 and CYP2B6 can be found at http://medicine.iupui.edu/clinpharm/ddis. Interacting drugs with irinotecan should be avoided or used with great caution.

4.2.6
The use of NSAIDS, clopidogrel, dypiridamole, or aspirin therapy > 81 mg/day is not permitted.

4.2.7
The routine use of growth factors is not recommended for the initial course of therapy, but may be used as clinically indicated at the discretion of the investigator.

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

### 4.3 TEMO+IRIN Course

The TEMO+IRIN treatment course will be repeated every 28 days at the same dose, provided there are no dose limiting toxicities. Temozolomide will be administered first, followed by irinotecan.

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

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

**Temozolomide: PO**
Days: 1 through 5.
Dose: 150 mg/m$^2$/dose.
Note: **Temozolomide given IV is not permitted.** Temozolomide will be given on an empty stomach (to improve absorption and reduce the incidence of nausea and vomiting) at least one hour **before** irinotecan administration. The temozolomide dose should be rounded off to the nearest 5 mg (round 2.5 mg down [see Appendix III]). For patients with a BSA < 0.5 m$^2$, temozolomide should be given at a dose of 5 mg/kg/day rounded off to the nearest 5 mg (round 2.5 mg down [see example in Appendix III]). If emesis occurs within 20 minutes of taking a given dose, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Guidelines for administration of oral temozolomide to patients who are unable to swallow capsules or tablets are provided in Appendix VI and instructions for the preparation of extemporaneous suspension are available in the drug monograph (section 6.3). Antiemetics should be given 30 minutes prior to each temozolomide dose.

Pharmacy note: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See drug monograph for additional details and examples.

**Irinotecan: IV, infuse the diluted solution over 90 minutes**
Days: 1 through 5.
Dose: 50 mg/m$^2$/dose.
Note: Irinotecan will be given at least one hour **after** temozolomide administration. Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates. To avoid extravasation; the use of a central line is suggested.

Following administration of irinotecan, monitor for signs and symptoms of diarrhea and dehydration. For diarrhea related to irinotecan therapy, the use of atropine for early-onset diarrhea and the use of loperamide for late-onset diarrhea are recommended. See

the COG Supportive Care Guidelines at https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols for dosing and schedule information.

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

The therapy delivery map (TDM) for this TEMO+IRIN course is on the next page.

Following completion of the first TEMO+IRIN course, the TEMO+IRIN course is repeated for up to 12 courses, as tolerated and in the absence of disease progression (see Section 10.4 for Response Evaluation). Subsequent TEMO+IRIN courses should begin on Day 29 or when blood parameters recover (whichever occurs later).

| 4.3.1 Temozolomide with Irinotecan (TEMO+IRIN)<br>Four consecutive weeks (28 days) will constitute one course.<br>This therapy delivery map relates to all courses of TEMO+IRIN.<br>Use a copy of this page once for each course. *(Please note course number below.)* | _____<br>Patient name or initials<br>_____<br>DOB |
|---|---|

Criteria to start this course: ANC ≥ 1000/µL and platelet count ≥ 100,000/µL. Details are in Section 4.0 (Treatment Overview). This course lasts 28 days and the TDM for this course is on **1** page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| Temozolomide (TEMO) | PO | 150 mg/m$^2$/dose<br>or<br>5 mg/kg/dose* for patients<br>< 0.5 m$^2$ | 1–5 | **Administer at least one hour prior to IRIN administration.**<br><br>*Round off to the nearest 5mg.<br><br>See Dosing Table in Appendix III and admin. guidelines in Section 4.3. | a) History & PE (Ht, Wt, VS)<br>b) CBC (diff/ platelets)<br>c) Electrolytes ($Ca^{++}$, $PO_4$, $Mg^{++}$)<br>d) ALT, AST, BUN, creatinine (or creatine clearance or radioisotope GFR), bilirubin<br>e) MRI of the Head with and without gadolinium<br>f) MRI of the Spine with gadolinium<br>g) CSF cytology<br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE.** |
| Irinotecan (IRIN) | IV over 90 minutes | 50 mg/m$^2$/dose | 1–5 | | |

**Please enter Course # _____ Ht_____cm Wt____kg BSA____m$^2$**

| Date Due | Date Given | Day | TEMO mg | IRIN mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | |
| | | 1 | _____mg | _____mg | a, b, c, d, e#, f^, g† | |
| | | 2 | _____mg | _____mg | | |
| | | 3 | _____mg | _____mg | | |
| | | 4 | _____mg | _____mg | | |
| | | 5 | _____mg | _____mg | | |
| | | 8 | | | b | |
| | | 15 | | | b | |
| | | 21 | | | b | |
| | | 28 | | | | See Section 7.1 for studies to be performed when patient is removed from protocol therapy. |
| | | 29 | Start next course on Day 29 or when blood count parameters are met (whichever occurs later). | | | |

OBSERVATION NOTES:

#Obtain within 1 week prior to the third course of therapy and prior to every other subsequent course of therapy (ie, 5th, 7th, etc.), up to 12 courses of therapy.

^ Obtain within 1 week prior to the third course of therapy and prior to every other subsequent course of therapy (ie, 5th, 7th, etc.) only if initially positive or clinically indicated.

† If baseline test is negative, repeat only if there is disease progression. If positive at baseline, repeat prior to every other course (ie, 3rd, 5th, etc.) until there are two negative cytologies. CSF cytology can be waived for patients where a lumbar puncture is not deemed to be safe.

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

## 4.4 TEMO+IRIN+BEVA Course

The TEMO+IRIN+BEVA treatment course will be repeated every 28 days at the same dose, provided there are no dose limiting toxicities. Temozolomide will be administered first, followed by irinotecan and bevacizumab.

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

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

**Temozolomide: PO**
Days: 1 through 5.
Dose: 150 mg/m$^2$/dose.
Note: **Temozolomide given IV is not permitted.** Temozolomide will be given on an empty stomach (to improve absorption and reduce the incidence of nausea and vomiting) at least one hour **before** irinotecan administration. The temozolomide dose should be rounded off to the nearest 5 mg (round 2.5 mg down [see Appendix III]). For patients with BSA < 0.5 m$^2$, temozolomide should be given at a dose of 5 mg/kg/day rounded off to the nearest 5 mg (round 2.5 mg down [see example in Appendix III]). If emesis occurs within 20 minutes of taking a given drug dose, then the dose may be repeated once. If emesis occurs after 20 minutes, the dose should not be repeated. Guidelines for administration of oral temozolomide to patients who are unable to swallow tablets are provided in Appendix VI and instructions for the preparation of extemporaneous suspension are available in the drug monograph (section 6.3). It is recommended that antiemetics be given 30 minutes prior to the temozolomide dose.

Pharmacy note: Temozolomide capsules are available in 6 different strengths. Daily doses are usually comprised of multiple capsules of different strengths. To prevent errors, each strength of temozolomide capsules must be dispensed in a separate bottle and the total number of each strength of capsules needed for the full course must be dispensed at one time. See drug monograph for additional details and examples.

**Irinotecan: IV, infuse the diluted solution over 90 minutes**
Days: 1 through 5.
Dose: 50 mg/m$^2$/dose.
Note: Irinotecan will be given at least one hour **after** temozolomide administration. Higher incidence of cholinergic symptoms has been reported with more rapid infusion rates. To avoid extravasation; the use of a central line is suggested.

Following administration of irinotecan, monitor for signs and symptoms of diarrhea and dehydration. For diarrhea related to irinotecan therapy, the use of atropine for early-onset diarrhea and the use of loperamide for late-onset diarrhea are recommended. See https://members.childrensoncologygroup.org/prot/reference_materials.asp for dosing and schedule information.

**Bevacizumab: IV over 90 minutes***
Days: 1 and 15.
Dose: 10 mg/kg/dose.
Note: *Infuse first dose over 90 minutes. If tolerated without infusion-related side effects, the second dose may be given over 60 minutes. Again, if tolerated, the third dose and all subsequent doses may be given over 30 minutes. Check vital signs prior to infusion and monitor for infusion-related reactions every 30 minutes (during 60 and 90 minute infusions) and at the end of the infusion. Monitor every 15 minutes while the infusion rate is being adjusted. Routine premedication is not required for the first dose of bevacizumab. If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.) Anaphylactic precautions should be observed during bevacizumab administration. If an infusion reaction occurs, subsequent doses of bevacizumab should be administered over the shortest period that was well-tolerated. Bevacizumab is incompatible with $D_5W$ (the drug is inactivated).

Special precautions: Black box warning includes risk of gastrointestinal perforation and wound healing complications (fatal results have occurred). Suspend dosing at least 28 days prior to elective surgery. Do not initiate bevacizumab for at least 28 days after a major surgery, for at least 14 days after intermediate surgical procedure, **and** until the surgical wound is fully healed. Minor surgical procedures (eg, biopsies, infusaport or Broviac line placement) need to have fully healed and occurred > 7 days prior to initiation of bevacizumab.

See Table in Section 3.2.5.3 for examples of major, intermediate, and minor surgical procedures.

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

The therapy delivery map (TDM) for the TEMO+IRIN+BEVA course is on the next page.

Following completion of the first TEMO+IRIN+BEVA course the TEMO+IRIN+BEVA course is repeated for up to 12 courses, as tolerated and in the absence of disease progression (see Section 10.4 for Response Evaluation).

Subsequent TEMO+IRIN+BEVA Courses should begin on Day 29 or when blood parameters recover (whichever occurs later).

| 4.4.1 TEMO+IRIN+BEVA Course<br>Four consecutive weeks (28 days) will constitute one course.<br>This therapy delivery map relates to all courses of TEMO+IRIN+BEVA.<br>Use a copy of this page once for each course. *(Please note course number below.)* | _____<br>Patient name or initials<br>_____<br>DOB |
|---|---|

Criteria to start this course: ANC ≥ 1000/μL and platelet count ≥ 100,000/μL. Details are in Section 4.0 (Treatment Overview). This course lasts 28 days and the TDM for this course is on 1 page.

| DRUG | ROUTE | DOSAGE | DAYS | IMPORTANT NOTES | OBSERVATIONS |
|---|---|---|---|---|---|
| Temozolomide (TEMO) | PO | 150 mg/m$^2$/dose or 5 mg/kg/dose* for patients < 0.5 m$^2$ | 1-5 | **Administer at least one hour prior to IRIN administration.**<br>*Round off to the nearest 5 mg.<br>See Dosing Table in Appendix III and admin. guidelines in Section 4.4. | a) History & PE (Ht, Wt, VS)<br>b) CBC (diff/ platelets)<br>c) Electrolytes ($Ca^{++}$, $PO_4$, $Mg^{++}$)<br>d) ALT, AST, BUN, creatinine (or creatine clearance or radioisotope GFR) , bilirubin<br>e) Urinalysis for protein (urine dipstick or UPC ratio)<br>f) MRI of the Head with and without gadolinium<br>g) MRI of the Spine with gadolinium<br>h) CSF cytology<br><br>**OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE** |
| Irinotecan (IRIN) | IV over 90 minutes | 50 mg/m$^2$/dose | 1-5 | | |
| Bevacizumab (BEVA) BB-IND#7921 | IV over 90* minutes | 10 mg/kg/dose | 1 and 15 | *May be given over shorter duration if well-tolerated.<br>See admin. guidelines in Section 4.4. | |

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

| Date Due | Date Given | Day | TEMO ____mg | IRIN ____mg | BEVA ____mg | Studies | Comments (Include any held doses, or dose modifications) |
|---|---|---|---|---|---|---|---|
| | | | **Enter calculated dose above and actual dose administered below** | | | | |
| | | 1 | ____mg | ____mg | ____mg | a, b, c, d, e#, f*, g^, h† | |
| | | 2 | ____mg | ____mg | | | |
| | | 3 | ____mg | ____mg | | | |
| | | 4 | ____mg | ____mg | | | |
| | | 5 | ____mg | ____mg | | | |
| | | 8 | | | | b | |
| | | 15 | | | ____mg | a$, b | |
| | | 21 | | | | b | |
| | | 28 | | | | | See Section 7.1 for studies to be performed when patient is removed from protocol therapy. |
| | | 29 | Start next course on Day 29 or when blood count parameters are met (whichever occurs later). | | | | |

OBSERVATION NOTES:

# Prior to the start of each course of bevacizumab. If urine dipstick is 2+ or greater for protein, hold bevacizumab and obtain UPC ratio. See bevacizumab dose modifications for proteinuria (Section 5.1).

* Obtain within 1 week prior to the third course of therapy and prior to every other subsequent course of therapy (ie, 5th, 7th, etc.), up to 12 courses of therapy.

^ Obtain within 1 week prior to the third course of therapy and prior to every other subsequent course of therapy (ie, 5th, 7th, etc.) if initially positive or clinically indicated.

† If baseline test is negative, repeat only if there is disease progression. If positive at baseline, repeat prior to every other course (ie, 3rd, 5th, etc.) until there are two negative cytologies. CSF cytology can be waived for patients where a lumbar puncture is not deemed to be safe.

$ Obtain BP only.

**See Section 5.0 for Dose Modifications for Toxicities. For general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.**

# 5.0 DOSE MODIFICATIONS FOR TOXICITIES

## 5.1 Dose Reduction

There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described in the table below.

If bevacizumab is interrupted for toxicities listed in the table below for > 4 weeks (unless otherwise specified), the patient should discontinue bevacizumab and be taken off protocol therapy.

## DOSE MODIFICATIONS FOR BEVACIZUMAB RELATED ADVERSE EVENTS

| Event | CTCAE v 4.0 Grade | Action to be Taken |
|---|---|---|
| **Allergic reactions,**<br>**Or**<br>**Infusion-related reactions**<br>**OR**<br>**Anaphylaxis** | Grade 1-2 | Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension.<br>For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.<br>If infusional reactions occur, acetaminophen [10-15 mg/kg (max 650 mg)], diphenhydramine [1 mg/kg (max 50 mg)], or other medications may be given for symptom control and for premedication as needed. (See Section 4.2 for concomitant therapy restrictions.)<br>Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab. |
| | Grade 3-4 | Discontinue bevacizumab. |
| **Thromboembolic Event (Arterial); arterial ischemia**<br>– Cardiac ischemia<br>– Myocardial infarction<br>– CNS ischemia (TIA, CVA)<br>– Any peripheral or visceral arterial ischemia/thrombosis | Grade 2<br>(if new or worsened since bevacizumab therapy) | Discontinue bevacizumab. |
| | Grade 3-4 | Discontinue bevacizumab. |

| Event | CTCAE v 4.0 Grade | Action to be Taken |
|---|---|---|
| **Thromboembolic Event (Venous)** | Grade 3 OR asymptomatic Grade 4 | ▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over.<br>▪ If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met:<br>– The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions).<br>– The subject must not have had hemorrhagic events while on study.<br>– The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab.<br>▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab. |
| | Grade 4 (symptomatic) | Discontinue bevacizumab. |
| **Hypertension**<br><br>**Use age and height appropriate normal values > 95th percentile ULN for pediatric patients (see Appendices I and II)** | [Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice.] | |
| | Grade 1<br>If age ≤ 17 years: Asymptomatic, transient (< 24 hrs) BP increase >ULN; intervention not indicated.<br>If age > 17 years: (SBP 120-139 mmHg or DBP 80-89 mmHg) | Consider increased BP monitoring; start anti-hypertensive medication if appropriate |
| | Grade 2 asymptomatic:<br>If age ≤ 17 years: Recurrent or persistent (≥ 24 hrs) BP > ULN;<br>If age > 17 years: (SBP 140-159 mmHg or DBP 90-99 mmHg) | If age ≤ 17 years: monotherapy indicated. Continue bevacizumab.<br><br>If age > 17 years: Begin anti-hypertensive therapy and continue bevacizumab. |
| | Grade 2 symptomatic:<br>**OR**<br>Grade 3:<br>>17 years: SBP >160 mmHg or DBP >100 mmHg)<br>requiring more than one drug or more intensive therapy than previously (all ages) | • Start or adjust anti-hypertensive therapy<br>• Hold bevacizumab until symptoms resolve **AND** BP < 95th percentile ULN for age and height, if age ≤ 17 years; or BP < 160/90mmHg if age > 17 years. |
| | Grade 4: (all ages)<br>life threatening (e.g. hypertensive crisis or malignant hypertension) | Discontinue bevacizumab. |
| **Heart Failure or LV dysfunction** | Heart failure ≥ grade 2 | Discontinue bevacizumab. |
| | LV dysfunction ≥ grade 3 | Discontinue bevacizumab. |

| Event | CTCAE v 4.0 Grade | Action to be Taken |
|---|---|---|
| **Proteinuria**<br>Proteinuria will be monitored by urine analysis for urine protein creatinine (UPC) ratio, or dipstick If Dipstick ≥ 2+ proteinuria or UPC ratio ≥ 1, 24 hour urine protein should be obtained | If 24-h urine protein < 2.0gm | Continue bevacizumab |
| | If 24-h urine protein ≥ 2.0 gm | • Hold bevacizumab until 24-h urine protein < 2.0 gm.<br>• Discontinue bevacizumab if urine protein does not recover to < 2.0 after 8 weeks of bevacizumab interruption |
| | Nephrotic syndrome | Discontinue bevacizumab. |
| **Hemorrhage (intracranial or pulmonary)** | Grade 1 | • Patients receiving full-dose anticoagulation should discontinue bevacizumab.<br>• For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:<br>– the bleeding has resolved and Hb is stable;<br>– there is no bleeding diathesis that would increase the risk of therapy;<br>– there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. |
| | Grade 2-4 | Discontinue bevacizumab. |
| **Hemorrhage (any other organ systems)** | Grade 3 | • Patients receiving full-dose anticoagulation should discontinue bevacizumab.<br>• For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met:<br>– the bleeding has resolved and Hb is stable;<br>– there is no bleeding diathesis that would increase the risk of therapy;<br>– there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence.<br>• Patients who experience recurrence of Grade 3 hemorrhage should discontinue study therapy. |
| | Grade 4 | Discontinue bevacizumab. |
| **RPLS** (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome) | | • Hold bevacizumab in patients with symptoms/signs suggestive of RPLS; subsequent management should include MRI scans and control of HTN.<br>• Discontinue bevacizumab upon diagnosis of RPLS. |
| **Wound dehiscence** requiring medical or surgical intervention or wound complications | Grade 2 | Hold bevacizumab until healing |

| Event | CTCAE v 4.0 Grade | Action to be Taken |
|---|---|---|
| | Grade 3-4 | Discontinue bevacizumab. |
| **Perforation (GI or any other organ)** | | Discontinue bevacizumab. |
| **Fistula (GI, pulmonary or any other organ)** | | Discontinue bevacizumab. |
| **Obstruction of GI tract** | Grade 2 requiring medical intervention | • Hold bevacizumab until complete resolution. |
| | Grade 3-4 | • Hold bevacizumab until complete resolution.<br>• If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion. |
| **Other Unspecified bevacizumab-related AEs** (except controlled nausea/vomiting). | Grade 3 | • Hold bevacizumab until symptoms resolve to ≤ grade 1 |
| | Grade 4 | • Discontinue bevacizumab. |

## 5.2 Hematologic Toxicity

If ANC is < 1,000/μL and platelets are < 100,000/μL at Day 28, further therapy should be delayed and counts should be checked at least weekly until counts recover. If the ANC is < 1,000/μL or platelets < 100,000/μL more than seven days beyond the time for the next treatment (ie, the subsequent course is delayed by > 7 days due to myelosuppression), reduce the temozolomide dose by 25% (112.5 mg/m$^2$ for BSA ≥ 0.5 m$^2$ or 3.75 mg/kg for BSA < 0.5 m$^2$; see Appendix IV). If a patient again experiences prolonged myelosuppression delaying the ability to deliver the subsequent course by Day 35 of a treatment course, the dose of temozolomide should be reduced again by 25% of the original dose (total of 50% dose reduction [75 mg/m$^2$ for BSA ≥ 0.5 m$^2$ or 2.5 mg/kg for BSA < 0.5 m$^2$; see Appendix V]). If, despite a 50% dose reduction, myelosuppression prevents delivery of the subsequent course by Day 35, the patient should be taken off protocol therapy.

## 5.3 Non-Hematologic Toxicity

Patients who experience Grade 3 or greater non-hematologic toxicity (NHT) (with the exception of diarrhea, alopecia, nausea or vomiting that occurs without anti-emetic treatment, infection or fever) which returns to Grade 1 or less by Day 35 will have the doses of irinotecan and temozolomide reduced by 25% of the original dose in subsequent courses (to 37.5 mg/m$^2$/dose for irinotecan, see Appendix IV for temozolomide doses). If, at the reduced dose, a patient again experiences Grade 3 or greater non-hematologic toxicity, (with the exception of diarrhea, alopecia, nausea or vomiting, infection or fever), the irinotecan and temozolomide doses will be reduced by an additional 25% of the original dose (ie, 50% of the original dose to 25 mg/m$^2$/dose for irinotecan, see Appendix V for temozolomide doses). If Grade 3 or higher NHT recurs despite the 50% dose reduction, the patient should be taken off protocol therapy.

Gastrointestinal Toxicity Secondary to Irinotecan

Patients with Grade 3-4 diarrhea will receive antibiotics and anti-diarrheals to prevent irinotecan induced diarrhea, per the COG supportive care guidelines; for detailed information please refer to (https://members.childrensoncologygroup.org/_files/protocol/Standard/SupportiveCareGuidelines.pdf). Patients who develop diarrhea and require antibiotics should continue to

receive antibiotics for every course of irinotecan during the study period. If patients continue to experience ≥ Grade 3 diarrhea despite maximum supportive care measures with prophylactic antibiotics and anti-diarrheals, subsequent irinotecan doses should be reduced by 25% of the original dose (to 37.5 mg/m$^2$/dose). If diarrhea persists further reduce irinotecan dose by 50% of original dose for subsequent cycles (to 25 mg/m$^2$/dose). If Grade 3 diarrhea persists despite the 50% dose reduction, the patient should be taken off protocol therapy.

Febrile Neutropenia
Uncomplicated febrile neutropenia is not a reason for dose reduction.

## 6.0 DRUG INFORMATION

The drugs are presented in alphabetical order.

Please see Appendix VIII for drug interactions associated with the drugs used in this study.

### 6.1 Bevacizumab

(rhuMAb VEGF, Avastin®) NSC# 704865 IND # 7921 (5/9/14)

**Source and Pharmacology:**
Bevacizumab is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab approximate molecular weight is 149,000 daltons. Bevacizumab blocks the binding of VEGF to its receptors resulting in inhibition of angiogenesis.

The estimated half-life of bevacizumab is approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days in 491 patients who received 1 to 20 mg/kg weekly, every 2 weeks, or every 3 weeks. The clearance and the central volume of distribution are higher in males than females. Clearance was higher in those patients with a higher tumor volume.

**Toxicity:**

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**
**for**
**Bevacizumab (rhuMAb VEGF, NSC 704865)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, August 1, 2013[1]**

| **Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term) [n= 3540]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 3)*** |
| | | Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy) | |
| | Febrile neutropenia | | ***Febrile neutropenia (Gr 3)*** |
| CARDIAC DISORDERS | | | |
| | | Acute coronary syndrome[2] | |
| | Cardiac disorders - Other (supraventricular arrhythmias)[3] | | ***Cardiac disorders - Other (supraventricular arrhythmias)[3] (Gr 3)*** |
| | | Heart failure | |
| | | Left ventricular systolic dysfunction | |
| | | Myocardial infarction[2] | |
| | | Ventricular arrhythmia | |
| | | Ventricular fibrillation | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 3)*** |
| | Colitis | | ***Colitis (Gr 3)*** |
| | Constipation | | ***Constipation (Gr 3)*** |
| | Diarrhea | | ***Diarrhea (Gr 3)*** |
| | Dyspepsia | | ***Dyspepsia (Gr 2)*** |
| | | Gastrointestinal fistula[4] | |
| | Gastrointestinal hemorrhage[5] | | ***Gastrointestinal hemorrhage[5] (Gr 2)*** |
| | Gastrointestinal obstruction[6] | | |
| | | Gastrointestinal perforation[7] | |
| | | Gastrointestinal ulcer[8] | |
| | Ileus | | |
| | Mucositis oral | | ***Mucositis oral (Gr 3)*** |
| | Nausea | | ***Nausea (Gr 3)*** |
| | Vomiting | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Fatigue | | ***Fatigue (Gr 3)*** |
| | Infusion related reaction | | ***Infusion related reaction (Gr 2)*** |
| | Non-cardiac chest pain | | ***Non-cardiac chest pain (Gr 3)*** |
| | Pain | | ***Pain (Gr 3)*** |
| IMMUNE SYSTEM DISORDERS | | | |
| | Allergic reaction | | ***Allergic reaction (Gr 2)*** |
| | | Anaphylaxis | |

| | | | |
|---|---|---|---|
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[9] | | ***Infection[9] (Gr 3)*** |
| | | Infections and infestations - Other (necrotizing fasciitis) | |
| | Infections and infestations - Other (peri-rectal abscess) | | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Injury, poisoning and procedural complications – Other (anastomotic leak)[10] | |
| | Wound complication | | ***Wound complication (Gr 2)*** |
| | Wound dehiscence | | ***Wound dehiscence (Gr 2)*** |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 3)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 3)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 3)*** |
| | Blood bilirubin increased | | ***Blood bilirubin increased (Gr 2)*** |
| | Cardiac troponin I increased | | |
| Neutrophil count decreased | | | ***Neutrophil count decreased (Gr 3)*** |
| | Platelet count decreased | | ***Platelet count decreased (Gr 4)*** |
| | Weight loss | | ***Weight loss (Gr 3)*** |
| | White blood cell decreased | | ***White blood cell decreased (Gr 3)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 3)*** |
| | Dehydration | | ***Dehydration (Gr 3)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | ***Arthralgia (Gr 3)*** |
| | Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[11] | | |
| | Myalgia | | ***Myalgia (Gr 3)*** |
| | Osteonecrosis of jaw[12] | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | ***Dizziness (Gr 2)*** |
| | Headache | | ***Headache (Gr 3)*** |
| | | Intracranial hemorrhage | |
| | | Ischemia cerebrovascular[2] | |
| | Peripheral sensory neuropathy[13] | | |
| | | Reversible posterior leukoencephalopathy syndrome | |
| | Syncope | | |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| | Hematuria | | ***Hematuria (Gr 3)*** |
| | Proteinuria | | ***Proteinuria (Gr 2)*** |
| | | Renal and urinary disorders - Other (Nephrotic Syndrome) | |
| | | Urinary fistula | |

| | | | |
|---|---|---|---|
| | | | |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | | | |
| Reproductive system and breast disorders - Other (ovarian failure)[14] | | | |
| | | Vaginal fistula | |
| | Vaginal hemorrhage | | ***Vaginal hemorrhage (Gr 3)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Allergic rhinitis | | ***Allergic rhinitis (Gr 3)*** |
| | | Bronchopleural fistula | |
| | | Bronchopulmonary hemorrhage | |
| | Cough | | ***Cough (Gr 3)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |
| | Epistaxis | | ***Epistaxis (Gr 3)*** |
| | Hoarseness | | ***Hoarseness (Gr 3)*** |
| | | Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation) | |
| | | Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Pruritus | | ***Pruritus (Gr 2)*** |
| | Rash maculo-papular | | ***Rash maculo-papular (Gr 2)*** |
| | Urticaria | | ***Urticaria (Gr 2)*** |
| VASCULAR DISORDERS | | | |
| Hypertension | | | ***Hypertension (Gr 3)*** |
| | Thromboembolic event | | ***Thromboembolic event (Gr 3)*** |
| | | Vascular disorders - Other (arterial thromboembolic event)[2,15] | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[3]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak

[11]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[12]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[13]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

*[14]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.*

[15]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack and stroke.

**Also reported on bevacizumab (rhuMAb VEGF) trials but with the relationship to bevacizumab (rhuMAb VEGF) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis
**CARDIAC DISORDERS** - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
**EAR AND LABYRINTH DISORDERS** - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism
**EYE DISORDERS** - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (floaters); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye disorders - Other (vitreous hemorrhage); Eye pain; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Watering eyes
**GASTROINTESTINAL DISORDERS** - Ascites; Chelitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis;Typhlitis

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
**HEPATOBILIARY DISORDERS** - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (aseptic meningitis)
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Generalized muscle weakness; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
**PSYCHIATRIC DISORDERS** - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
**RENAL AND URINARY DISORDERS** - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Renal and urinary disorders - Other (dysuria); Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
**VASCULAR DISORDERS** - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

**Note**: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

**Effect in Pregnancy and Lactation:**
Bevacizumab has been shown to be teratogenic in rabbits when administered in doses that are two-fold greater than the recommended human dose on a mg/kg basis. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorption, and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of Bevacizumab is likely to result in adverse effects on pregnancy. It is not known whether Bevacizumab is secreted in human milk. Because human IgG1 is secreted into human milk, the potential for absorption and harm to the infant after ingestion is unknown.

A prospective study of 179 premenopausal women with stage II or III colorectal cancer given adjuvant therapy with mFOLFOX alone (n= 84) or mFOLFOX with bevacizumab (n=95) suggests that the use of bevaciumab with chemotherapy may result in ovarian failure. In this study, ovarian failure was defined as amenorrhea lasting 3 or more months, FSH level $\geq$ 30 mIU/mL and a negative serum β-HCG pregnancy test. A new onset of ovarian failure was documented in 34% (32/95) of women who received bevacizumab with chemotherapy compared to 2% (2/84) of women given chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. Recovery of ovarian function occurred in 22% (7/32) of these women after discontinuation of bevacizumab. Additional long term effects of bevacizumab on fertility are unknown.

**Effect on Growth and Development:**
Studies of bevacizumab in animals showed a decrease in ovarian function and abnormal bone growth. These and other effects of bevacizumab may potentially impair growth and development. Abnormal changes in the bones after treatment with bevacizumab have been observed in young children with growing bones. This side effect appeared to be reversible after the treatment was stopped, but has not been assessed with long-term use of the drug.

**Formulation and Stability:** Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400 mg (25 mg/mL, 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Upon receipt, refrigerate the intact bevacizumab vials at 2-8°C (36-46°F). Store in the outer carton to protect bevacizumab vials from light. Do not freeze. Do not shake.

Bevacizumab vials contain no antibacterial preservatives and are labeled for single use. Discard any unused portion left in the vial immediately after use.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.
Do not administer as an intravenous (IV) push or bolus. Prior to administration, dilute the dose in 0.9% sodium chloride for injection to a final concentration of 1.4-16.5 mg/mL. Inspect visually for particulate matter and discoloration prior to administration.

The chemical and physical stability of the diluted solution in 0.9% sodium chloride is 48 hours at 2°C-30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the

responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. Bevacizumab is incompatible with D5W.

To ensure complete delivery of bevacizumab IV infusion line must be flushed with 0.9% sodium chloride. The following are two recommended methods for flushing the line:

1. When the bevacizumab infusion is complete, while maintaining a closed system, add an additional 50 mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50 mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.
   Please note: the flush is not included in the total recommended infusion times.

**Supplier:** Supplied by Genentech and distributed by the NCI DTCD. **Do not use commercially available drug.**

**Agent Ordering**

NCI supplied agent may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees must submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

**Agent Accountability**

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and http://ctep.cancer.gov/forms/default.htm to obtain a copy of the DARF and Clinical Drug Request form.)

**Agent Returns**

Investigators/Designees must return unused DCTD supplied investigational agent to the NCI clinical repository as soon as possible when: the agent is no longer required because the study is completed or discontinued and the agent cannot be transferred to another DCTD sponsored protocol; the agent is outdated or the agent is damaged or unfit for use. Regulations require that all agents received from the DCTD, NCI be returned to the DCTD, NCI for accountability and disposition. Return only unused vials/bottles. Do NOT return opened or partially used vials/bottles unless specifically requested otherwise in the protocol. See the CTEP web site for Policy and Guidelines for Investigational agent Returns at: http://ctep.cancer.gov/protocolDevelopment/default.htm#agents_drugs. The appropriate forms may be obtained at: http://ctep.cancer.gov/forms/default.htm.

## 6.2 IRINOTECAN

[CPT-11,Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348 (05/09/11)

**Source and Pharmacology:**

Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from *Camptotheca acuminata)*. Irinotecan is a prodrug that requires conversion, by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN-38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea, vomiting, anorexia, fever, asthenia, cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea) | Constipation, headache, diarrhea (L) | Anaphylaxis, dehydration with dizziness & hypotension, bradycardia, dyspnea and cough, disorientation/confusion, somnolence, pain at infusion site |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Neutropenia, alopecia, eosinophilia, elevations in transaminases, alkaline phosphatase, bilirubin, mucositis, infection | Anemia, rash, dyspepsia, thrombocytopenia | Colitis, renal failure (secondary to severe dehydration), thromboembolic events, ileus |
| **Delayed:**<br>Any time later during therapy | | | Pneumonitis |
| **Late:**<br>Any time after completion of treatment | | | |
| **Unknown Frequency and Timing**: | Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk. | | |

*(L) Toxicity may also occur later.*

**Formulation & Stability**:
Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL) and 100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL). Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

**Guidelines for Administration:** See Treatment and Dose Modifications sections of the protocol.

Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in 5% D5W, (preferred) or NS, to a final concentration range of 0.12-2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in D5W and stored at refrigerated temperatures (approximately 2°-8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using NS is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

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

## 6.3 TEMOZOLOMIDE

(Temodar®, Temodal®) NSC# 362856 (05/10/11)

**Source and Pharmacology:**
An orally administered alkylating agent, a second generation imidazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. Exerts its effect by cross-linking DNA. This is likely a site specific alkylation at the $O^6$-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13 hr (intraperitoneally) and 1.29 hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100 mL/min/$m^2$ and plasma elimination half-life is ~ 100 minutes.

Toxicity

| | **Common** Happens to 21-100 subjects out of every 100 | **Occasional** Happens to 5-20 subjects out of every 100 | **Rare** Happens to < 5 subjects out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Anorexia, constipation, nausea, vomiting, | Abdominal pain, diarrhea, headache, rash, itching, urinary frequency and/or infection | Convulsions, anaphylaxis, hemiparesis, dizziness, ataxia, confusion, dysphagia, anxiety, thrombo-embolism (L) |
| **Prompt:** Within 2-3 weeks, prior to next course | Myelosuppression | Mucositis, lethargy, peripheral edema | Prolonged lymphopenia with increased risk of infection or death, amnesia, insomnia, depression, myalgia, diplopia, visual changes |
| **Delayed:** Anytime later during therapy | | Alopecia, hepatotoxicity | |
| **Late:** Anytime after completion of therapy | | | Secondary tumors or cancer |

**Formulation and Stability:** Temozolomide capsules are available in six different strengths (5, 20, 100,
140, 180, 250 mg). The capsules vary in size, color, and imprint according to strength. In the US, capsules are packaged in 5-count and 14-count bottles. In other countries temozolomide may be packaged in 5-count, 14-count or 20-count bottles. Temozolomide capsules are stored at controlled room temperature.

**Guidelines for Administration:** See Treatment and Dose Modifications sections of the protocol.

There is a potential for medication errors involving temozolomide capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule.

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing.

When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

Each strength of temozolomide must be dispensed in a separate vial or in its original glass bottle. Based on the dose prescribed, determine the number of each strength of temozolomide capsules needed for the full course as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250 mg capsules, five 20 mg capsules, and five 5 mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each bottle or vial to equal the total daily dose prescribed by the physician. Institutions that have the capability to dispense temozolomide as daily doses in a blister pack may do so, taking specific precautions to ensure that the appropriate dose is provided and that the patient is educated to understand the daily dosing regimen.

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10mg/mL suspension triturate the contents of ten 100 mg capsules (1000 mg), 500 mg povidone K-30 and 25mg anhydrous citric acid dissolved in 1.5mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100 mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension is stable for 7 days at room temperature or 60 days in the refrigerator. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension. (Trissel LA, Yanping Z, Koontz SE. Temozolomide stability in extemporaneously compounded oral suspensions. *Int J Pharm Compounding* 10:396-9, 2006.)

Alternatively, the capsules can be opened and mixed with apple sauce or juice (see Appendix VI).

**Supplier:** Commercially available. See package insert for further information.

## 7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

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

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

| STUDIES TO BE OBTAINED | Baseline | Prior to Each Course | During Each Course | Prior to every other Course | When Patient is Removed From Protocol Therapy |
|---|---|---|---|---|---|
| History | X | X | | | X |
| Physical Exam (Ht, Wt, VS) | X | X | BP: Prior to every dose of bevacizumab[A] | | X |
| Performance Status | X | | | | X |
| CBC (differential, platelets) | X | X | Weekly | | X |
| Electrolytes, including $Ca^{++}$, $PO_4$, $Mg^{++}$ | X | X | | | X |
| Urinalysis for dipstick protein and urine protein creatinine (UPC) ratio | X[B] | X[B] | | | |
| Creatinine (OR creatinine clearance OR radioisotope GFR), BUN, AST, ALT, bilirubin | X | X | | | X |
| INR/PT | X | | | | |
| Pregnancy test (for females of childbearing potential) | X | | | | |
| Brain MRI with and without gadolinium | X[C] | | | X[D] | X |
| Spine MRI with gadolinium | X[C] | | | X[D] | X[D] |
| CSF cytology | X[E] | | | X[E] | X[E] |

A For patients receiving bevacizumab only.

B Obtain prior to the start of each course of bevacizumab. If urine dipstick is 2+ or greater for protein, hold bevacizumab and obtain UPC ratio. See bevacizumab dose modifications for proteinuria (Section 5.1).

C Obtain within 2 weeks prior to study enrollment.

D Obtain within one week prior to the third course of therapy and prior to every other subsequent course of therapy (ie, 5th, 7th, etc.) for up to 12 courses of therapy. Repeat spine MRI only if initially positive or clinically indicated.

E Obtain within 14 days prior to start of course 1 if feasible and not contraindicated. If baseline test is negative, repeat only if there is disease progression. If positive at baseline, repeat prior to every other course (ie, 3rd, 5th, etc.) until there are two negative cytologies. CSF cytology can be waived for patients where a lumbar puncture is not deemed to be safe.

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

### 7.2 Follow-up

See COG Late Effects Guidelines for recommended post treatment follow-up http://www.childrensoncologygroup.org/disc/LE/default.htm.

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

### 8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease (see definition in Section 10.4).

b) Grade 3 or higher non-hematologic toxicity despite two dose reductions (as stated in Section 5.0).

c) Prolonged myelosuppression that prevents delivery of subsequent course by Day 35 despite dose reductions (See Section 5.2).

d) Adverse event requiring discontinuation of bevacizumab (as stated in Section 5.1).

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

f) Completion of 12 courses of therapy.

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

h) 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.

### 8.2 Off Study Criteria

a) Death.

b) Lost to follow-up.

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

d) Withdrawal of consent for any further data submission.

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

## 9.0 STATISTICAL CONSIDERATIONS

### 9.1 Sample Size and Study Duration

Based on A09071, we estimate 36 eligible patients will be available for enrollment annually, at a rate of 3 patients per month for 36 months, for a total of approximately 108 eligible patients. An additional 11 patients will be added to accommodate for a 10% inevaluable and ineligible rate to a maximum accrual of 120 patients. The last patient enrolled will be followed for six months after enrollment at which time the definitive analysis for the study will be conducted.

### 9.2 Study Design

This is a randomized, phase II screening trial comparing temozolomide with irinotecan to temozolomide, irinotecan and bevacizumab, for the treatment of recurrent/refractory medulloblastoma/PNET. Patients will be randomized at the time of enrollment to receive

one of two regimens with equal probability: (1) temozolomide (TEMO) with irinotecan (IRIN), or (2) temozolomide with irinotecan plus bevacizumab (TEMO+IRIN+B). Treatment will continue for up to 12 courses as long as there is no tumor progression and/or untoward toxicity. Patients will be stratified for randomization to each treatment arm according to whether or not they have measurable disease.

## 9.3 Methods of Analysis

Survival will be the primary outcome measure used to determine whether the addition of bevacizumab to temozolomide/irinotecan reduces the risk of death to warrant further study. The secondary objective includes estimation of the risk of disease progression and response rate for each treatment arm.

### 9.3.1 Efficacy Endpoint

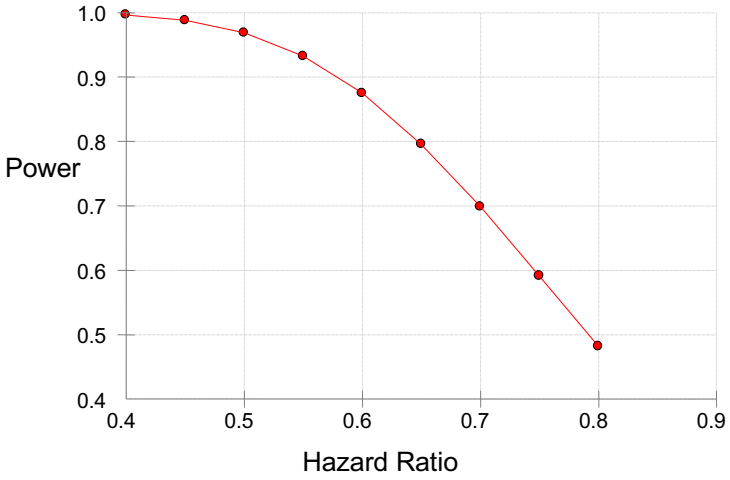
Any patient who dies will be considered to have experienced an event, regardless of the cause of death. Otherwise, the patient will be considered censored at last contact.

All eligible patients who are randomized and receive at least one dose of their assigned regimen will be considered in the analysis. The primary analysis will be done with each patient's outcome assigned to her or his randomized regimen. A secondary analysis will be done with each patient's outcome assigned to her or his actual treatment regimen, if there are any patients whose randomized regimen is switched. The risk of death of two regimens will be compared using the log-rank test.

Patients will be enrolled for thirty-six months (108 eligible patients). The last patient enrolled will be followed for six (6) months. At that point, the primary study analysis can be accomplished.

Data from patients enrolled on CCG-0962, P9761, P9963, A09713 and A09705 provide an estimate of the median survival of 45 weeks from study enrollment for patients with recurrent medulloblastoma. TEMO+IRIN+B will be considered of sufficient interest for further development if the one-sided test of equality of risk of death between TEMO+IRIN *v.* TEMO+IRIN+B has an associated p-value of 0.15 or less. The power characteristics of this design are given in the following figure:

Power as a Function of the Hazard Ratio Associated with Bevacizumab Containing Therapy




For example, this design has approximately 87% power for the alternative of a 40% reduction in risk of death associated with TEMO+IRIN+B.

Each regimen will be monitored for toxicity, however, as described below.

In addition to overall survival, the event-free survival (EFS) will be determined for each patient and compared across regimens using the log-rank test. The EFS interval for a patient will be defined to be the time from enrollment to: (1) disease progression; (2) second malignant neoplasm; (3) death regardless of cause; or (4) date of last contact, whichever comes first. Patients whose EFS follow-up is terminated because of reasons (1)-(3) above will be considered to have experienced an event; otherwise the patient will be considered censored at the conclusion of EFS-time. Kaplan-Meier estimates of the EFS for each of the randomized regimens will be constructed.

9.3.2 Interim Montioring

We will monitor for emerging differences between the randomized treatments using the Lan and DeMets spending function approach. [54] The test statistic used for this for interim monitoring will be:

$$\frac{\ln\{\text{Hazard Ratio for Death for Experimental: Standard Therapy}\}}{\sqrt{\text{Estimated Variance of the Hazard Ratio}}}$$

where the hazard ratio is estimated from a proportional hazards regression stratified according to the factors by which randomization is stratified. The bevacizumab-containing therapy is considered the experimental therapy. The spending function will be $\alpha(t)=\alpha t^2$. We will monitor for differences in survival across the regimens at the times shown below. The projected expected information times are presented in the tables as well.

| Monitoring Time (Years Since Study Opening) | Expected Information Time | Lower Monitoring Boundary | Cumulative α |
|---|---|---|---|
| 1.5 | 0.23 | -2.4 | 0.008 |
| 2.5 | 0.51 | -1.8 | 0.04 |
| 3.5 | 1.0 | -1.1 | 0.15 |

At each of the monitoring times above, we will test the alternative hypothesis. If the p-value obtained by that procedure is less than or equal to 0.004, the study will be identified for possible closure of accrual because the alternative hypothesis is not tenable ('futility monitoring').

9.3.3 Response Rate for Each Regimen

Only patients who are enrolled with measurable disease will be considered in the evaluation of response rate.

Disease response will be assessed according to the response criteria described in Section 10.4.

Any patient who receives at least one dose of protocol therapy will be considered for this assessment. Any patient who demonstrates an overall response of complete or partial response at any time will be considered as a "responder". All other evaluable patients who have had protocol therapy terminated will be considered non-responders. The response rate will be estimated separately for each regimen by the number of responders divided by the number of response-evaluable patients. The response rates will be compared by means of the exact conditional test of proportions, but decisions regarding the relative efficacy of the two regimens will be made based on the risk for adverse event as described above.

The estimated response rate for patients with medulloblastoma treated with temozolomide (Temodar) from A09701 was 16%. If this response rate holds for the two regimens in this study, the expected 95% confidence intervals for the response rates will be 7.36%-28.9%. The response rates will be compared by means of the exact conditional test of proportions, but decisions regarding the relative efficacy of the two regimens will be made based on the risk for death.

## 9.4 Interim Safety Monitoring

The feasibility of these two regimens will be monitored as well. A patient will be considered to have experienced a feasibility- event if the patient dies while receiving protocol therapy and treatment is considered the principal cause of death or the patient is removed from protocol therapy prior to month four because of toxicity. If, at any time, seven or more patients experience feasibility-events, the regimen on which this occurs will be considered for modification or termination. If the true feasibility- event rate is 21% and enrollment proceeds to the full 54 for a particular regimen, the regimen will be considered tolerable with probability 0.05. In addition, each time the study is reported to the COG Data and Safety Monitoring Committee, the proportion of eligible patients on each therapy that have experienced a feasibility-event will be reported along with the

95% confidence interval for that rate. If the lower boundary for the confidence interval exceeds 5%, the particular therapy will be identified for modification.

Furthermore, the dosing regimen will be re-evaluated with consideration for a protocol amendment if: (1) > 30% of patients require a dose reduction on either arm by the 4-month time point, or (2) > 25% of patients need to discontinue bevacizumab by 4 months for bevacizumab-related toxicity.

Each regimen will be considered separately with respect to the incidence of intracranial hemorrhage. Every patient considered evaluable for feasibility-event will also be considered for the assessment of rate of intracranial hemorrhage. A feasibility-evaluable patient who experiences a grade 2 or greater intracranial hemorrhage at any time during protocol therapy will be considered to have experienced a CNS-hemorrhage event (CHE). A feasibility-evaluable patient who terminates protocol therapy without experiencing a CHE at any time up to 30 days after the termination of protocol therapy or the patient's death, whichever comes first, will be considered not to have experienced a CHE.

If, at any time, three CHEs are observed on either regimen, the study will be identified for possible modification. For either regimen, if the true CHE rate is 10%, the regimen will be identified as being associated with an excessive CHE rate with probability of at least 91%. At each formal interim monitoring, the CHE-time will be calculated for every feasibility-evaluable patient. This will be the time from enrollment until CHE event, 30 days after completion of protocol therapy or last patient status, whichever occurs first. Patients who experience a grade 2 or greater intracranial hemorrhage according to CTC version 4 will be considered to have experience a CHE; otherwise the patient will be considered censored for CHE at the end of the CHE-time. The proportion of patients who experience a CHE event as a function of time since enrollment will be calculated according to the method of Kaplan and Meier, as well as the 95% confidence interval associated with that proportion.

### 9.5 Detection of Progression

The administration of bevacizumab may modify the radiographic appearance of the tumor and mask anatomical progressive disease. We will compare the sites of disease at recurrence to obtain preliminary data on this hypothesis. At disease progression, the sites of recurrence will be classified as: (1) recurrence at the primary site only; or (2) recurrence at a site other than one initially involved at the time enrollment onto ACNS0821. The cumulative incidence of each type of disease progression will be calculated for each regimen separately and compared using the methods of Fine and Gray[53]. A higher cumulative incidence of new sites of disease relative to those observed at enrollment will be taken to support the possibility that bevacizumab may mask anatomical progression. Because the study is designed to obtain the target power for the overall survival comparison, the power for detecting differences in the modalities by which recurrence is detected will be limited when using a conventional statistical test of size 0.05.

### 9.6 Gender and Minority Accrual Estimates

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

| Accrual Targets | | | |
|---|---|---|---|
| **Ethnic Category** | **Sex/Gender** | | |
| | **Females** | **Males** | **Total** |
| Hispanic or Latino | 0 | 7 | 7 |
| Not Hispanic or Latino | 43 | 70 | 113 |
| **Ethnic Category: Total of all subjects** | 43 | 77 | 120 |
| **Racial Category** | | | |
| American Indian or Alaskan Native | 4 | 6 | 10 |
| Asian | 0 | 4 | 4 |
| Black or African American | 16 | 6 | 22 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 |
| White | 23 | 61 | 84 |
| **Racial Category: Total of all subjects** | 43 | 77 | 120 |

This distribution was derived from A09071, A Phase II Study of Temodar (Temozolomide) in Children and Adolescents with Recurrent Central Nervous System Tumors.

## 10.0 EVALUATION CRITERIA

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

**This study will utilize the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting.** A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
Additionally, toxicities are to be reported on the appropriate data collection forms.

### 10.2 Methodology to Determine Tumor Measurement

Patients must have clear residual disease, defined as tumor that is measurable in two perpendicular diameters on MRI OR diffuse leptomeningeal disease OR clear MRI evidence of disease that may not be measurable in two perpendicular diameters.

#### 10.2.1 Assessments of Tumor that is Measurable in Two Perpendicular Diameters

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

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. Either T1 or T2 weighted images are used - whichever gives the best estimate of tumor size.

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

1. For MRI imaging (preferred), 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. Longest diameter of target lesion(s) should be selected in the axial plane only for CT.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The perpendicular measurement should be determined (transverse (T) measurement- perpendicular to the width in the selected plane.
4. The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis compose the majority of the lesion, the lesion may not be "measurable".
   Options:
   - if the cyst/necrosis is eccentric, the W and T of the solid portion should be measured, the cyst/necrosis excluded from measurement
   - if the cyst/necrosis is central but represents a small portion of the tumor (< 25%), disregard and measure the whole lesion
   - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured.

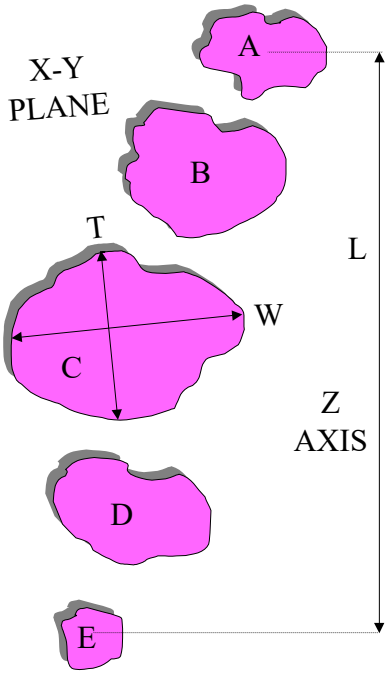
10.2.2 Assessments of Diffuse Leptomeningeal Disease or Disease that may not be measurable in Two Diameters

Patients enrolled without measurable disease as defined above but with diffuse leptomeningeal disease OR clear MRI evidence of disease that is not measurable in two perpendicular diameters (see Figure 10.1 below) will be assessed for disease response with scheduled MRI evaluations and CSF cytology as detailed in Section 7.1. Clear, unequivocal disease extension will be at the discretion of the clinical radiologist and must be noted in the MRI report. If there is concern for disease extension that is not clear, CSF can be obtained and if newly positive for malignant cells should be considered disease progression. Presence and location of leptomeningeal tumor spread should be noted, and change in extent/thickness assessed on follow up studies.

10.2.3 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, as defined in Table 10.2a and 10.2b. Response classifications for target lesions, non-target lesions and disease not measurable in two perpendicular diameters are defined in Section 10.4.

**Figure 10.1: COG Guidelines for Measurement of Tumor Size**




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

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

**Table 10.1: RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST) AND PRODUCT OF TWO DIAMETERS (WHO)**
**(Modified from Appendix II, Table 2, JNCI 92:213, 2000)**

| | Diameter, 2R | Product, $(2R)^2$ |
|---|---|---|
| **Response** | **Decrease** | **Decrease** |
| | 30% | 50% |
| | 50% | 75% |
| **Disease Progression** | **Increase** | **Increase** |
| | 12% | 25% |
| | 20% | 44% |
| | 25% | 56% |
| | 30% | 69% |

**Table 10.2a Overall Response Assessment for Target Tumor Measurable in Two Diameters**

| 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

**Table 10.2b Overall Response Assessment for Disease Not Measurable in Two Perpendicular Diameters**

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

*New CSF positive for malignant cells will be considered Progressive Disease. Persistence of CSF positive for malignant cells will be considered Stable Disease even if target lesions demonstrate response.

## 10.3 Selection of Target and Non-Target Lesions

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

## 10.4 Response Criteria for Target Lesions

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

WxT (current scan)
WxT (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)**: The disappearance of all target lesions.
**Partial response (PR)**: ≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
**Stable Disease (SD)**: Neither sufficient decrease in 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% increase in the product of perpendicular diameters of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more lesions.

Local progression is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant progression is defined as the appearance of tumor at sites other than known prior sites of disease. Distant progression most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant progression is defined when evaluation of the entire neuraxis reveals local and distant progression.

5. For patients enrolled without "measurable disease" but with clear MRI evidence of recurrent disease:

**Complete Response (CR)**: Disappearance of all lesions.
**Stable Disease (SD) / Incomplete Response (IR)**: The persistence of one or more non-target lesions but without evidence of progressive disease at any site.
**Progressive Disease (PD)**: The appearance of one or more new lesions and/or unequivocal progression of existing lesions. New CSF positive for malignant cells.

### 10.5 Response Criteria for Non-target Lesions

Non-target lesions will only be evaluated in patients with measurable disease.

**Complete Response (CR)**: Disappearance of all non-target lesions.
**Stable Disease (SD) / Incomplete Response (IR)**: The persistence of one or more non-target lesions.
**Progressive Disease (PD)**: The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

# 11.0 ADVERSE EVENT REPORTING REQUIREMENTS

## 11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

## 11.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

## 11.3 Expedited Reporting Requirements – Serious Adverse Events (SAEs)

To ensure compliance with these regulations/this guidance, as IND/IDE sponsor, NCI requires that AEs be submitted according to the timeframes in the AE reporting tables assigned to the protocol, using the CTEP Adverse Event Reporting System (CTEP-AERS).

***Any AE that is serious qualifies for expedited reporting***. An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A Serious Adverse Event (SAE) is any adverse drug event (experience) occurring at any dose that results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse drug experience.
3) An adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours). This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

## 11.4 Special Situations for Expedited Reporting

### 11.4.1 SAEs Occurring More than 30 Days After Last Dose of Study Drug

Any Serious Adverse Event that occurs more than 30 days after the last administration of the investigational agent/intervention **and** has an attribution of a possible, probable, or definite relationship to the study therapy must be reported according to the CTEP-AERS reporting tables in this protocol.

### 11.4.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies or birth defects, must be reported via CTEP-AERS if it occurs at any time following treatment with an agent under a NCI IND/IDE since these are considered to be serious AEs.

### 11.4.3 Death

**Reportable Categories of Death**

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Sudden Death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with grade 5.
- Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)" under the system organ class (SOC) of the

same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

11.4.4 Secondary Malignancy

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

The NCI requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

11.4.5 Pregnancy, Fetal Death, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form, available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf, needs to be completed and faxed along with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

11.4.5.1 **Pregnancy**

Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via CTEP-AERS as **Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*"** under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Pregnancy needs to be followed **until the outcome is known**. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

11.4.5.2 **Fetal Death**

Fetal death, defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation*", needs to be reported expeditiously, as **Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*"**. Do NOT report a fetal death as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

11.4.5.3 **Death Neonatal**

Neonatal death, defined in CTCAE as *"A disorder characterized by cessation of life occurring during the first 28 days of life*" needs to be reported expeditiously, as **Grade 4 "*General disorders and administration - Other (neonatal loss)*" when the death is the result of a patient pregnancy or pregnancy in partners of men on study**. Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men on study as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

## 11.5 Reporting Requirements for Specialized AEs

11.5.1 Baseline AEs

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as "Course Zero" using CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (eg, elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the study and reported if it fulfills expedited AE reporting guidelines.

a. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required.
b. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required.
c. No modification in grading is to be made to account for abnormalities existing at baseline.

11.5.2 Persistent AEs

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

ROUTINE reporting: The AE must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.
EXPEDITED reporting: The AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

11.5.3 Recurrent AEs

A recurrent AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.
ROUTINE reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.
EXPEDITED reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases OR
2) Hospitalization is associated with the recurring AE.

## 11.6 Exceptions to Expedited Reporting

11.6.1 Specific Protocol Exceptions to Expedited Reporting (SPEER)

SPEER: Is a subset of AEs within the Comprehensive Adverse Events and Potential Risks (CAEPR) that contains a list of events that are considered expected for CTEP-AERS reporting purposes. (Formerly referred to as the Agent Specific Adverse Event List (ASAEL).)

AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS ONLY if they exceed the grade of the event listed in parentheses after the event. If the CAEPR is part of a combination IND using multiple investigational agents and has an SAE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

11.6.2 Special Situations as Exceptions to Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures will be specified in the protocol. The protocol specific guidelines supersede the NCI Adverse Event Reporting Guidelines. These special situations are listed under the CTEP-AERS reporting Table A for this protocol.

## 11.7 Reporting Requirements - Investigator Responsibility

Clinical investigators in the treating institutions and ultimately the Study Chair have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention. It is the responsibility of the treating physician to supply the medical documentation needed to support the expedited AE reports in a timely manner.

Note: All expedited AEs (reported via CTEP-AERS) must also be reported via routine reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database.

### 11.8 General Instructions for Expedited Reporting via CTEP-AERS

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

An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS at: https://eapps-ctep.nci.nih.gov/ctepaers.

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.
In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Expedited AE reporting timelines are defined as:
  - **24-Hour; 5 Calendar Days -** The AE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - **7 Calendar Days -** A complete expedited report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via CTEP-AERS **if the event occurs following investigational agent administration.**

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

- Any death occurring greater than 30 days of the last dose with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting **within 24 hours**.

CTEP-AERS Medical Reporting includes the following requirements as part of the report: 1) whether the patient has received at least one dose of an investigational agent on this study; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

**Any medical documentation supporting an expedited report (eg, H & P, admission and/or notes, consultations, ECG results, etc.) MUST be faxed within 48-72 hours to the NCI. NOTE: English is required for supporting documentation submitted to**

**the numbers listed below in order for the NCI to meet the regulatory reporting timelines.**

Fax supporting documentation **for AEs related to investigational agents supplied under a CTEP IND** to: **301-230-0159** (back-up: 301-897-7404).

Also: Fax or email supporting documentation to COG for **all** IND studies (Fax # 626-303-1768; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

- **ALWAYS include the ticket number on all faxed documents.**
- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.9 **Reporting Table for Late Phase 2 and Phase 3 Studies – Table A**

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:
1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations that are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|---|---|---|---|---|
| **Resulting in Hospitalization ≥ 24 hrs** | **7 Calendar Days** | | | **24-Hour Notification 5 Calendar Days** |
| **Not resulting in Hospitalization ≥ 24 hrs** | **Not Required** | | **7 Calendar Days** | |

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

**Expedited AE reporting timelines are defined as:**
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
**Expedited 24-hour notification followed by complete report within 5 calendar days for:**
- All Grade 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

## 11.10 Protocol Specific Additional Instructions and Reporting Exceptions

- **Grades 1-4 myelosuppression (anemia, neutropenia, thrombocytopenia) do not require expedited reporting.**
  - G3-4 Decreased neutrophil count/febrile neutropenia, regardless of hospitalization

- G3-4 Diarrhea, Nausea, Vomiting, or Dehydration, regardless of hospitalization

## 11.11 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 7 calendar days** of learning of the event.

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

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

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

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

## 11.12 Routine Adverse Event Reporting

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

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 CTEP-AERS reportable events and Grade 3 and higher Adverse Events.

## 12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*".

### 12.1 CDUS

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

### 12.2 Data and Safety Monitoring Committee

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

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

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

### 12.3 CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data
for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the

study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.–Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as

possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or
publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator(s) confidential/ proprietary information.

## 13.0 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).

### 13.1 Timing of MRIs

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

- within 2 weeks preceding enrollment into the study
- prior to every other course of therapy
- when patient is removed from protocol therapy

In addition, for patients who have undergone surgical tumor debulking prior to protocol therapy, pre-operative and post-operative imaging must be obtained preferably within 48 hours of surgery.

### 13.2 Whole Brain MRI With and Without Contrast

Recommended sequences:

1. Sagittal T1 localizer; 4 mm skip 0.4 mm
2. Axial FSE T2; 4 mm, skip 0.4 mm
3. Axial T2 FLAIR; 4 mm skip 0.4
4. Axial diffusion; 4-5 mm skip 0 (single shot, matrix 128 x 128 or 128 x 192, B=1000)
5. Axial T1; 4 mm skip 0.4 mm
6. Axial gradient echo (susceptibility sequence); 4-5 mm skip 1-2 mm. TE=20, flip angle =20.
7. Axial T1 with contrast; 4 mm skip 0.4 mm

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

Optional sequences (depending on tumor)
Precontrast :

1. Sagittal or coronal FSET2; 4 mm skip 0.4 mm, depending on tumor configuration/orientation
2. Axial diffusion tensor (see optional sequences, Section 16.8)

Post contrast :

1. Coronal T1 : 4mm skip 0.4
2. T1-weighted gradient echo volume sequence (SPGR or equivalent)
3. Axial Perfusion (see optional sequences, Section 16.8)

NOTES:

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

13.3 **Spine MRI With Contrast**

The MRI scan must be performed of the entire spine with contrast, and must be performed in at least two planes.

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

Technical notes:

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

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

Technical notes:

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

For primary tumors of the spinal cord, add:

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

Technical notes:

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

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

NOTE:

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

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

### 13.4 Tumor Response Assessment

For the response assessment, MRI scans obtained within the first 8 weeks (after Course 2) and within the first 16 weeks (after Course 4) will be compared to the baseline MRI scan. **Exception:** In cases of progressive disease, the reference scan should be the MRI with the smallest product observed since the start of treatment (not necessarily at week 8).

## APPENDIX I: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN GIRLS AGE 1-17 YEARS

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 90th | 97 | 97 | 98 | 100 | 101 | 102 | 103 | 52 | 53 | 53 | 54 | 55 | 55 | 56 |
| | 95th | 100 | 101 | 102 | 104 | 105 | 106 | 107 | 56 | 57 | 57 | 58 | 59 | 59 | 60 |
| 2 | 90th | 98 | 99 | 100 | 101 | 103 | 104 | 105 | 57 | 58 | 58 | 59 | 60 | 61 | 61 |
| | 95th | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 62 | 62 | 63 | 64 | 65 | 65 |
| 3 | 90th | 100 | 100 | 102 | 103 | 104 | 106 | 106 | 61 | 62 | 62 | 63 | 64 | 64 | 65 |
| | 95th | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| 4 | 90th | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 64 | 64 | 65 | 66 | 67 | 67 | 68 |
| | 95th | 105 | 106 | 107 | 108 | 110 | 111 | 112 | 68 | 68 | 69 | 70 | 71 | 71 | 72 |
| 5 | 90th | 103 | 103 | 105 | 106 | 107 | 109 | 109 | 66 | 67 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 70 | 71 | 71 | 72 | 73 | 73 | 74 |
| 6 | 90th | 104 | 105 | 106 | 108 | 109 | 110 | 111 | 68 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95th | 108 | 109 | 110 | 111 | 113 | 114 | 115 | 72 | 72 | 73 | 74 | 74 | 75 | 76 |
| 7 | 90th | 106 | 107 | 108 | 109 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| | 95th | 110 | 111 | 112 | 113 | 115 | 116 | 116 | 73 | 74 | 74 | 75 | 76 | 76 | 77 |
| 8 | 90th | 108 | 109 | 110 | 111 | 113 | 114 | 114 | 71 | 71 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| 9 | 90th | 110 | 110 | 112 | 113 | 114 | 116 | 116 | 72 | 72 | 72 | 73 | 74 | 75 | 75 |
| | 95th | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| 10 | 90th | 112 | 112 | 114 | 115 | 116 | 118 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| 11 | 90th | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 74 | 75 | 76 | 77 | 77 |
| | 95th | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| 12 | 90th | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 75 | 75 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 119 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| 13 | 90th | 117 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 80 | 80 | 80 | 81 | 82 | 83 | 83 |
| 14 | 90th | 119 | 120 | 121 | 122 | 124 | 125 | 125 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| | 95th | 123 | 123 | 125 | 126 | 127 | 129 | 129 | 81 | 81 | 81 | 82 | 83 | 84 | 84 |
| 15 | 90th | 120 | 121 | 122 | 123 | 125 | 126 | 127 | 78 | 78 | 78 | 79 | 80 | 81 | 81 |
| | 95th | 124 | 125 | 126 | 127 | 129 | 130 | 131 | 82 | 82 | 82 | 83 | 84 | 85 | 85 |
| 16 | 90th | 121 | 122 | 123 | 124 | 126 | 127 | 128 | 78 | 78 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 82 | 82 | 83 | 84 | 85 | 85 | 86 |
| 17 | 90th | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 78 | 79 | 79 | 80 | 81 | 81 | 82 |
| | 95th | 125 | 126 | 127 | 129 | 130 | 131 | 132 | 82 | 83 | 83 | 84 | 85 | 85 | 86 |

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

## APPENDIX II: 90th and 95th PERCENTILE BLOOD PRESSURE BY PERCENTILE HEIGHT IN BOYS AGE 1-17 YEARS

| Age (Year) | BP Percentile ↓ | Systolic BP (mmHg) ← Percentile of Height → | | | | | | | Diastolic BP (mmHg) ← Percentile of Height → | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5th | 10th | 25th | 50th | 75th | 90th | 95th | 5th | 10th | 25th | 50th | 75th | 90th | 95th |
| 1 | 90th | 94 | 95 | 97 | 99 | 100 | 102 | 103 | 49 | 50 | 51 | 52 | 53 | 53 | 54 |
| | 95th | 98 | 99 | 101 | 103 | 104 | 106 | 106 | 54 | 54 | 55 | 56 | 57 | 58 | 58 |
| 2 | 90th | 97 | 99 | 100 | 102 | 104 | 105 | 106 | 54 | 55 | 56 | 57 | 58 | 58 | 59 |
| | 95th | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| 3 | 90th | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95th | 104 | 105 | 107 | 109 | 110 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| 4 | 90th | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 63 | 64 | 65 | 66 | 66 | 67 |
| | 95th | 106 | 107 | 109 | 111 | 112 | 114 | 115 | 66 | 67 | 68 | 69 | 70 | 71 | 71 |
| 5 | 90th | 104 | 105 | 106 | 108 | 110 | 111 | 112 | 65 | 66 | 67 | 68 | 69 | 69 | 70 |
| | 95th | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 71 | 72 | 73 | 74 | 74 |
| 6 | 90th | 105 | 106 | 108 | 110 | 111 | 113 | 113 | 68 | 68 | 69 | 70 | 71 | 72 | 72 |
| | 95th | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| 7 | 90th | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 70 | 70 | 71 | 72 | 73 | 74 | 74 |
| | 95th | 110 | 111 | 113 | 115 | 117 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| 8 | 90th | 107 | 109 | 110 | 112 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 75 | 76 |
| | 95th | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| 9 | 90th | 109 | 110 | 112 | 114 | 115 | 117 | 118 | 72 | 73 | 74 | 75 | 76 | 76 | 77 |
| | 95th | 113 | 114 | 116 | 118 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 81 | 81 |
| 10 | 90th | 111 | 112 | 114 | 115 | 117 | 119 | 119 | 73 | 73 | 74 | 75 | 76 | 77 | 78 |
| | 95th | 115 | 116 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 81 | 81 | 82 |
| 11 | 90th | 113 | 114 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95th | 117 | 118 | 119 | 121 | 123 | 124 | 125 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| 12 | 90th | 115 | 116 | 118 | 120 | 121 | 123 | 123 | 74 | 75 | 75 | 76 | 77 | 78 | 79 |
| | 95th | 119 | 120 | 122 | 123 | 125 | 127 | 127 | 78 | 79 | 80 | 81 | 82 | 82 | 83 |
| 13 | 90th | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 75 | 76 | 77 | 78 | 79 | 79 |
| | 95th | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| 14 | 90th | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 75 | 76 | 77 | 78 | 79 | 79 | 80 |
| | 95th | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| 15 | 90th | 122 | 124 | 125 | 127 | 129 | 130 | 131 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| | 95th | 126 | 127 | 129 | 131 | 133 | 134 | 135 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| 16 | 90th | 125 | 126 | 128 | 130 | 131 | 133 | 134 | 78 | 78 | 79 | 80 | 81 | 82 | 82 |
| | 95th | 129 | 130 | 132 | 134 | 135 | 137 | 137 | 82 | 83 | 83 | 84 | 85 | 86 | 87 |
| 17 | 90th | 127 | 128 | 130 | 132 | 134 | 135 | 136 | 80 | 80 | 81 | 82 | 83 | 84 | 84 |
| | 95th | 131 | 132 | 134 | 136 | 138 | 139 | 140 | 84 | 85 | 86 | 87 | 87 | 88 | 89 |

Source: Adapted from: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents; NIH Publication No. 05-5267.

## APPENDIX III: TEMOZOLOMIDE DOSING TABLE - STARTING DOSE= 150 mg/m$^2$

For patients <0.5m$^2$ use 5 mg/kg. Round dose to the nearest 5mg. Round 2.5 down. Example: For a patient that is 0.3 m$^2$ and weighs 5.3 kg, the calculated dose is 5.3 kg x 5mg/kg = 26.5 mg rounded to the nearest 5 mg = 25 mg temozolomide/day.

| BSA (m$^2$) | Administered daily dose (mg) |
|---|---|
| 0.50-0.51 | 75 |
| 0.52-0.55 | 80 |
| 0.56-0.58 | 85 |
| 0.59-0.61 | 90 |
| 0.62-0.65 | 95 |
| 0.66-0.68 | 100 |
| 0.69-0.71 | 105 |
| 0.72-0.75 | 110 |
| 0.76-0.78 | 115 |
| 0.79-0.81 | 120 |
| 0.82-0.85 | 125 |
| 0.86-0.88 | 130 |
| 0.89-0.91 | 135 |
| 0.92-0.95 | 140 |
| 0.96-0.98 | 145 |
| 0.99-1.01 | 150 |
| 1.02-1.05 | 155 |
| 1.06-1.08 | 160 |
| 1.09-1.11 | 165 |
| 1.12-1.15 | 170 |
| 1.16-1.18 | 175 |
| 1.19-1.21 | 180 |
| 1.22-1.25 | 185 |
| 1.26-1.28 | 190 |
| 1.29-1.31 | 195 |
| 1.32-1.35 | 200 |
| 1.36-1.38 | 205 |
| 1.39-1.41 | 210 |
| 1.42-1.45 | 215 |
| 1.46-1.48 | 220 |
| 1.49-1.51 | 225 |
| 1.52-1.55 | 230 |
| 1.56-1.58 | 235 |
| 1.59-1.61 | 240 |
| 1.62-1.65 | 245 |
| 1.66-1.68 | 250 |
| 1.69-1.71 | 255 |
| 1.72-1.75 | 260 |
| 1.76-1.78 | 265 |

Continue on next page

| BSA ($m^2$) | Administered daily dose (mg) |
|---|---|
| 1.79-1.81 | 270 |
| 1.82-1.85 | 275 |
| 1.86-1.88 | 280 |
| 1.89-1.91 | 285 |
| 1.92-1.95 | 290 |
| 1.96-1.98 | 295 |
| 1.99-2.01 | 300 |
| 2.02-2.05 | 305 |
| 2.06-2.08 | 310 |
| 2.09-2.11 | 315 |
| 2.12-2.15 | 320 |
| 2.16-2.18 | 325 |
| 2.19-2.21 | 330 |
| 2.22-2.25 | 335 |
| 2.26-2.28 | 340 |
| 2.29-2.31 | 345 |
| 2.32-2.35 | 350 |
| 2.36-2.38 | 355 |
| 2.39-2.40 | 360 |

## APPENDIX IV: TEMOZOLOMIDE DOSING TABLE-REDUCED DOSE = 112.5 mg/m$^2$

For patients <0.5m$^2$ use 3.75 mg/kg. Round dose to the nearest 5mg. Round 2.5 down. Example: For a patient that is 0.3 m$^2$ and weighs 5.3 kg, the calculated dose is 5.3 kg x 3.75mg/kg = 19.875mg rounded to the nearest 5 mg = 20 mg temozolomide/day.

| BSA (m$^2$) | Administered daily dose (mg) |
|---|---|
| 0.50-0.51 | 55 |
| 0.52-0.55 | 60 |
| 0.56-0.60 | 65 |
| 0.61-0.64 | 70 |
| 0.65-0.68 | 75 |
| 0.69-0.73 | 80 |
| 0.74-0.77 | 85 |
| 0.78-0.82 | 90 |
| 0.83-0.86 | 95 |
| 0.87-0.91 | 100 |
| 0.92-0.95 | 105 |
| 0.96-1.00 | 110 |
| 1.01-1.04 | 115 |
| 1.05-1.08 | 120 |
| 1.09-1.13 | 125 |
| 1.14-1.17 | 130 |
| 1.18-1.22 | 135 |
| 1.23-1.26 | 140 |
| 1.27-1.31 | 145 |
| 1.32-1.35 | 150 |
| 1.36-1.40 | 155 |
| 1.41-1.44 | 160 |
| 1.45-1.48 | 165 |
| 1.49-1.53 | 170 |
| 1.54-1.57 | 175 |
| 1.58-1.62 | 180 |
| 1.63-1.66 | 185 |
| 1.67-1.71 | 190 |
| 1.72-1.75 | 195 |
| 1.76-1.80 | 200 |
| 1.81-1.84 | 205 |
| 1.85-1.88 | 210 |
| 1.89-1.93 | 215 |
| 1.94-1.97 | 220 |
| 1.98-2.02 | 225 |
| 2.03-2.06 | 230 |
| 2.07-2.11 | 235 |
| 2.12-2.15 | 240 |
| 2.16-2.20 | 245 |
| 2.21-2.24 | 250 |
| 2.25-2.28 | 255 |
| 2.29-2.33 | 260 |
| 2.34-2.37 | 265 |
| 2.38-2.40 | 270 |

## APPENDIX V: TEMOZOLOMIDE DOSING TABLE - REDUCED DOSE= 75 mg/m$^2$

For patients <0.5m$^2$ use 2.5mg/kg. Round dose to the nearest 5mg. Round 2.5mg down. Example: For a patient that is 0.3 m$^2$ and weighs 5.3 kg, the calculated dose is 5.3 kg x 2.5 mg/kg = 13.25mg rounded to the nearest 5 mg = 15 mg temozolomide/day.

| BSA (m$^2$) | Administered daily dose (mg) |
|---|---|
| 0.50 | 35 |
| 0.51-0.56 | 40 |
| 0.57-0.63 | 45 |
| 0.64-0.70 | 50 |
| 0.71-0.76 | 55 |
| 0.77-0.83 | 60 |
| 0.84-0.90 | 65 |
| 0.91-0.96 | 70 |
| 0.97-1.03 | 75 |
| 1.04-1.10 | 80 |
| 1.11-1.16 | 85 |
| 1.17-1.23 | 90 |
| 1.24-1.30 | 95 |
| 1.31-1.36 | 100 |
| 1.37-1.43 | 105 |
| 1.44-1.50 | 110 |
| 1.51-1.56 | 115 |
| 1.57-1.63 | 120 |
| 1.64-1.70 | 125 |
| 1.71-1.76 | 130 |
| 1.77-1.83 | 135 |
| 1.84-1.90 | 140 |
| 1.91-1.96 | 145 |
| 1.97-2.03 | 150 |
| 2.04-2.10 | 155 |
| 2.11-2.16 | 160 |
| 2.17-2.23 | 165 |
| 2.24-2.30 | 170 |
| 2.31-2.36 | 175 |
| 2.37-2.40 | 180 |

## APPENDIX VI: RECOMMENDATIONS FOR ADMINISTRATION OF TEMOZOLOMIDE (PATIENTS WHO ARE UNABLE TO SWALLOW CAPSULES AND CANNOT OBTAIN A SUSPENSION)

Temozolomide is an oral cancer medicine that your child will be taking for treatment of his/her medulloblastoma/PNET. If your child is unable to swallow capsules, the following instructions must be followed for safe administration of this medicine.

- Temozolomide must be kept in a dark container.
- Temozolomide should be taken the same time every day.
- If your child requires nausea medicine it should be taken prior to the temozolomide.
- If the dose of temozolomide is vomited (which is unusual) within the first 20 minutes after it is taken, the dose should be repeated. If your child vomits more than 20 minutes after the temozolomide has been taken, do not repeat the dose.
- If the caregiver administering this medicine is pregnant or suspects she is pregnant she should not handle this medicine.

Since temozolomide is an anti-cancer agent, special precautions must be taken when handling this medicine. There is potential hazard to anyone who handles this medicine once the protective capsule is opened. Since your child is unable to swallow the capsule you will be required to open the capsules and mix the contents of the capsule in apple sauce or apple juice. This process must be done according to the following guidelines to ensure safe administration of this medicine.

- Find a place that is free from drafts or wind and is not an area where food is stored or prepared.
- The work surface should be covered with an impermeable and disposable mat such as the one a pharmacy uses to reduce exposure to other members of the family.
- Temozolomide can be mixed in apple sauce or apple juice.
- Place the apple sauce or apple juice in a disposable container.
- Put on gloves, mask and goggles (eye protection).
- Open each capsule and place the powder in a medicine cup.
- Add the whole contents of the medicine cup to either apple sauce or apple juice. The medicine will not dissolve completely if mixing in apple juice so have extra apple juice on hand so you can add it to any remaining powder in the bottom of the cup.
- If you need to have additional juice or apple sauce remove your gloves before touching the main container then place new gloves on before adding the additional juice or apple sauce to the medicine. (You do not want to contaminate the main container with any powder that may be on your gloves).
- Anything that comes into contact with the medicine must be disposable, such as the spoon used for mixing or eating the apple sauce.
- Once all of the medicine is taken, throw away the following in the plastic bags provided to you by the clinic: Medicine cup, the container the medicine was mixed in, the cover for the work surface, mask, gloves and anything else that has been in contact with the medicine.
- Once a course of medicine is completed bring the plastic bag with you to the clinic so it can be disposed of properly.

## APPENDIX VII: YOUTH INFORMATION SHEETS

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

**A Study of New Drug Combinations in Children and Teens with Brain Tumors That are Difficult to Treat or Have Come Back after Treatment**

1. We have been talking with you about your brain tumor. Your brain tumor has either come back or not gone away with the treatments you already got.

2. We are asking you to take part in a research study because other treatments did not get rid of your tumor. 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 new combinations of anti-cancer medicines can make your tumor get smaller or go away. We do not know if one drug combination is better than the other. That is why we are doing this study.

3. All children who are part of this study will be treated with two drugs. Half of the children in this study will also be treated with a third drug. You will either get two drugs or three drugs. How many drugs you will get is decided on by chance. This is like flipping a coin and saying, "Heads means I get the two-drug treatment, but tails means I get the three-drug treatment." A computer decides which treatment you will get, not you or your doctor.

4. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the drug combinations will work to make your tumor smaller or go away but we do not know for sure if there is any benefit of being part of this study.

5. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that the study treatments may not work as well as other treatments to get rid of the tumor for as long as possible. Another risk is that you may have more side effects from the three-drug treatment than the two-drug treatment. Other things may happen to you that we do not yet know about.

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

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

**A Study of New Drug Combinations in Children and Teens with Brain Tumors That are Difficult to Treat or Have Come Back after Treatment**

1. We have been talking with you about medulloblastoma/PNET tumors. Medulloblastoma and PNET are types of cancer that grow in the brain. Your tumor has either come back or not gone away with previous treatments.

2. We are asking you to take part in a research study because other treatments did not get rid of your medulloblastoma/PNET tumor. A research study is when doctors work together to try out new ways to help people who are sick. In this study, doctors want to try new combinations of anti-cancer drugs (chemotherapy) to see if these new drug combinations will work well to make your tumor get smaller or go away.

3. All children and teens who are part of this study will be treated with a combination of two chemotherapy drugs, called temozolomide and irinotecan. This drug combination has been used to treat children and teens with other types of cancer. This study will also see if adding another drug to the combination will work better to make the tumor smaller or go away. This added drug is called bevacizumab. It has been used in studies of adults and children with other types of tumors.

4. This study is called a randomized study, because you will be randomly assigned to get one drug combination or the other. This is like flipping a coin and saying, “Heads means I get the two-drug chemotherapy, but tails means I get the three-drug chemotherapy.” A computer decides which chemotherapy plan you will be on, not you or your doctor. Studies like this one are done to learn which drug combination works best and to make sure the number of people is equal among the groups. We do not know if one drug combination is better than another.

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 the drug combinations will make your tumor get smaller or go away, 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.” One risk to you from this study is that the treatment you get may not work as well as other treatments to get rid of the tumor for as long as possible. Another risk is that you may have more side effects from the drugs if you get the three-drug combination. 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 you have.

## APPENDIX VII: POSSIBLE DRUG INTERACTIONS

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

### Bevacizumab

| **Drugs that may interact with bevacizumab*** |
|---|
| • Clozapine<br>• Some chemotherapy (be sure to talk to your doctor about this) |

| **Food and supplements that may interact with bevacizumab**** |
|---|
| • Unknown |

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

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

### Irinotecan

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

| |
|---|
| • Bosentan, sitaxentan, aprepitant, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, succinylcholine |

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

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

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

**Temozolomide**

| **Drugs that may interact with temozolomide*** |
|---|
| • Clozapine, leflunomide, natalizumab, tofacitinib |

| **Food and supplements that may interact with temozolomide**** |
|---|
| • 0. |

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

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

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