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The world's childhood cancer experts

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March 23rd, 2017

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Dear Ms. Kruhm,

Enclosed please find Amendment #4 to **ADVL1411**, *A Phase 1/2 Study of BMN 673 (IND #121510), an Oral Poly(ADP-ribose) Polymerase Inhibitor, Plus Temozolomide in Children with Refractory or Recurrent Malignancies*.

The Protocol has been amended to reflect modified risk information for BMN 673 (talazoparib). The CAEPR and risk profile have been updated to CAEPR Version 2.1, December 29, 2016.
The amendment is being submitted in response to an RRA from Dr. Richard Piekarz (piekarzr@mail.nih.gov).

Additional administrative changes were made for clarity and consistency.

SUMMARY OF CHANGES

The following specific revisions have been made to the protocol and informed consent document.

I. Changes to the Protocol:

#	Section	Comments
1.	Title	The version date and amendment # have been updated.
2.	Title	The additional participating sites have been updated.
3.	TOC	The Table of Contents has been updated.

4.	9.1.7	The CAEPR has been updated to Version 2.1, December 29, 2016.
		
		• Added New Risk:
		  • Less Likely: Dyspepsia; Epistaxis; Pain
		  • Rare but Serious: Typhlitis
		  • Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal distension; Dry skin; Dysgeusia; Hepatic failure; Insomnia; Neck pain; Non-cardiac chest pain; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain); Small intestinal obstruction; Weight loss
		
		• Increase in Risk Attribution:
		  • Changed to Likely from Less Likely: Anemia; Diarrhea; Platelet count decreased
		  • Changed to Less Likely from Rare but Serious: Febrile neutropenia
		  • Changed to Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Abdominal pain
		  • Changed to Less Likely from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution: Anorexia; Fever; Headache; Hypokalemia; Infection; Nervous system disorders - Other (neuropathy peripheral); Rash maculo-papular; White blood cell decreased
		
		• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
		  • Added: Abdominal pain; Alopecia; Anorexia; Dizziness; Fever; Headache; Infection; Pain; Vomiting
		
		• Provided Further Clarification:
		  • Peripheral sensory neuropathy (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Nervous system disorders - Other (neuropathy peripheral) (under Less Likely).
		  • Lung infection and Sepsis (previously under Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution) is now reported as Infection (under Less Likely).

#	Section	Comments
		• A new footnote #2 has been added as follows: "Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC." • A new footnote #3 has been added as follows: "Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOUS SYSTEM DISORDERS."

II. Changes to the Informed Consent Document:

#	Section	Comments
1.	ICD	The version date has been updated.

2.	What side effects…? (Part A)	The Risk List has been updated according to CAEPR Version 2.1, December 29, 2016.
		• Added New Risk:
		  • Occasional: Heartburn; Nose bleed
		  • Rare but Serious: Swelling of the bowels which may require surgery
		  •
		• Increase in Risk Attribution:
		  • Changed to Common from Occasional: Anemia which may require blood transfusion; Diarrhea; Bruising, bleeding
		  • Changed to Occasional from Rare: Infection, especially when white blood cell count is low
		  • Changed to Common from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain
		Changed to Occasional from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Loss of appetite; Fever; Headache; Muscle weakness; Numbness, tingling or pain of the arms and legs; Rash

3.	What side effects…? (Part B)	The Risk List has been updated according to CAEPR Version 2.1, December 29, 2016.
		• Added New Risk:
		  • Occasional: Heartburn; Nose bleed
		  • Rare but Serious: Swelling of the bowels which may require surgery
		  •
		• Increase in Risk Attribution:

#	Section	Comments
		• Changed to Common from Occasional: Anemia which may require blood transfusion; Diarrhea; Bruising, bleeding • Changed to Occasional from Rare: Infection, especially when white blood cell count is low • Changed to Common from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain Changed to Occasional from Also Reported on Talazoparib Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Loss of appetite; Fever; Headache; Muscle weakness; Numbness, tingling or pain of the arms and legs; Rash

Sincerely,
Michael Weiss, Ph.D., Protocol Coordinator, for
Eric Schafer, M.D., **ADVL1411** Study Chair, and
Brenda Weigel, M.D., PI, COG Phase 1/Pilot Consortium

Activated: April 21, 2014 Version Date: 03/23/17
Closed: Amendment: 4

CHILDREN'S ONCOLOGY GROUP

ADVL1411

A PHASE 1/ 2 STUDY OF BMN 673 (IND# 121510), AN ORAL POLY(ADP-RIBOSE) POLYMERASE INHIBITOR, PLUS TEMOZOLOMIDE IN CHILDREN WITH REFRACTORY OR RECURRENT MALIGNANCIES

Lead Organization: COG Phase 1/Pilot Consortium (COGC)

Participating Organization: COG

*** Participation is limited to the following COG sites and credit will be assigned to COGC in OPEN: ****

OR010 / Oregon Health and Science University
WI053 / Children's Hospital of Wisconsin

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AGENT NSC# AND IND#'s

NCI-Supplied Agent:
BMN 673 (BMN 673ts, talazoparib, MDV3800) NSC#771561 IND# 121510

Commercial Agent:
Temozolomide (Temodar®, Temodal®) NSC #362856

IND Sponsor: CTEP

SEE APPENDICES VI, VII AND VIII FOR SPECIMEN SHIPPING ADDRESSES.

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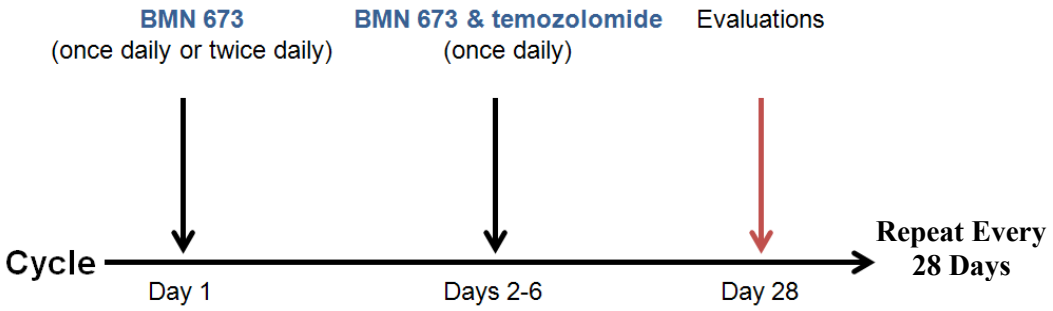
ABSTRACT

Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes involved in DNA repair through the recruitment and activation of proteins that primarily utilize the base excision repair (BER) pathway. PARP1, the family's founding member, binds to damaged DNA through its N-terminal zinc finger motifs; binding activates its catalytic C-terminal domain to hydrolyze NAD+ and produce linear and branched poly(ADP-ribose) (PAR) chains. These PAR chains have a net negative charge, which promotes recruitment of DNA repair proteins involved in the BER pathway to the site of DNA damage, and facilitates removal of PARP1 from damaged sites allowing access to other repair proteins. PARP2 is essential for the viability of PARP1. BMN 673 is a novel, highly potent orally administered PARP 1/2 inhibitor which was shown to be well tolerated and have great therapeutic promise in adult patients harboring intrinsic DNA repair deficits, such as germline *BRCA1/2*, in an early phase 1 clinical trial. Preclinical studies have strongly suggested that PARP inhibitors have additional mechanisms of action against certain cancers. For example, it has been shown that PARP1 is a key co-factor in ETS positive tumors such as *EWS-FLI1* and *EWS-ERG* chimera Ewing sarcoma which *in vitro* is exquisitely sensitive to available PARP inhibitors. Temozolomide, an orally administered monofunctional SN-1 alkylating agent, which is used in the treatment of a variety of pediatric tumors, has been theorized to potentiate PARP inhibition through the creation of persistent single nucleotide gaps in double stranded DNA which would normally be repaired by endogenous PARP enzymes. When BMN 673 in combination with low-dose short duration temozolomide was modeled through *in vitro* and mouse human tumor xenograft models, the treatment showed impressive activity in a broad range of pediatric cancers including Ewing sarcoma, Wilms tumor, medulloblastoma and acute lymphoblastic leukemia (ALL).

This study is a Phase 1/2 trial of BMN 673 in combination with low-dose short duration temozolomide in children with relapsed or refractory malignancies. This trial will be the first assessment of BMN 673 in children. In addition, it is testing a novel mechanism of temozolomide in combination such that it is almost exclusively used as a potentiating agent; not in a manner that would be classically "synergistic." Temozolomide will be given, at early dose levels, in low doses that are individually sub-therapeutic and therefore, minimally toxic. This allows for BMN 673 to be given on an intermittent schedule in combination with temozolomide, at or near the maximum tolerated dose (MTD) when given as a single agent on a continuous, daily schedule in adults. Part A of the trial (Phase 1) will be a traditional dose escalation study using a 3+3 design to find the MTD and/or recommended Phase 2 dose (RP2D), in each 28 day cycle, of once daily temozolomide given for 5 days when combined with a dose of BMN 673 (400 mcg/m^2/dose or 600 mcg/m^2/dose) given once daily for 5 days after a one day dose of BMN 673 (400 mcg/m^2/dose or 600 mcg/m^2/dose). The Day 1 dose for BMN 673 will be administered either once daily or twice daily. Part B and Part C of the trial (Phase 2) will examine the efficacy of this combination at the MTD/ RP2D in Ewing

sarcoma/Peripheral primitive neuroectodermal tumor (PNET) and ALL patients using a Simon's optimal two stage design. For the first time, the pharmacokinetics of BMN 673 when administered in combination with temozolomide will be examined in children with recurrent or refractory malignancies. In the Phase 2 portion of the study, potential biomarkers of treatment response will be explored in Ewing sarcoma archived tumor samples.

EXPERIMENTAL DESIGN SCHEMA



Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy (Section 6.0). Therapy may otherwise continue for up to 24 cycles for an approximate total treatment course of two years provided the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims for Phase 1

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of temozolomide when combined with a dose of BMN 673 given once daily for 5 days after a one day dose of BMN 673 administered orally (either once daily or twice daily), every 28 days to children with refractory or recurrent solid tumors.

1.1.2 To define and describe the toxicities of BMN 673 given with temozolomide administered on this schedule.

1.1.3 To characterize the pharmacokinetics of BMN 673 and temozolomide when given in combination to children with refractory or recurrent cancer.

1.2 Primary Aim for Phase 2

1.2.1 To define the antitumor activity of BMN 673 when given with temozolomide in recurrent/ refractory Ewing sarcoma and recurrent acute lymphoblastic leukemia (ALL).

REMOVED

1.3 Secondary Aims

1.3.1 To preliminarily define the antitumor activity of BMN 673 and temozolomide in pediatric patients with recurrent or refractory solid tumors within the confines of a Phase 1 study.

1.3.2 To explore possible predictive biomarkers in archival tumor tissue from Ewing sarcoma patients in Phase 2.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

BMN 673 is a new, orally available, highly potent and specific inhibitor of PARP 1 and 2 designed to have an improved therapeutic index relative to existing PARP inhibitors in development.

2.1.1 Poly(ADP-ribose) Polymerase (PARP)

DNA damage caused by toxins, including both naturally occurring environmental poisons and chemotherapy, is repaired by a number of mechanisms including base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), single strand annealing (SSA), homologous recombination (HR) and nonhomologous end joining (NHEJ). Poly(ADP-ribose) polymerases (PARPs) are a family of enzymes involved in DNA repair through the recruitment and activation of proteins that utilize primarily the BER pathway,[2] but also the NHEJ[3] and HR[4] pathways. PARP1, the family's founding member, binds to damaged DNA through its N-terminal zinc finger motifs; binding activates its catalytic C-terminal domain to hydrolyze NAD+ and produce linear and branched poly(ADP-ribose) (PAR) chains. These PAR chains have a net negative charge, which promotes recruitment of DNA repair proteins, involved in the BER pathway, to the site of DNA damage, and facilitates removal of PARP1 from damaged sites allowing access to other repair proteins.[5] PARP2 is essential for the viability of PARP1 knockout mice.[5] PARP inhibitors mimic NAD+ and bind to the protein's catalytic domain.[6] This both inhibits necessary NAD+ binding and inhibits the auto-modification needed for PARP to eventually release from its complex with DNA[6]. Both catalytic inhibition and trapping of PARP-DNA complexes lead to replication fork damage and cellular apoptosis.[6]

It has been noted, that in several tumor types, that PARP1 is over expressed and that its overexpression is associated with an overall poor prognosis. Most recently, it was noted that certain tumors, such as those harboring *BRCA1/2* and *PTEN* mutations have a high rate of defects in the HR pathway of DNA repair and therefore, by using a PARP inhibitor, salvage pathways of DNA repair are blocked and apoptosis results.[7] Several PARP inhibitors have been developed and in pre-clinical models have not only shown powerful cytotoxicity in *BRCA1/2* and *PTEN* aberrant cell lines but have also had proof of targeting concept confirmed through demonstration that these compounds are in fact inhibitors of PARP enzymes 1 and 2.[8,9] For tumors that carry *BRCA1/2* and *PTEN* mutations, PARP inhibition with first generation PARP inhibitors such as veliparib and olaparib are being investigated and thus far show much promise in terms of anti-cancer activity.[10,11]

2.1.2 Enhancing PARP inhibitory effects through its combination with temozolomide

Temozolomide is an orally administered monofunctional SN-1 alkylating agent that creates DNA damage by adding methyl adducts to nitrogen atoms in the DNA ring and the extracyclic oxygen group.[12] After being converted to MTIC (5-3-methyltriazen-1-yl) imidazole-4-carboximide) at physiologic pH, methyl groups are transferred preferentially to the N7 position of guanine followed by the N3

position of adenine and O6 position of guanine.[12] Although it is the least frequently methylated adduct, O6 methylguanine is regarded as responsible for the direct cytotoxicity of temozolomide[13] because it initiates MutSα and MutLα dependent mismatch repair during second or later cell cycles (after the methylation insult) leading to double-strand break formation and apoptosis.[14]

Temozolomide has been shown to have limited activity as a single agent in pediatric early phase clinical trials. Estlin, et al. reported responses (complete response [CR] and partial response [PR]) in the single agent phase 1 setting, in 2 out of 5 patients with high grade astrocytomas and long term stable disease (SD) in one out of 10 patients with diffuse intrinsic pontine glioma[15] while a similar study by Nicholson, et al. reported, out of 59 evaluable patients, 10 with SD, 2 with a PR and 1 with a CR.[16] In the single agent phase 2 setting, DeSio, et al., reported a 13.4% CR+PR+minor response (MR) rate and a 38.5% SD rate among 52 pediatric patients with relapsed solid tumors using 215 mg/m^2/day x 5 days in patients with no history of craniospinal irradiation (CSI) and 180 mg/m^2/day x 5 days in those with a history of CSI.[17] The median survival was 7.8 months.[17] Responding tumors were mostly CNS tumors and neuroblastomas with no responses seen in those with Ewing sarcoma family of tumors.[17] In a similar phase 2 single agent setting, Nicholson, et al. noted 5 PRs and 1 CR among 113 children with relapsed/refractory CNS tumors.[18] In leukemias, Horton, et al., reported a PR in 2 of 16 pediatric patients with relapsed/refractory acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) receiving temozolomide single agent once daily for 5 days at either 200 mg/m^2/dose or 270 mg/m^2/dose.[19]

Temozolomide has been far more effective in combination with additional agents. Activity in this setting has been seen in a broad range of tumors including CNS tumors, Ewing[20] and other sarcomas,[21] neuroblastoma[22] and CNS lymphoma.[23] The concept of combining temozolomide with PARP inhibitors has recently been particularly attractive. Methylated DNA bases, created with temozolomide treatment, are repaired through the BER pathway.[24] An intermediate of this process has a single nucleotide gap in double stranded DNA containing the 5'-deoxyribose phosphate (dRP) group at one margin.[24] PARP1 binds to and is activated by the dRP group and is important in an efficient repair.[24] Therefore, when combined with PARP inhibitors, which would block BER, temozolomide induced cytotoxicity would result not only directly from O6 methylguanine but also indirectly from N7 methylguanine and N3 methyladenine.[24] Several early studies have suggested *in vitro* legitimacy of this theory as temozolomide has shown an impressive ability to sensitize Pol β-null mouse fibroblasts,[24] lymphoid and myeloid leukemias[25] and neuroblastoma[26] to PARP inhibitors in model systems.

2.1.3 PARP inhibition in Pediatric Tumors

As outlined below, there is a role for the use of PARP inhibitors, particularly administered in combination with DNA damaging agents, in a variety of pediatric malignancies, including CNS and solid tumors as well as hematologic malignancies.

Medulloblastoma: *BRCA1/2* aberrant tumors have not been reported to occur in childhood.[27,28] However, like *BRCA1/2*, *PTEN* is a tumor suppressor gene known to play a critical role in the DNA damage response and DNA repair. Because *PTEN* inactivation spontaneously causes double stranded DNA breaks and

diminishes the NER, HR and NHEJ DNA repair mechanisms[29] PARP inhibition would be a rational therapy in tumors with aberrant PTEN activity such as medulloblastoma, the most common malignant CNS tumor of childhood. Roughly 40% of patients with medulloblastoma will die from their disease and therefore, it accounts for almost 10% of all pediatric cancer deaths.[30] Through both loss of heterozygosity of chromosome 10q (where *PTEN* is located)[31] and through promoter hypermethylation, *PTEN* mRNA and protein levels are known to be significantly lower in medulloblastoma when compared to normal cerebellar tissue.[32] For this reason PARP inhibitors are already being explored in medulloblastoma although mainly as a sensitizing agent concomitant with chemotherapy or radiation therapy.[33]

Germ Cell Tumors: PARP inhibitors may also serve as a rational targeted agent in testicular germ cell tumors. While these tumors generally have an excellent survival rate, an estimated 350 people die of testicular germ cell tumors per year in the United States.[34] Recent evidence shows that testicular germ cell tumors have high levels of PARP and a high rate of DNA repair mechanism defects.[35] Proof of concept has been shown *in vitro* as germ cell tumor lines proved to be sensitive to the PARP inhibitor olaparib both as monotherapy and in combination with cisplatin.[36]

Ewing sarcoma: Ewing sarcoma is a primitive tumor, likely of mesenchymal stem cells, which when clinically localized at diagnosis has a 5-year overall survival (OS) of approximately 70%, but when metastatic, has an overall survival rate between 20-30%.[37,38] Patients with recurrent Ewing sarcoma also have a dismal prognosis, with a 5-year OS of 30% when the disease recurs after 2 years and 7% when the disease recurs within 2 years.[39] The most recent Phase 3 Children's Oncology Group study in Ewing sarcoma demonstrated that compressed delivery (every 2 weeks) of cycles of vincristine, adriamycin and cyclophosphamide (VAdrC) alternating with cycles of ifosfamide and etoposide (IE) had superior outcome with minimal additional toxicity when compared to the same therapy given every 3 weeks.[40] Nevertheless, major advances in outcome using standard chemotherapeutic approaches have been elusive. Even maximizing cytotoxicity in the setting of hematopoietic stem cell transplant has failed to show improved outcome for Ewing sarcoma, with the risk of death approaching 8%[41] from treatment-related complications (i.e. treatment related AML/MDS, graft-versus-host disease, infection) indicating that a limit of effectiveness of standard chemotherapy has been reached as a result of offsetting increases in toxicity.[42,43]

Despite the fact that the cancer stem cell or cell of origin continues to be enigmatic, unlike survival advances using standard chemotherapy, the biological understanding of Ewing's sarcoma has improved in recent years. It is now known that Ewing sarcoma is a classic example of a malignancy driven by a fusion oncogene. Oncogenic fusions in Ewing sarcoma arise from specific chromosomal translocations that yield an in-frame fusion of the amino terminus of the *EWS* gene on chromosome 22 and the carboxyl terminus, including the DNA binding domain, of an ETS family gene. The ETS gene is *FLI1* in 85% of cases, *ERG* in 10% of cases and *ETV1*, *ETV4* or *FEV* in the remaining 5% of cases.[44] In-frame fusion of *EWS* to an ETS factor in Ewing sarcoma, yields a highly expressed non-physiologic transcription factor, which activates an oncogenic program in the cell of origin.[45] *In vitro*, the down regulation of the *EWS-FLI1* fusion via antisense

oligonucleotides, dominant-negative transcripts and RNAi has been shown to dramatically limit malignant transformation and reduce cell growth.[46,47] However, translation of these basic science findings to the clinical setting has been challenging, limited in part by the inability of these agents to enter the cell as required to exert their respective effects.[48] Early phase trials have begun with agents thought to indirectly interfere with the *EWS-ETS* translocations in Ewing sarcoma such as IGF1-R inhibitors and ET-743 (trabectedin).[49,50] However, recent pre-clinical data has demonstrated that a powerful inhibitor of *EWS-ETS* fusion can be found in PARP inhibition.

In 2011, Brenner, et al., showed that PARP1 along with DNA-dependent protein kinase (DNA-PKcs) are key co-factors in ETS positive prostate cancer mediated by the ETS DNA binding domain.[51] This finding suggested that PARP inhibition might have key implications in treating cancer outside of their negative influence on DNA damage repair. They demonstrated proof of concept by showing that therapeutic inhibition of PARP1 disrupted the growth of ETS positive but not ETS negative prostate cancer xenografts. Secondary to the fact that the ETS interaction site is also present in *EWS-FLI1* and *EWS-ERG* chimeras, they hypothesized that PARP1 is also critical in the oncogenesis of Ewing sarcoma. It was subsequently shown that, in fact, the *EWS-FLI1* and *EWS-ERG* fusion proteins do interact with and are dependent on PARP1 and that Ewing cell lines are exquisitely sensitive to the PARP1/2 inhibitor olaparib *in vitro*.[52] Furthermore, olaparib drastically decreased the rate of metastasis in murine Ewing sarcoma xenograft models.[52] Contemporaneously and independently, a large screen of 130 drugs on 639 human cell lines unexpectedly found a highly significant association between the *EWS-FLI1* rearrangement and sensitivity to olaparib.[53] Screening of a structurally distinct PARP inhibitor, AG-014699, across a large panel of cell lines confirmed overwhelming sensitivity of Ewing sarcoma cell lines to PARP inhibition. Furthermore, the same screen found that sensitivity of Ewing cell lines to AG-014699 were comparable to *BRCA1/2* cell lines over 6 days and more sensitive than *BRCA1/2* lines when tested over 3 days. In summary, PARP inhibition appears to be a potential strategy in Ewing sarcoma not only secondary to its ability to potentiate DNA damage but also in its ability to inhibit the EWS-ETS-PARP1 positive feedback loop in oncogenic transcriptional activation.

Hematologic malignancies: Recent work has shown that PARP inhibition is a logical strategy to test in hematologic malignancies in addition to solid tumors. It has been shown that myeloid leukemia cells exhibit constitutive DNA damage and pronounced error-prone double stranded break DNA repair, which in part, explain the genomic instability of acute myelogenous leukemia (AML).[54,55] Follow-up experiments demonstrated that exposure to PARP inhibitors can induce cell cycle arrest and apoptosis of primary AML samples and AML cell lines *in vitro*; further analysis revealed that PARP inhibitor sensitivity was due to a defect in homologous recombination DNA repair.[56] In a similar manner, certain lymphoid malignancies have been shown to be susceptible to PARP inhibition. Ataxia Telangiectasia Mutated (ATM) gene mutant cells are known to exhibit impaired DNA double stranded break repair. Weston, et al. consequently showed that ATM deficient chronic lymphocytic leukemia cells, T-prolymphocytic leukemia cells and mantle cell lymphoma cells were sensitive to the PARP inhibitor olaparib *in vitro*.[57] In addition, PARP inhibition may be logical in T-cell acute lymphoblastic leukemia (T-ALL). It is well known that over 50% of cases of childhood and adult

T-ALL harbor activating mutations of NOTCH1, a regulatory transmembrane receptor that plays a crucial developmental role in cell fate determination and pattern formation, and in hematopoietic stem cell maintenance and T cell fate specification in the mature organism.[58,59] Silva, et al., recently showed that T-ALL cells with NOTCH1 mutations had decreased PTEN mRNA expression.[60] This decreased PTEN expression may make T-ALL cells susceptible to PARP inhibition.

2.2 Preclinical Studies

2.2.1 Antitumor Activity of BMN 673

BMN 673 is a new, highly potent and specific inhibitor of PARP 1 and 2 designed to have an improved therapeutic index relative to existing PARP inhibitors in development. BMN 673 has been shown to have comparable inhibition of PARP 1 and 2 both in cell culture and in MX-1 mammary tumor xenograft models and *in vitro* at a lower concentration (IC_{50}=0.57nM) than PARP inhibitors ABT 888 (IC_{50}=4.73nM), AG 14447 (IC_{50}=1.98nM) and olaparib (IC_{50}=1.94nM). Assessment of BMN 673 was performed on human cell lines harboring mutations that compromise DNA repair pathways. Gene mutations that confer selective tumor cell cytotoxicity included *BRCA1* (MX-1 mammary tumor cells), *BRCA2* (Capan-1 pancreatic tumor cells), *PTEN* (MDA-MB-468 mammary, LNCaP and PC-3 prostate tumor cells) and *MLH-1* mutations (HCT-116 colorectal tumor cells). The IC_{50} values of BMN 673 in these tumor cell lines were in the single digit nanomolar or sub-nanomolar range. In contrast, the IC_{50} of BMN 673 against normal human primary cell MRC-5 and several tumor cell lines that do not have reported DNA repair related mutations was significantly greater (250 nM to >1000 nM).[61]

In *BRCA1* deficient MX-1 mouse xenograft models, oral administration of BMN 673 at 0.33 mg/kg once daily for 28 days resulted in significant antitumor activity (tumor growth delay/tumor regression). Dose-related inhibition of tumor growth was observed at lower doses until doses higher than 1 mg/kg/day induced not only tumor suppression but also significant body weight loss with associated mortality. Consistent with the anti-tumor effect in this model, profound reduction in poly(ADP-ribose) (PAR) levels (the product of PARP1/2 and therefore, a measure of PARP activity) was observed in the MX-1 xenografts when mice were treated with BMN 673 orally. Oral administration of BMN 673 also demonstrated anti-tumor activity in the PTEN-deficient LNCaP, MDA-MD-468 and PC-3 mouse xenograft models. In addition, twice-a-day oral administration of BMN 673 delayed the growth of the *MLH-1* deficient HCT-116 xenograft tumor in nude mice. Assessment of various dosing schedules in the mouse xenograft models indicated that continuous suppression of PARP activity is required for optimal anti-tumor activity.[61]

2.2.2 Animal Toxicology of BMN 673

Five day repeat dose toxicity and toxicokinetic (TK) studies with a 28-day recovery were conducted in rats and dogs. In dogs (the most sensitive species) BMN 673 was administered at several dose levels with severe pancytopenia being observed at the two highest dose levels (0.03 and 0.1 mg/kg/day). At these doses the mean reticulocyte nadir occurred on Day 6 and the platelet and WBC nadirs were on Day 11. These changes were reversed in the 0.03 mg/kg/day group on Days 17-18 (i.e. 12-13 days after the last administration of drug). Several dogs treated at the highest dose level (0.1 mg/kg/day) died secondary to bacterial sepsis and others experienced hypoactivity, hyperthermia and fecal abnormalities on day 12-13. Coagulation parameters were unaffected. Therefore, at 5 day repeat dosing the highest non-severely toxic dose (HNSTD) was 0.03 mg/kg/day. Twenty-eight day repeat dose toxicity and TK studies were also performed on rats and dogs. In dogs (the most sensitive species) the only major toxicity at the doses studied were hematologic in nature at 0.005 and 0.01 mg/kg/day. Mildly lowered red cell mass, mildly lowered platelet and absolute reticulocyte counts were noted but all recovered during the 28 day recovery phase. Therefore, the HNSTD was determined to be 0.01 mg/kg/day. From this the estimated safe clinical starting dose in humans was determined to be 1 µg/kg/day.[61]

2.2.3 Preclinical Pharmacokinetic Studies of BMN 673

Pharmacokinetic studies have been performed in rats and dogs. The oral bioavailability, calculated from AUC following oral administration relative to AUC following IV administration was 42.7% in rats and 50.5% in dogs. The terminal half-life of BMN 673 was between 28.5-30.2 hours in rats and between 69.7-91.2 hours in dogs that allows for once daily dosing. [^{14}C]-labeled BMN 673 studies indicated that the drug was rapidly (but incompletely) absorbed within 15-30 minutes post dose. Maximum plasma radioactivity was reached within 2-4 hours and declined to non-detectable levels within 48 hours in rats and within 72-96 hours in dogs. Steady state concentrations were reached on Day 15 in rats and on Day 20 in dogs using daily administration of BMN 673. Excluding the GI tract, the highest levels of BMN 673 were observed in the kidney and liver. Distribution to target organs of toxicity (thymus, bone marrow, lymph nodes, spleen) BMN 673 was at levels higher than blood at 8 hours and continued to be detected at 24-72 hours when blood levels were below limits of quantitation. Radioactivity in the brain was generally below the level of quantitation except in the choroid plexus. All [^{14}C]-BMN 673 decreased to baseline by 168 hours post dose. Elimination of BMN 673 was 90% at 24 hours post dose in the rat and 84% at 72 hours post dose in the dog. Fecal elimination was the major route of excretion. *In vitro* metabolism studies demonstrated that BMN 673 has > 90% stability over 2 hours in hepatic microsomes. However, in human hepatic tissues at concentrations up to 10 µM BMN 673 did not inhibit any of the five major human hepatic CYP isoenzymes (CYP1A2, 2C9, 2C19, 2D6 and 3A4).[61]

2.2.4 The Preclinical testing of BMN 673 and temozolomide from the Pediatric Preclinical Testing Program (PPTP)

In order to test the hypothesis that temozolomide would create a DNA environment which would not only invite "classic" PARP inhibitor mechanisms in tumors deficient in HR DNA repair when treated with such drugs, but be able to expand the portfolio of malignancies which may respond to PARP inhibition by creating DNA adducts, the Pediatric Preclinical Testing Program (PPTP) evaluated BMN 673 alone and in combination with temozolomide.[62] Temozolomide doses of 0, 8, 12, 30, 35 and 100 mg/kg/day were combined with doses of BMN 673 of 0, 0.1, 0.2, 0.25, 0.33 and 0.5 mg/kg/day in tolerability (weight loss) experiments in mice. Determined tolerable, temozolomide at 30 mg/kg/day and BMN 673 at 0.1 mg/kg/day x 5 days was compared to temozolomide at 12 mg/kg/day and BMN 673 at 0.25 mg/kg/day x 5 days along with single agents and vehicles in mouse explant experiments. Single agent *in vitro* testing of BMN 673 against the PPTP cell lines were consistent with earlier reported sensitivity of Ewing sarcoma. The median relative IC50 (rIC50) value for the PPTP cell lines to BMN 673 was 28.4 nM with the Ewing cell lines being the most sensitive (rIC50 = 6.4 nM) and significantly more sensitive than non-Ewing sarcoma cell lines (rIC50 = 40.1 nM, p=0.048). However, in xenograft models, while BMN 673 showed some activity in Wilms tumor (KT-10) and medulloblastoma (BT-45), there was complete lack of activity in the Ewing sarcoma xenografts SK-NEP-1 and EW8 at 0.33 mg/kg/day x 28 days. An interesting observation during this phase of testing is that there appeared to be sensitivity phenocopy between BMN 673 and cisplatin. Repeat *in vitro* testing was performed using temozolomide from 0.3 µM to 1000 mM in the presence of 10 nM BMN 673 with the median rIC50 value for temozolomide being 19.8 µM. The cell lines with the lowest rIC50 values were those of Ewing sarcoma and acute lymphoblastic leukemia (ALL). In addition, it was noted that the level of potentiation with temozolomide exceeded that described for other PARP inhibitors and exceeded that described for the combination of PARP inhibitors and topotecan. Mouse xenograft models recapitulated combination *in vitro* testing and with treatment consisting of low dose temozolomide (12 mg/kg/dose daily) and BMN 673 (0.25mg/kg/dose twice daily) for 5 days responses were seen in Ewing, glioblastoma and Wilms tumor models with high level synergy demonstrated in 2 Ewing sarcoma xenografts (CHLA-258 and TC-71) and synergy in 1 additional Ewing sarcoma xenograft (EW5). These responses were noted with minimal animal weight loss and other general toxicities. In mice, the single agent MTD of temozolomide is known to be 60 mg/kg. Because the tolerability of temozolomide in the presence of BMN 673 was 12 mg/kg and the adult clinical dose of temozolomide administered daily x 5 is 150-200 mg/m^2, the clinical dose of temozolomide likely to be tolerated with a "high" dose of BMN 673 is 30-40 mg/m^2/day.[61]

2.3 Adult Studies

2.3.1 Phase 1 Studies of BMN 673

At the American Society of Clinical Oncology Annual Meeting 2013, de Bono, et al., presented data for the first-in-human trial of BMN 673 performed in patients with solid tumors with known or suspected DNA repair abnormalities (e.g. germline BRCA mutations, PTEN loss). The trial was performed in patients ≥ 18 years of age with a standard 3+3 dose escalation design and included an expansion in ovarian, breast, prostate and pancreas cancers with germline BRCA mutations and additionally included patients with Ewing sarcoma family tumors and small cell lung cancer. Dosing was once daily, continuously, in 28-day cycles and began with a dose of 25 µg/day. Thirty-nine patients were enrolled in the escalation and 31 patients into the expansion. Overall, BMN 673 was well tolerated. The recommended Phase 2 dose was 1000 µg with dose limiting toxicity (DLT) being thrombocytopenia. Myelosuppression occurred in 10-20% of patients with chronic dosing requiring 11 patients to have dose reductions. Fatigue, nausea and alopecia occurred in 20-30% of patients with no discontinuations necessary for adverse events. Elimination appeared to be bi-exponential with a t½, at the upper end of the dose range (900-1100 µg) ranging from 53.5 to 66.1 hours and from 40.4 to 51.8 hours on Days 1 and 35, respectively. Steady state was apparent in most patients by two weeks with daily dosing. Inhibition of PARP activity in peripheral blood mononuclear cells was detected in patients dosed at ≥100 µg/day leading to substantial single agent anti-tumor activity in deleterious germline BRCA ovarian and breast cancer. Germline BRCA ovarian RECIST response rate was 44%, CA-125 response rate was 70% and clinical benefit response rate was 82%, while germline BRCA breast response rate was 39% and clinical benefit response rate was 67%.[63] Updates on the expansion cohort were provided at the 2013 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics and the ESMO/ECCO European Cancer Congress. No additional toxicities of treatment were noted. With a total of 28 BRCA aberrant ovarian cancer patients the clinical benefit response was 82% and with a total of 18 BRCA aberrant breast cancer patients the clinical benefit response was 78%. Treatment was reported as on-going in 5/7 small cell lung cancer patients and 2 of 8 Ewing sarcoma patients with no objective responses noted as of the time of the report.[64,65] A second trial in adults with advanced hematologic malignancies with demonstrated or potential defects in DNA-repair pathways, including RAD51 foci formation or ATM deletions is also ongoing. Pharmacokinetic and pharmacodynamic (PD) results are thus far similar, as are the adverse events; however, dose-limiting neutropenia has occurred in 2 of 5 patients with chronic lymphocytic leukemia or chronic myeloid leukemia at 900 µg/day with one patient experiencing neutropenic sepsis and both patients missing > 4 days of dosing due to Grade 4 neutropenia. In 3 patients with MDS/AML, 1350 µg/day was well tolerated although 2000 µg/day resulted in dose limiting toxicities in 2/4 MDS/AML patients (personal communication, Andrew Dorr, BioMarin).

2.4 Pediatric Studies

2.4.1 PARP inhibitors in combination with temozolomide in children

There is no experience with BMN 673 in children. There is, however, recent phase 1 experience with the PARP inhibitor veliparib (ABT-888), which was studied in combination with intermediate and standard dose temozolomide, in Pediatric Brain Tumor Consortium study PBTC-027. Temozolomide was given once daily and ABT-888 given twice daily by mouth for 5 days every 28 day cycle to pediatric patients with recurrent central nervous system tumors. Five ABT-888/temozolomide dose levels were studied: 20/180, 15/180, 15/150, 20/135 and 25/135 mg/m^2/dose, respectively. Dose limiting toxicities included Grade 4 neutropenia and thrombocytopenia at the 20/180 and 15/180 mg/m^2/dose levels. The Phase 2 recommended dose was 15 mg/m^2/dose of ABT-888 with 135 mg/m^2/dose for 5 days in 28 day cycles. No objective responses were seen although 4 subjects had stable disease > 6 months.[66]

2.4.2 Rationale for the first in children combination Phase 1 study

BMN 673 shows potent single agent *in vitro* activity in pediatric tumors, particularly against Ewing sarcoma cell lines. Preclinical evaluation in mouse xenograft models performed by the PPTP demonstrated a dramatic reduction of tumor burden in a variety of pediatric solid tumor models (e.g., Ewing sarcoma, Wilms tumor, glioblastoma multiforme) when the PARP inhibitor BMN 673 was combined with a low dose, 5 day course of temozolomide. The level of potentiation with temozolomide exceeds that described with many other PARP inhibitors or combinations of PARP inhibitors with other cytotoxic agents. The preclinical results are consistent with the hypothesis that BMN 673 is converting relatively nontoxic N7 and N3 methylation adducts induced by temozolomide into toxic lesions. In addition, there is the reasonable expectation that this combination will be safe. The proposed starting dose for BMN 673 is less than 25% of its single agent recommended Phase 2 dose, per course, and the starting dose of temozolomide is only 10% of its single agent recommended Phase 2 dose. Furthermore, there is considerable clinical experience with other PARP inhibitors administered with temozolomide and other than the expected enhancement of myelosuppression, unanticipated adverse events appear uncommon. Thus, this combination represents a novel strategy for the treatment of a variety of pediatric solid (including CNS) and hematologic malignancies.

In the first in human study of BMN 673, PAR activity decrease was seen within hours even after a single dose of 100 µg.[67] PAR activity decrease was consistently and predictably seen at 2 and 4 hours after the first dose of BMN 676 and then pre-dose on Days 2, 3 and 5. Therefore, steady state did not have to be reached in order to see significant decreases in PAR levels with BMN 673. In addition, significant PAR levels were decreased at drug trough levels on Days 2, 3 and 5 even when well below MTD dosing (personal communication, Andrew. Dorr, BioMarin). However, optimal cell kill would be postulated when BMN 673 and temozolomide are close to steady state in plasma. Because BMN 673 has a long half-life, pharmacokinetic modeling was performed to determine most efficiently to achieve a steady state of BMN 673. A lead in phase of one day of twice daily BMN 673 prior to the 5 day course of once daily BMN 673 with once daily temozolomide was determined to provide optimal exposure base on pharmacokinetic modeling. In addition, this modeling predicts that even with day

1 twice daily administration, plasma drug levels should not exceed that achieved by adults during phase 1 trials [redacted]

[redacted]

Intra-patient dose escalation in part B (Amendment #3): Patients enrolled in Part B of the trial will receive Cycle 1 treatment at the RP2D defined in Part A. Following completion of Cycle 1, up to two intra-patient dose escalations may proceed in subsequent cycles if the patients have had no more than minimal toxicities (as defined in Section 5.3.3.2) and the criteria to advance to the next cycle have been met. [redacted]

2.4.3 Potential biomarkers to predict response in Ewing sarcoma patients

The identification of prognostic biomarkers will be important for the future development of BMN673 in Ewing sarcoma. Several studies of PARP inhibitors have explored both baseline PAR levels and PAR level dynamics in peripheral blood mononuclear cells (PBMCs) as an easily accessible tumor-surrogate tissue which could provide outcome predictions. While PAR levels have uniformly decreased with PARP inhibitor treatment, no correlation has been made between PAR levels or PAR level changes in PBMCs and levels seen in tumor tissue or with disease response[66,68,69] However, potential predictive biomarkers from disease tissue may correlate with response and should be explored. Because of the importance placed on the discovery

of reliable biomarkers as a predictor of response in developmental therapeutics, the submission of archival tissue will be required for patients in the Ewing sarcoma stratum of Phase 2. Archival tissue will be assayed for potential biomarkers by immunohistochemistry. Since PARP and PARP inhibitors play a critical role in DNA repair, markers such as BRCA1, XPA and Chk2 will be explored.[70] In addition, markers of interest, which have been correlated with disease outcome in Ewing sarcoma such as Cx43 and desmoplakin will be explored.[71] Of particular interest will be exploring PARP-1 which has been noted to be highly expressed in Ewing sarcoma samples[72] and those markers which have both been shown to correlate with outcome in Ewing sarcoma and are cell cycle regulators such as CDKN2A and TP53.[70,71]

2.5 Overview of Proposed Pediatric Study

This is a Phase 1 study of BMN 673 in combination with low dose temozolomide in patients with recurrent or refractory solid tumors including CNS tumors, and a Phase 2 study of BMN 673 in combination with low dose temozolomide in recurrent or refractory Ewing sarcoma and recurrent acute lymphoblastic leukemia (ALL). BMN 673 will be given orally on Day 1 (either once or twice daily) followed by BMN 673 and low dose temozolomide given together once per day on Days 2-6 of each 28-day cycle. This study will aim to describe the pharmacokinetics and the toxicities of BMN 673 when given with low dose temozolomide with the goal of determining the MTD or recommended Phase 2 dose of this regimen. The antitumor effect of this combination will also be described, more specifically in the Phase 2 portion of the study in pediatric patients with Ewing sarcoma and ALL. Additionally, during Phase 2 in patients with Ewing sarcoma, this study will explore potential predictive biomarkers using archival tumor tissue.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the page CTSU OPEN (Oncology Patient Enrollment Network) to ensure that a reservation for the study is available. To access the Slot Availability page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

3.2 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 (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.

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made in OPEN and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

3.5 **Informed Consent/Assent**

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 **Screening Procedures**

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 **Eligibility Checklist**

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 **Institutional Pathology Report**

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 **Study Enrollment**

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx or the ADVL1411 COG Study Assigned Research Coordinator. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Bone marrow aspiration or biopsy should be performed within 14 days prior to start of protocol therapy for Phase 2 patients with bone marrow involvement (Part B and Part C). Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

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 or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age:

4.1.1.1 *Phase 1 (Part A)*

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

4.1.1.2 *Phase 2 (Part B and Part C)*

Patients must be > than 12 months and ≤ 30 years of age at the time of study enrollment.

4.1.2 Body Surface Area (For Parts A, B and C):

Patients must have a BSA of ≥ 0.42 m^2 at the time of study enrollment.

4.1.3 Diagnosis:

4.1.3.1 *Phase 1 (Part A)*

i. *Solid tumors (Part A1):* Patients with relapsed or refractory solid tumors including CNS tumors without bone marrow involvement are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

ii. *Ewing sarcoma or Peripheral PNET (Part A2):* Patients with relapsed or refractory Ewing sarcoma or Peripheral PNET without bone marrow involvement will be eligible for Part A2 if there are no available slots on Part A1. These patients will be enrolled at one dose level below the dose

level at which patients on Part A1 are actively enrolling, or at the starting dose level (Dose Level 1) if dose escalation has not yet occurred. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.3.2 *Phase 2 (Part B)*
Ewing Sarcoma or Peripheral PNET: Patients with relapsed or refractory Ewing sarcoma or Peripheral PNET are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.3.3 *Phase 2 (Part C)*
Acute Lymphoblastic Leukemias (ALL): Patients must have 2nd or greater relapse of pre-B ALL or T-cell ALL. Patients may not have refractory disease.

Patients with ALL must have had histologic verification of the malignancy at the most recent relapse, including immunophenotyping to confirm diagnosis.

REMOVED

4.1.4 Disease Status:

4.1.4.1 *Phase 1 (Part A):*
Patients must have either measurable or evaluable disease (see Section 12.2 and Section 12.3 for definitions).

4.1.4.2 *Phase 2 (Part B):*
Ewing sarcoma or Peripheral PNET: Patients must have measurable disease (see Section 12.2). See also Section 4.1.10.

4.1.4.3 *Phase 2 (Part C):*
Acute Lymphoblastic Leukemias (ALL): Patients with ALL must have an M3 marrow with or without extramedullary site of relapse OR an M2 bone marrow with an extramedullary site of relapse. Patients with CNS 3 status are not eligible for enrollment (See Section 4.3).

REMOVED

4.1.5 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.6 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Note: Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.7 Prior Therapy

4.1.7.1 Patients who have received prior therapy with a temozolomide-based regimen are eligible. **Note:** Patients who have progressed on a PARP

inhibitor and temozolomide regimen are not eligible for Part A of the study (see also Section 4.2.10).

4.1.7.2 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy.

a. Myelosuppressive chemotherapy:
   i. Solid Tumors (Part A and Part B): At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
   ii. Acute Lymphoblastic Leukemias (ALL) (Part C):
   - Patients with leukemia who relapse while receiving standard maintenance chemotherapy will not be required to have a waiting period before enrollment onto this study.
   - Patients who relapse while they are not receiving standard maintenance therapy, must have fully recovered from all acute toxic effects of prior therapy. At least 14 days must have elapsed after the completion of cytotoxic therapy, with the exception of hydroxyurea.
   - **Note:** Cytoreduction with hydroxyurea can be initiated and continued for up to 24 hours prior to the start of BMN 673.
   - **Note:** Patients with leukemia are permitted to receive intrathecal chemotherapy, including methotrexate or cytarabine. Intrathecal therapy should be restricted to Days 15 and 22 of each 28 day cycle (see also Section 5.1.1).

REMOVED

b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.

c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.

d. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.

e. Monoclonal antibodies: At least 3 half-lives of the antibody after the last dose of a monoclonal antibody. (See table on DVL homepage listing monoclonal antibody half-lives.)

f. XRT: At least 14 days after local palliative XRT (small port); At least 42 days must have elapsed if other substantial BM radiation. Patients with prior TBI, craniospinal XRT and/or ≥ 50% radiation of the pelvis are not eligible.

g. Stem Cell Infusion without TBI: No evidence of active graft vs. host disease and at least 84 days must have elapsed after transplant or stem cell infusion.

4.1.7.3 PARP Inhibitor Exposure:

a. Part A: Patients who have received prior therapy with a PARP inhibitor, with the exception of BMN 673, are eligible; however, patients who have progressed on a PARP inhibitor and temozolomide regimen are not eligible.

b. Part B and Part C: Patients who have previously been exposed to a PARP inhibitor are not eligible.

4.1.8 Organ Function Requirements

4.1.8.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

All patients enrolled on Part A of the study must be evaluable for hematologic toxicity.

b. Patients on Part B of the study with known bone marrow metastatic disease will be eligible for the study provided they meet the blood counts in 4.1.8.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity.

c. Patients on Part C with acute lymphoblastic leukemia:
- Platelet count ≥ 20,000/mm^3 (may receive platelet transfusions). These patients must not be known to be refractory to red cell or platelet transfusion.

REMOVED

4.1.8.2 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 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.

4.1.8.3 Adequate Liver Function Defined as:

i. Patients on Part A and Part B:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

ii. Patients on Part C with Acute Lymphoblastic Leukemias (ALL):

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 225 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

REMOVED

4.1.9 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.10 For patients enrolling on Part B: Tissue blocks or slides must be sent per Section 8.4. If tissue blocks or slides are unavailable, the study chair must be notified prior to enrollment.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding
Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies with temozolomide; the teratogenic potential is unknown with BMN 673. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except leukemia patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy]. Patients with acute lymphoblastic leukemia may receive intrathecal

therapy as outlined in Section 5.1.1.

4.2.2.4 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.3 Patients must be able to swallow capsules whole.

4.2.4 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.5 For Part C (Phase 2): Recurrent acute lymphoblastic leukemia (ALL) patients with CNS 3 status are not eligible (See Section 4.3).

REMOVED

4.2.6 Patients who have received a prior solid organ transplantation are not eligible.

4.2.7 Patients with prior TBI, craniospinal XRT and/or those with ≥ 50% radiation of the pelvis are not eligible.

4.2.8 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

4.2.9 Patients with known hypersensitivity to temozolomide or dacarbazine are not eligible.

4.2.10 Phase 1 (Part A): Patients who have progressed on a PARP inhibitor and temozolomide regimen are not eligible.

4.2.11 Phase 2 (Part B and Part C): Patients who have previously been exposed to a PARP inhibitor are not eligible.

4.2.12 Phase 1 (Part A): Patients with known bone marrow involvement are not eligible (see Section 4.1.8.1).

4.3 Leukemia Definitions

4.3.1 Bone marrow status

M1 < 5% lymphoblasts
M2 5 - 25% lymphoblasts
M3 > 25% lymphoblasts

4.3.2 Leukemia Relapse

- **Isolated Bone Marrow Relapse**: M3 marrow confirmed by bone marrow aspirate or biopsy.
- **Isolated CNS Relapse**: Positive cytomorphology and WBC ≥ 5/µL OR positive cytomorphology with CSF WBC 0-4/µL on 2 successive occasions 1 month apart. If any CSF evaluation shows positive cytomorphology and WBC < 5/µL, a second CSF evaluation is required in greater or equal to 4 weeks. Identification of leukemic clone in CSF by flow cytometry (TdT, CD19, CD10, etc.) or FISH for diagnostic karyotypic abnormality is encouraged.
- **Isolated Testicular Relapse**: Confirmation by testicular biopsy preferred but not required.

- **Combined Relapse**: Documented extramedullary relapse and an M2 or M3 bone marrow.

4.3.3 **Central nervous system (CNS) involvement of leukemia at relapse diagnosis**

- **CNS 1**: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.

- **CNS 2**: In CSF, presence < 5/µL WBCs and cytospin positive for blasts, or ≥ 5/µL WBCs but negative by Steinherz/Bleyer algorithm:
  - CNS 2a: < 10/µL red blood cells (RBCs); < 5/µL WBCs and cytospin positive for blasts;
  - CNS 2b: ≥ 10/µL RBCs; < 5/µL WBCs and cytospin positive for blasts; and
  - CNS 2c: ≥ 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below);

- **CNS 3**: In CSF, presence of ≥ 5/µL WBCs and cytospin positive for blasts **and/or** clinical signs of CNS leukemia or lymphoma:
  - CNS 3a: < 10/µL RBCs; ≥ 5/µL WBCs and cytospin positive for blasts;
  - CNS 3b: ≥ 10/µL RBCs, ≥ 5/µL WBCs and positive by Steinherz/Bleyer algorithm (see below);
  - CNS 3c: Clinical signs of CNS leukemia or lymphoma (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

4.3.4 **Method of evaluating initial traumatic lumbar punctures (LPs)**

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/µL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/µL blasts, whose CSF WBC/RBC ratio is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

Example: CSF WBC = 60/µL; CSF RBC = 1,500/µL; blood WBC = 46000/µL; blood RBC = 3.0 X 10^6/µL:

$$\frac{60}{1{,}500} = 0.04 > 2X \frac{46{,}000}{3.0 \times 10^6} = 0.015$$

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

	Day 1	Days 2-6	Day 28
Dose Levels -1 & 1	**BMN 673** (once daily)	**BMN 673** (once daily), and **Temozolomide** (once daily)	Evaluation
Dose Levels 2 to 6	**BMN 673** (twice daily)	**BMN 673** (once daily), and **Temozolomide** (once daily)	Evaluation

BMN 673 will be administered orally once daily or twice daily on Day 1. The second dose of BMN 673 on Day 1 for Dose Levels 2-6 will be administered 12 hours after the first dose. On Days 2-6, BMN 673 will be administered orally once daily (immediately before the temozolomide dose in the morning.

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

Temozolomide will be administered orally once daily in the morning on Days 2-6 immediately after the BMN 673 dose. At the discretion of the treating physician, the use of antiemetic therapy is allowed prior to low-dose temozolomide administration. For PCP prophylaxis guidelines refer to Section 7.3.1.

On days on which pharmacokinetic samples are collected, BMN 673 (during Cycle 1 on Day 1, and on Day 5 or 6) and temozolomide (during Cycle 1 on Day 5 or 6) should be administered on an empty stomach (1 hour before or 2 hours after food or drink except water). **Note:** Day 2 BMN 673 and temozolomide do not need to be administered on an empty stomach during Cycle 1. On non-pharmacokinetic study days, BMN 673 and temozolomide can be administered without food or drink restrictions (i.e., with or without food).

A cycle of therapy is considered to be 28 days. A cycle may be repeated for a total of 24 times, up to a total duration of therapy of approximately 24 months.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle (see Appendix II-A and Appendix II-B).

The capsules should not be opened or crushed but should be swallowed whole.

If a patient vomits **within 30 minutes** after the dose of BMN 673 and/or temozolomide is administered, that dose of BMN 673 and/or temozolomide may be repeated. Otherwise, that dose of BMN 673 or temozolomide will not be repeated.

If the dose of BMN 673 or temozolomide is **missed and less than 6 hours have passed** since the scheduled dosing time, the BMN 673 or temozolomide dose should be taken immediately. If more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose but should wait and take the next regularly scheduled dose.

Update: The MTD/RP2D of Part A1 was determined to be: Day 1: 600 mcg/m^2/dose BMN 673 PO BID; Days 2-6: 600 mcg/m^2/dose BMN 673 and 30 mg/m^2/dose temozolomide PO; on a 28-day cycle, maximum BMN

673 dose: 1000 mcg/day.

5.1.1 Intrathecal Therapy for Relapsed Acute Lymphoblastic Leukemia (ALL) Patients
Patients may receive intrathecal chemotherapy in the second and subsequent cycles at the treating physician's discretion. Intrathecal therapy, if given, should be restricted to Days 15 and 22 of each 28 day cycle and its administration should be reflected on the respective roadmaps and reporting period case report forms.

REMOVED

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0.

5.3 Dose Escalation Schema

5.3.1 Inter-Patient Escalation [Phase 1 (Part A1) only]
The starting dose of BMN 673 will be 400 mcg/m^2/dose (maximum daily dose is 800 mcg/day). Subsequently, the BMN 673 dose for Dose Levels 3-6 will be fixed at 600 mcg/m^2/dose (maximum daily dose is 1000 mcg/day). The starting dose of temozolomide will be 20 mg/m^2/dose (Dose Level 1) with dose levels for subsequent groups of patients as follows.

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

Dose Level	BMN 673 Dose		Temozolomide Dose (mg/m^2/dose)
	mcg/m^2/dose	Max. Daily Dose (mcg/Day)	
-1	400#	800	15
1*	**400#**	**800**	**20**
2	400&	800	20
3	600&	1000	20
4	600&	1000	30
5	600&	1000	40
6	600&	1000	55^

* Starting Dose Level
# Once daily on Days 1-6.
& Twice daily on Day 1, and then once daily on Days 2-6.
^ In the event that the recommended Phase 2 dose has not been reached by Dose Level 6, additional dose levels may be added with BMN 673 dosed at 600 mcg/m^2/dose and temozolomide escalated in 30% increments to a maximum of 150 mg/m^2/dose (i.e. 70 mg/m^2/dose, 90 mg/m^2/dose, 120 mg/m^2/dose and 150 mg/m^2/dose).

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a BMN 673 dose of 400 mcg/m^2/dose and a temozolomide dose of 15 mg/m^2/dose (Dose Level -1).

If Dose Level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

5.3.2 Ewing sarcoma or Peripheral PNET [Phase 1 (Part A2) only]: If an objective

response is observed in a patient with Ewing sarcoma or Peripheral PNET on Part A1 of the study, Part A2 of the study will open so that patients with Ewing sarcoma or Peripheral PNET may actively enroll at any time. Patients with Ewing sarcoma or Peripheral PNET may enroll onto Part A2 if there are no available patient slots at the current dose level on Part A1. These patients may enroll one dose level below the current dose level at which patients on Part A1 are actively enrolling, or at the starting dose level (Dose Level 1) if dose escalation has not yet occurred.

5.3.3 Intra-Patient Escalation

5.3.3.1 Phase 1 (Part A2) only

Intra-patient dose escalation to a higher dose level will be allowed for Part A2 patients on study in cycles of therapy subsequent to Cycle 1, provided the patient has not experienced dose-limiting toxicity (DLT) at the dose at which they began therapy. Part A2 patients who are more than one dose level below the actively enrolling dose level in Part A1 can escalate one dose level per cycle until they reach the actively enrolling dose level, provided they do not experience a DLT when escalating.

5.3.3.2 Phase 2 (Part B – Ewing sarcoma and peripheral PNET) only

Patients enrolled onto Part B of this study will receive study drug at the R2PD in Cycle 1. Intra-patient dose escalation, to the next highest Dose Level (as defined in Section 5.3.1) will be allowed in cycles of therapy subsequent to Cycle 1, only for patients who do not have PD and have experienced no more than minimal toxicities (defined below), considered at least possibly related to study drug. These patients may be dose escalated (per Section 5.3.1) to RP2D + 1 Dose Level for at least one cycle, and subsequently may be escalated to RP2D + 2 Dose Levels if the subject continues to have never experienced more than minimal toxicities during therapy. A patient may not dose escalate beyond RP2D + 2 Dose Levels. In patients not eligible for dose escalation after any course due to greater than minimal toxicities, there will be no further attempt to dose escalate. Patients eligible to dose escalate after cycle 1, who are not dose escalated due to site related issues may start dose escalation in a subsequent cycle provided they meet all criteria for dose escalation. For patients who experience any dose limiting toxicity (DLT), as defined in Section 5.5, after a dose escalation, dose modification rules defined in Section 6 should be followed. Once a patient has required a single dose modification, no further dose escalations are permitted in that patient and the patient will receive the remaining therapy at the highest Dose Level at which no dose-limiting toxicities were observed in the patient.

Minimal toxicity for intra-patient dose escalation: Dose escalation is not allowed if any of the following conditions occur during a cycle:

Hematological Toxicity

- >Grade 2 thrombocytopenia
- >Grade 3 neutropenia

Non-hematological Toxicity

- Any Grade 3 or 4 non-hematological toxicity with the specific exclusion of:
  - Grade 3 nausea and vomiting < 3 days duration

- Grade 3 liver enzyme elevation, including ALT/AST/GGT elevation that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.

- Any grade 2 non-hematological toxicity that persists for > 7 days and is considered medically significant or sufficiently intolerable by patients that requires treatment interruption.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.5 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.5.1 Non-hematological dose-limiting toxicity

5.5.1.1 Any Grade 3 or Grade 4 non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT elevation that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.

5.5.1.2 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

5.5.1.3 **Note:** Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

5.5.2.1 Hematological dose limiting toxicity is defined as:

- In patients evaluable for hematological toxicity (see Section 4.1.8.1),
  - Grade 4 neutropenia for > 7 days
  - Platelet count < 20,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period
  - Myelosuppression that causes a delay of > 14 days between treatment cycles.
- In patients with acute lymphoblastic leukemia, DLT will be defined as failure to recover a peripheral ANC > 500/mm^3 and platelets > 20,000/mm^3 by 42 days after the first treatment day, not due to malignant infiltration.

5.5.2.2 **Note:** Grade 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

Note: Patients with dose limiting toxicity should receive subsequent cycles at the next lower dose level (See Section 5.3.1). See Appendix II-A and Appendix II-B for dosing nomogram.

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the next lower dose level. Patients who experience dose-limiting thrombocytopenia after two dose reductions must be removed from protocol therapy. If a patient who was originally assigned to Dose Level 1 experiences dose-limiting thrombocytopenia after a dose reduction to Dose Level -1 then that patient must be removed from protocol therapy.

6.1.2 Patients who have dose-limiting neutropenia (Grade 4 neutropenia of > 7 days duration or delay in the start of the next cycle for > 14 days due to neutropenia) with no other dose-limiting toxicity should receive the same dose in the next cycle with myeloid growth factor support. **Note:** Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy (See Section 7.4). If Grade 4 neutropenia recurs after myeloid growth factor is added, then the patient should receive treatment at the next lower dose level for subsequent cycles, and G-CSF 5 mcg/kg/day SC or IV should be administered, starting 24 hours after the last dose of chemotherapy and continuing until the post-nadir ANC is ≥ 2,000/µl. Patients who experience dose-limiting neutropenia after addition of myeloid growth factor and one dose reduction must be removed from protocol therapy.

6.1.3 Patients who have a dose-limiting hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements (or baseline if not specifically defined in the eligibility criteria in Section 4.0) but should receive subsequent doses at the next lower dose level.

6.2.2 If non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.3 Dose Modifications for Intra-patient Dose Escalation Part B

For patients who experience any dose limiting toxicity (DLT), as defined in Section 5.5, after a dose escalation, dose modification rules defined in Section 6.1 and Section 6.2 should be followed. Once a patient has required a single dose modification, no further dose escalations are permitted and the patient will receive the remaining therapy at the highest Dose Level at which no dose-limiting toxicities were observed in the patient.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy. See Section 4.1.7.2.a and Section 5.1.1 for the exception related to intrathecal chemotherapy for patients with acute lymphoblastic leukemia.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 6.0).

7.3.1 Pneumocystis Pneumonia (PCP) Prophylaxis (Recommended)

There have been multiple episodes of PCP reported in patients receiving temozolomide. For this reason, patients should receive PCP prophylaxis during treatment. TMP/SMX is recommended; monthly pentamidine or other appropriate alternative antibiotic are also acceptable. PCP prophylaxis should be discontinued 3 months after chemotherapy has been discontinued.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be

administered in accordance with Section 6.1 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Bone marrow aspiration or biopsy should be performed within 14 days prior to start of protocol therapy for Phase 2 patients with bone marrow involvement (Part B and Part C). Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^,*	End of Study^^
History	X	Weekly	X	X
Physical Exam with vital signs	X	Weekly	X	X
Height, weight, BSA	X		X	X
Performance Status	X			
Pregnancy Test[1]	X		Every other cycle x 2 then q 3 cycles	X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[2]	Weekly[3]	X
Pharmacokinetics[4]	X	X		
Urinalysis	X			
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X	X
Creatinine, ALT, bilirubin	X	Weekly	X	X
Albumin	X		X	X
Tumor Disease Evaluation[5]	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles	X
Patient Diary[6]		End of Cycle 1	End of Cycle	
Bone marrow aspirate or biopsy[7]	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles	X
CSF cytology[8]	X	End of Cycle 1	X	X
Tumor Tissue (Required)[9]	X	Clinically indicated		

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

* For patients who progress on study, the imaging that confirmed progression, if obtained, will be documented, but full "Prior to Subsequent Cycle" imaging studies will not be performed unless these studies were the ones that documented progression. To the extent possible, the "Prior to Subsequent Cycle" laboratory evaluations should be obtained in patients with progressive disease.

^^ "End of Study" evaluations are to be performed 30 days after the last dose of the investigational agent(s) for patients who complete 24 cycles of therapy.

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control. Pregnancy testing is required prior to tumor imaging as per institutional guidelines.

2 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity (see Section 6.1).

3 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3.

4 This applies to all Part A patients. See Section 8.3 for timing of PK studies.

5 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

6 Patient diary (see Appendix III) should be reviewed after completion of each treatment cycle and uploaded into RAVE.

7 This only applies to Part B and Part C patients with bone marrow involvement. Bone marrow aspirates or biopsies must be done for diagnostic and staging purposes prior to enrollment on study and as indicated in the table above.

8 For Part C acute lymphoblastic leukemia patients only.

9 For Part B patients (See Section 8.4). Archival tumor tissue should be submitted if available for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response:

Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1411) and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, Imaging Research Center
Data Administrator
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054
E-mail: saamer@chla.usc.edu

8.3 Pharmacology Studies (Required for Cycle 1) (Part A ONLY)

8.3.1 Description of Studies and Assay

8.3.1.1 Pharmacokinetic analysis for BMN 673 will be conducted by Alliance Pharma using validated assays by HPLC with MS/MS detection in plasma samples.

8.3.1.2 Pharmacokinetic analysis for temozolomide will be conducted by Dr. Joel Reid at the Mayo Clinic using validated assays by HPLC with MS/MS detection in plasma samples.

8.3.2 Sampling Schedule (See Appendix V)

8.3.2.1 Blood samples (2-3 mL per sample) will be collected at the following time points during Cycle 1:

- **Day 1 (Required from all patients):** Pre-dose, and then at 1, 2, 4 and 8 hours after the first BMN 673 dose.
- **Day 2 (Optional):** In consenting patients, a pre-dose Day 2 sample will be collected (24 hours after the first BMN 673 dose).
- **Day 5 or 6 (Required from all patients):** Pre-dose, and then at 1, 2, 4 and 8 hours after BMN 673 and temozolomide administration.

  NOTE: On days on which pharmacokinetic samples are collected, BMN 673 (during Cycle 1 on Day 1, and on Day 5 or 6) and temozolomide (during Cycle 1 on Day 5 or 6), should be administered on an empty stomach (1 hour before or 2 hours after food or drink except water). Day 2 BMN 673 and temozolomide do not need to be administered on an empty stomach.

- **Days 8 and 15 (Required from patients > 10 kg):** These samples are collected at time of CBC evaluation.

8.3.3 Sample Collection and Handling Instructions

Each blood sample must be centrifuged **within 30-60 minutes** of draw and frozen at – 70 ºC until shipment.

Keep BMN 673 samples **at room temperature** during the blood collection and samples should be processed as described in Section 8.3.4.1.

Keep temozolomide samples **at 4 ºC** during the blood collection and samples should be processed as described in Section 8.3.4.2.

- **Day 1, Pre-dose:** Two consecutive 2 mL blood samples (a total of 4 mL) will be collected from the patient's vein (peripheral or central) before BMN 673 administration.
  - **Sample 1 for BMN 673 pharmacokinetic studies:** The first 2 mL blood sample should be collected into a **room temperature** 4 mL K_3EDTA vacutainer tube containing anticoagulant and processed as described in Section 8.3.4.1.
  - **Sample 2 for temozolomide pharmacokinetic studies:** The second

2 mL blood sample should be collected into a **pre-chilled** vacutainer tube containing sodium heparin and processed as described in Section 8.3.4.2.

- **Day 1 and 2:** Blood samples (3 mL per sample) will be collected from the patient's vein (peripheral or central) at each designated time point (1, 2, 4, 8, and 24 hours) post-first BMN 673 administration into **room temperature** 4 mL K_3EDTA vacutainer tubes containing anticoagulant for the preparation of plasma. See Section 8.3.4.1 for BMN 673 processing instructions.

- **Day 5 or 6:** For each designated time point, two consecutive 2 mL blood samples (a total of 4 mL per time point) will be collected from the patient's vein (peripheral or central).

  - **Sample 1 for BMN 673 pharmacokinetic studies:** The first 2 mL blood sample should be collected into a **room temperature** 4 mL K_3EDTA vacutainer tube containing anticoagulant and processed as described in Section 8.3.4.1.

  - **Sample 2 for temozolomide pharmacokinetic studies:** The second 2 mL blood sample should be collected into a **pre-chilled** vacutainer tube containing sodium heparin and processed as described in Section 8.3.4.2.

- **Days 8 and 15 (only from patients > 10 kg):** Blood samples (3 mL per sample) will be collected from the patient's vein (peripheral or central) into **room temperature** 4 mL K_3EDTA vacutainer tubes containing anticoagulant for the preparation of plasma. See Section 8.3.4.1 for BMN 673 processing instructions.

Record the exact time that the sample is drawn along with the exact time that the drug is administered (Appendix V).

8.3.4 Sample Processing

8.3.4.1 Sample processing for BMN 673 pharmacology studies

1. Invert vacutainer gently 8 to 10 times.
2. Separate plasma by centrifugation at 1500 x g for 10 minutes at **room temperature**.
3. Transfer the plasma (about 1.0 mL) into a 2 mL-cryovial. To avoid contamination always use a new transfer pipette for each sample, and do not remove the plasma near the precipitate.
4. Transfer plasma samples to -70 ºC freezer (within 1 hour of collection) and store until shipment.
5. Ship plasma samples on dry ice to Alliance Pharma (see Section 8.3.6.1 and Appendix VI).

8.3.4.2 Sample processing for temozolomide pharmacology studies

1. Blood samples (2 mL) will be collected in **pre-chilled** heparinized tubes.
2. Invert tube 8-12 times and place in an ice water bath.
3. Centrifuge at 2,000 rpm for 10 min in a refrigerated centrifuge set at 4°C.
4. Following centrifugation, transfer 1 mL of plasma to a microcentrifuge tube containing 0.1 mL 1 M HCl.
5. Vortex briefly and transfer to a -70 ºC freezer (within 30 minutes of collection).

8.3.5 See Section 8.3.6.2 and Appendix VII for shipping instructions.Sample Labeling
Each tube must be labeled with the COG patient ID and accession number, the study I.D. (ADVL1411), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (Appendix V), which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

8.3.6.1 **Sample Shipping Instructions for BMN 673:**
The BMN 673 samples must be batched, and maintained at -70 ºC until shipment. Ship samples for each patient together. See Appendix VI for guidelines and the mailing address for shipping samples to Alliance Pharma.

8.3.6.2 **Sample Shipping Instructions for temozolomide:**
Day 1 pre-dose, and Day 5 or 6 temozolomide samples should be batched, and maintained at -70 ºC until shipment. Ship samples together for each patient. See Appendix VII for guidelines and the mailing address for shipping samples to Dr. Joel Reid at the Mayo Clinic.

8.4 Tumor Tissue Studies (Required, Part B ONLY)

Note: Archival tumor tissue should be submitted if available for all Phase 2 Ewing sarcoma or Peripheral PNET patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.4.1 Description of Studies

If multiple biopsies have been performed, tissue from the most recent biopsy is preferred. Tumor tissue will be analyzed by immunohistochemistry.

8.4.2 Sampling Schedule

Either paraffin-embedded tissue block or unstained slides are required for enrollment.

- Tumor tissue or slides may be from original diagnosis or from any resections or biopsies that occurred prior to enrollment. **Samples from the most recent procedure are desired.**

- A block or slides from any resections or biopsies occurring after the start of ADVL1411 protocol therapy are also requested.

8.4.3 Sample Collection Instructions

A paraffin-embedded tissue block should be submitted. If a tissue block is unavailable, at least 10 unstained standard sections of 3 to 4 µM thickness must be sent (15 slides are recommended).

8.4.4 Sample Labeling

Each tube must be labeled with the COG patient ID and accession number, the study I.D. (ADVL1411), the collection date and the collection time point of the sample. Data should be recorded on the Tumor Tissue Study Form (Appendix VIII), which must accompany the sample(s). The Tumor Tissue Study Form (Appendix VIII) must be completed for each time point.

8.4.5 Sample Shipping Instructions

See Appendix VIII for guidelines and the mailing address for shipping samples to Dr. Alex Bishop's laboratory. **Samples must be shipped at room temperature via overnight FedEx. Shipments should be sent Monday through Thursday only.**

9.0 AGENT INFORMATION

9.1 BMN 673

(BMN 673ts, talazoparib, MDV3800) NSC#771561 IND# 121510

9.1.1 Structure and molecular weight

The chemical name of BMN 673 is 3*H*-Pyrido[4,3,2-de]phthalazin-3-one, 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1*H*-1,2,4-triazol-5-yl)-, (8***S***,9***R***)-, 4-methylbenzenesulfonate (1:1). The structure and molecular weight of BMN 673ts are $C_{26}H_{22}F_2N_6O_4S$ and 552.5624, respectively. BMN 673 is a potent and specific inhibitor of poly(ADP-ribose) polymerase (PARP) inhibitors (i.e., PARP1 and PARP2), which prevents PARP-mediated DNA repair of single strand DNA breaks via the base-excision repair pathway. It has demonstrated synthetic lethality in tumors with defects in DNA repair pathways, such as BRCA mutations and PTEN dysfunction. BMN 673 free base is the active moiety of the BMN 673ts (tosylate salt) formulation.

9.1.2 Supplied by:

BMN 673 capsules are supplied by Medivation, Inc, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

9.1.3 Formulation

BMN 673 is supplied as 100 mcg (opaque ivory, size 4) and 250 mcg capsules (opaque white, size 4) packaged in 30-count HDPE bottles with an induction seal and child-resistant cap. The hypromellose capsules contain a blend of BMN 673 drug substance, silicified microcrystalline cellulose, titanium dioxide, red iron oxide, and yellow iron oxide.

9.1.4 Storage

Store BMN 673 capsules at room temperature (15-30 °C/ 59-86 °F), protected from light, in the original container. BMN 673 capsules may be repackaged from the manufacturer-supplied HDPE bottle into a pharmacy-supplied HDPE bottle for dispensing purposes.

9.1.5 Stability

Shelf-life stability studies of BMN 673 capsules are ongoing.

9.1.6 Administration

Give/take BMN 673 by mouth on an empty stomach either one hour before or two hours after a meal on pharmacokinetic study days (during Cycle 1 on Day 1, and on Day 5 or 6). **Note:** Day 2 BMN 673 do not need to be administered on an empty stomach during Cycle 1. On non-pharmacokinetic study days, BMN 673 can be administered without food or drink restrictions (see Section 5.1). BMN 673 should be taken immediately prior to temozolomide on Days 2 through 6 of each cycle.

Based on *in vitro* data, BMN 673 is not likely to inhibit metabolism via human cytochrome P450 (CYP 450) enzymes. Effects of co-administration of repeat dosing of BMN 673 with other drugs are unknown.

The capsules should not be opened or crushed but should be swallowed whole.

9.1.7 Comprehensive Adverse Events and Potential Risks list (CAEPR)

The Comprehensive Adverse Events 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 232 patients*. Below is the CAEPR for talazoparib (BMN 673).

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 2.1, December 29, 2016[1]

Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 4.0 Term) [n= 232]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
Abdominal pain			***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
Nausea			***Nausea (Gr 2)***
		Typhlitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection [2] (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
Platelet count decreased			***Platelet count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypokalemia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral)[3]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			

Adverse Events with Possible Relationship to Talazoparib (BMN 673) (CTCAE 4.0 Term) [n= 232]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Epistaxis		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Rash maculo-papular		

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

[3]Neuropathy peripheral may include both Peripheral sensory neuropathy and Peripheral motor neuropathy under the NERVOURS SYSTEM DISORDERS.

Adverse events reported on talazoparib (BMN 673) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that talazoparib (BMN 673) caused the adverse event:

CARDIAC DISORDERS - Atrial flutter
GASTROINTESTINAL DISORDERS - Abdominal distension; Flatulence; Small intestinal obstruction; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Non-cardiac chest pain **HEPATOBILIARY DISORDERS** - Hepatic failure
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Weight loss
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Musculoskeletal and connective tissue disorder - Other (muscle cramps); Musculoskeletal and connective tissue disorder - Other (muscle spasm); Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Dysgeusia
PSYCHIATRIC DISORDERS - Anxiety; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin

Note: Talazoparib (BMN 673) 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.

9.2 Agent Ordering and Agent Accountability

BMN 673 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.

9.3 **Clinical Drug Request**

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at 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.

9.4 **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 (DAR) Form (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).

9.5 **Temozolomide-Oral**

(Temodar®, Temodal®) NSC #362856 **(09/09/13)**

9.5.1 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.

9.5.2 The table below lists the anticipated toxicity profile of temozolomide (oral):

Incidence	Toxicities
Common (>20% of patients)	Constipation, nausea, vomiting, diarrhea, anorexia, alopecia, alanine aminotransferase increased, aspartate aminotransferase increased, ataxia, anxiety, depression, insomnia, nervous system disorders – other: hemiparesis or paresis, dizziness, gait disturbance, amnesia, paresthesia, somnolence, headache, seizure, fatigue
Occasional (4-20% of patients)	Edema limbs, localized edema, rash maculopapular, dysphagia, mucositis oral, anemia, platelet count decreased, white blood cell count decreased, lymphocyte count decreased, aplastic anemia, blood bilirubin increased, urinary frequency, cough, upper respiratory infection, sinusitis
Rare (≤ 3% of patients)	Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, hypercalcemia, lower gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, cholecystitis, alkaline phosphatase increased, myelodysplastic syndrome, leukemia secondary to oncology chemotherapy, infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatic failure

Incidence	Toxicities
Pregnancy & Lactation	**Pregnancy Category** Adequate, well-controlled studies have not been conducted in humans. Women of childbearing potential should be advised against becoming pregnant while taking temozolomide and for at least 6 months following the end of therapy. Temozolomide administration to rats and rabbits at 3/8 and 3/4 the human dose resulted in the development of malformations of the external organs, soft tissues, and skeleton. These animal studies also demonstrated embryolethality (increased resorptions) at similar doses. There is no information available regarding the transmission of temozolomide during lactation; women should avoid breastfeeding while receiving temozolomide.

9.5.3 Formulation and Stability:

Temozolomide capsules are available in six different strengths (5, 20, 100 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.

9.5.4 Guidelines for Administration:

See Treatment and Dose Modifications sections of the protocol (See Section 5.0 and Section 6.0). The capsules should not be opened or crushed but should be swallowed whole.

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 container (e.g., bottle or sachet). 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, 25 mg/day for 5 days would be dispensed as 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.

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section 6.0).
c) Refusal of further protocol therapy by patient/parent/guardian.
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 24 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of BMN 673 (See Section 4.0 and Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy.

Patients who are removed from protocol therapy during cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any further required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Strata:

Part A1: Patients with relapsed or refractory solid tumors and CNS tumors (Phase 1)
Part A2: Patients with relapsed or refractory Ewing sarcoma or Peripheral PNET (Phase 1)
Part B: Patients with relapsed or refractory Ewing sarcoma or Peripheral PNET (Phase 2)
Part C: Patients with relapsed acute lymphoblastic leukemias (ALL) (Phase 2)

REMOVED

Phase 1 (Part A1):
A minimum of 3 evaluable patients will be entered at each dose level for determination of MTD. Once the MTD or recommended Phase 2 dose (RP2D) has been defined, up to 6 additional patients with relapsed or refractory solid tumors may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Review of the enrollment rate into previous COG Phase 1 new agent studies indicates that 1-2 patients per month are available, which will permit completion of Part A of the study within 21-42 months if six evaluable patients are studied at each of six dose levels to determine the MTD or RP2D. A maximum of 94 patients is anticipated, assuming a 20% inevaluability rate.

Phase 1 (Part A2):
If an objective response is observed in a patient with Ewing sarcoma or Peripheral PNET on Part A1 of the study, Part A2 of the study will open so that patients with Ewing sarcoma or Peripheral PNET may actively enroll at any time. Patients with Ewing sarcoma or Peripheral PNET may enroll onto Part A2 if there are no available patient slots at the current dose level on Part A1. These patients may enroll one dose level below the current dose level at which patients on Part A1 are actively enrolling, or at the starting dose level (dose level 1) if dose escalation has not yet occurred. Up to 6 patients may enroll at each lagging dose level, for a maximum total of 30 patients in Part A2. Once the MTD or RP2D has been determined in Part A1, Part A2 will be closed to accrual.

Intra-patient dose escalation to a higher dose level will be allowed for Part A2 patients on study in cycles of therapy subsequent to cycle 1, provided the patient has not experienced dose-limiting toxicity (DLT) at the dose at which they began therapy. Part A2 patients who are more than one dose level below the actively enrolling dose level in Part A1 can escalate one dose level per cycle until they reach the actively enrolling dose level, provided they do not experience a DLT when escalating.

Phase 2 (Parts B and C):
Accrual to Parts B and C will only open once the MTD or RP2D has been determined in Part A1, and may open concurrently with the PK expansion described above. Review of patient accrual onto recent Phase 2 studies indicates the following entry rates for the various tumors under study can be achieved:

Disease Group	Patients/Year
Ewing Sarcoma or Peripheral PNET	10
Acute Lymphoblastic Leukemias (ALL)	5

REMOVED

A minimum of 10 evaluable patients and a maximum of 24 patients are expected to enroll in Parts B and C combined, assuming an inevaluability rate of 20%. We anticipate that the entire study will require 12-29 months for enrollment and evaluation of all parts.

> Update: The MTD/RP2D of Part A1 was determined to be: Day 1: 600 mcg/m^2/dose BMN 673 PO BID; Days 2-6: 600 mcg/m^2/dose BMN 673 and 30 mg/m^2/dose temozolomide PO; on a 28-day cycle, maximum BMN 673 dose: 1000 mcg/day.

Intra-patient dose escalation to a higher dose level will be allowed for Part B patients on study in cycles of therapy subsequent to cycle 1, provided the patient has not experienced more than minimal toxicities at the dose at which they began therapy. Part B patients may be dose escalated to RP2D + 1 Dose Level for at least one cycle, and subsequently may be escalated to RP2D + 2 Dose Levels if the patient continues to have never experienced more than minimal toxicities (as defined in Section 5.3.3.2) during therapy.

11.2 Definitions [Phase 1 (Part A1)]

11.2.1 Evaluable For Adverse Effects

Any patient who experiences DLT at any time during protocol therapy is considered evaluable for Adverse Effects. (Note: patients who experience dose-limiting PCP must have received PCP prophylaxis to be considered evaluable for this Adverse Effect). Patients without DLT who receive at least 85% of the prescribed dose per protocol guidelines and had the appropriate toxicity monitoring studies performed are also considered evaluable for Adverse Effects. Patients who are not evaluable for Adverse Effects at a given dose level during Cycle 1 will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients on Part A1 experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  In Part A1, expansion will proceed according to the rules of the 3+3 design (see Section 11.3): Three additional patients will be studied. If none of the initial three additional patients experiences DLT, the dose will be escalated.* If one of the initial three additional patients experiences DLT, expansion to a total of 12 patients will continue. If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.*

* If the expansion occurs in the last dose level, the recommended phase 2 dose has been defined and Part A1 will be closed.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Escalation and Determination of MTD [Phase 1 (Part A1)]

As an added safety precaution, one evaluable patient will be initially enrolled at the first dose level. Additional patients may continue to enroll as described below only after this patient has been evaluated by the study leadership for treatment-related toxicities from his/her first course of therapy.

11.3.1 Three patients are studied at the first dose level.

11.3.2 If none of these three patients experience DLT, then the dose is escalated to the next higher level in the three subsequent patients.

11.3.3 If one of three patients experiences DLT at the current dose, then up to three more patients are accrued at the same level.

a) If none of these three additional patients experience DLT, then the dose is escalated in subsequent patients. If there are no further dose escalations, then the RP2D has been confirmed.

b) If one or more of these three additional patients experiences DLT, then patient entry at that dose level is stopped. (See Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six patients have already been treated at that prior dose).

11.3.4 If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule). Up to three more patients are treated at the next lower dose (unless six or more patients have already been treated at that prior dose). The highest dose with less than two DLTs out of six evaluable patients will be the estimated MTD.

11.3.5 Using this dose escalation scheme, the probability of escalating to the next dose level, based on the true rate of DLT at the current dose, is given by the following table when there are 6 evaluable patients at the current dose:

	True Adverse Effects at a Given Dose					
	10%	20%	30%	40%	50%	60%
Probability of Escalating	.91	.71	.49	.31	.17	.08

Thus, if the true underlying proportion of toxic events is 30% at the current dose, there is a 49% chance of escalating to the next dose.

In addition to determination of the MTD or RP2D, a descriptive summary of all toxicities will be reported.

Update: The MTD/RP2D of Part A1 was determined to be: Day 1: 600 mcg/m^2/dose BMN 673 PO BID; Days 2-6: 600 mcg/m^2/dose BMN 673 and 30 mg/m^2/dose temozolomide PO; on a 28-day cycle, maximum BMN 673 dose: 1000 mcg/day.

11.4 Pharmacokinetic Studies and Response Analysis [Phase 1 (Part A)]

A descriptive analysis of pharmacokinetic (PK) parameters of BMN 673 will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of BMN 673 in combination with temozolomide, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors (Section 12.2) and according to criteria for CNS tumors (Section 12.6). All disease responses will be reported descriptively.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

11.5 Study Design [Phase 2 (Parts B and C)]

The best response of disease to BMN 673 plus temozolomide will be examined separately in each of the two disease strata for Ewing sarcoma and ALL. Patients with Ewing sarcoma from Part A1 or A2 treated at the MTD/RP2D and who meet eligibility criteria for Part B of the study will be counted in the Phase 2 evaluation. The following Simon's optimal two stage design will be used in each stratum.

The two stage design for Part B and Part C is illustrated below:

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 evaluable patients	0	Terminate the trial because the agent is ineffective.
	1 or more	Proceed to Stage 2.
Stage 2: Enter 10 additional evaluable patients	2 or less	Terminate the trial because the agent is ineffective.
	3 or more	Terminate the trial because the agent is effective.

We will consider BMN 673 plus temozolomide not of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If BMN 673 plus temozolomide has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If BMN 673 plus temozolomide has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis $P = 0.25$).

11.6 Method of Analysis [Phase 2 (Parts B and C)]

Response in Ewing sarcoma or peripheral PNET patients will be determined according to RECIST as defined in Section 12.0. For patients with ALL, response criteria will be based on the standard definitions of complete remission (CR), partial remission (PR), partial remission, cytolytic (PR_{CL}), stable disease (SD), and progressive disease (PD) using the leukemia rating scale and peripheral blood counts (See Section 12.5). These responses will be reported descriptively. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

Toxicities for patients will be described separately. Every effort will be made to accrue the number of patients needed to evaluate efficacy according to the schema in Section 11.5. For strata not appropriately filled, descriptive statistics will be employed to describe outcomes.

11.7 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

12.2 Response Criteria for Patients with Solid Tumors

See the table in section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained 28 days following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable for response. For all other patients, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

12.2.1.2 Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2.2 Disease Parameters

12.2.2.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

12.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and

measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

12.2.2.3 Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

12.2.2.5 Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.3.1 Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.2.3.2 Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

12.2.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.2.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.2.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

12.2.3.6 Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.3.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A 'positive' FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline

sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.2.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease
The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.3.2 Complete Response
Disappearance of all evaluable disease.

12.3.3 Partial response
Partial responses cannot be determined in patients with evaluable disease

12.3.4 Stable Disease (SD)
That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.3.5 Progressive Disease
The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.3.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 MIBG Positive Lesions
Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.4.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

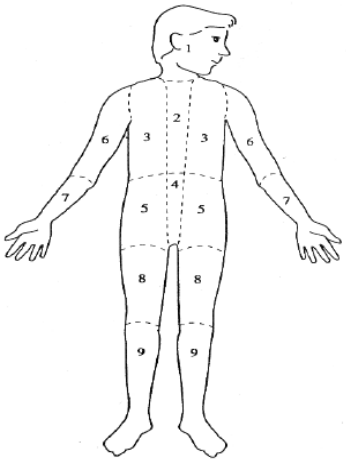
NOTE: This scoring should also be done by the treating institution for end of

course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 5 in Section12.7.1.

12.5 Response Criteria for Patients with Relapsed Acute Lymphoblastic Leukemia

12.5.1 Complete Remission (CR)

Attainment of an M1 bone marrow (< 5% blasts in the bone marrow aspirate or biopsy if aspirate not available) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral counts (absolute neutrophil count (ANC) > 500/µL and platelet count > 50,000/µL).

12.5.2 Partial Remission (PR)

Complete disappearance of circulating blasts and achievement of M2 marrow status (≥ 5% or < 25% blast cells in the bone marrow aspirate or biopsy if aspirate not available). Attainment of a bone marrow CR (above) with proven persistence of extramedullary disease qualifies as a PR.

12.5.3 Partial Remission –Cytolytic (PR_{CL})

Complete disappearance of circulating blasts and achievement of at least 50% reduction from baseline in bone marrow blast count.

12.5.4 Stable Disease (SD)

This is present when the patient fails to qualify for either a CR, PR, PR_{CL} or progressive disease.

12.5.5 Progressive Disease (PD)

An increase of at least 25% in the maximum Absolute Peripheral Blast Count measured pre-therapy or during the first 14 days following start of therapy; or in patients who achieve a PR an increase in the bone marrow blast count of ≥ 25% relative to the minimum bone marrow blast count; or in patients who achieve a CR an increase in the bone marrow blast count to ≥ 5%, the development of new extramedullary disease, or other clinical evidence of progressive disease.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

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. 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. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. 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. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** ≥50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.
- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

12.6.5 Response Criteria for Non-Target Lesions:

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

12.6.6 Response criteria for tumor markers (if available):

Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment

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

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

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥28 days Confirmation**
CR	Non-CR/Non-PD	No	PR	≥28 days Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥28 days from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

Table 3. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

Table 4: Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

Table 5: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

12.7.2 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); 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.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 4.0. The descriptions and grading scales found in the revised CTCAE version 4.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: Phase 1 and Early Phase 2 Studies: 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, 2]

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) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
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 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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.

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 report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events 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 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or

birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Nausea
GASTROINTESTINAL DISORDERS	Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
NERVOUS SYSTEM DISORDERS	Dizziness
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.7 of the protocol.

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at:
  http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7**

calendar days of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the CTEP Adverse Event Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. If prompted to enter a sponsor email address, please type in: COGCADEERS@childrensoncologygroup.org.

Fax supporting documentation to the NCI (fax # 301-230-0159) and send by email to the ADVL1411 COG Study Assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

13.4 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG data submission forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the data form packet (See Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.5.3 Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Reporting Secondary AML/MDS

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

CTEP 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 (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

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

13.7 Reporting Pregnancy, Fetal Death, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and faxed along with any additional medical information to (301) 230-0159 (see Appendix IX). Copies of all documents faxed to the NCI must also be emailed to the ADVL1411 COG Study Assigned Research Coordinator. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy)

under the Pregnancy, puerperium and perinatal conditions SOC and reported as Grade 3.

- Pregnancy should be followed until the outcome is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all follow-ups. If the baby is born with a birth defect or other anomaly, then a second CTEP-AERS report is required.

13.7.2 Fetal Death

- Fetal death is 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."

- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.

- A fetal death should NOT be reported as "Fetal death," a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration- Other (neonatal loss)" under the General disorders and administration SOC.

- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

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

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the data form packet.

   See separate Data Form Packet, which includes submission schedule.

14.2 CDUS

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

14.3 CRADA/CTA/CSA

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) 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/industryCollaborations2/intellectual_property.htm) 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 as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). 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:

Email: ncicteppubs@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.

14.4 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the developmental therapy scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.4.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

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APPENDIX I: PERFORMANCE STATUS SCALES/ SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II-A: BMN 673 DOSING NOMOGRAM

Note: Patients must have a BSA of ≥ 0.42 m^2 at the time of study enrollment.

NOTE: All doses for BMN 673 are in MICROGRAMS (mcg)

Dose Level -1 to 1: Days 1-6 (Once Daily)
BMN 673 Dose Assignment: 400 mcg/m^2/dose
Maximum Daily Dose is 800 mcg/Day

BSA (m^2)	Total Dose (mcg/day)	Number of 100 mcg capsules	Number of 250 mcg capsules
0.42-0.56	200	2	0
0.57-0.68	250	0	1
0.69-0.81	300	3	0
0.82-0.93	350	1	1
0.94-1.06	400	4	0
1.07-1.18	450	2	1
1.19-1.31	500	0	2
1.32-1.43	550	3	1
1.44-1.56	600	1	2
1.57-1.68	650	4	1
1.69-1.81	700	2	2
1.82-1.93	750	0	3
≥1.94	800	3	2

Dose Level 2: Day 1 (Twice Daily)
BMN 673 Dose Assignment: 400 mcg/m^2/dose
Maximum Daily Dose is 800 mcg/Day

BSA (m^2)	BMN 673 AM Day 1 Dose (mcg/dose)	BMN 673 PM Day 1 Dose (mcg/dose)	Number of 100 mcg capsules per dose	Number of 250 mcg capsules per dose	Total Dose (mcg/day)
0.42-0.56	200	200	2	0	400
0.57-0.68	250	250	0	1	500
0.69-0.81	300	300	3	0	600
0.82-0.93	350	350	1	1	700
≥0.94	400	400	4	0	800

Dose Level 2: Days 2-6 (Once Daily)

BSA (m^2)	Total Dose (mcg/ day)	Number of 100 mcg capsules	Number of 250 mcg capsules
0.42-0.56	200	2	0
0.57-0.68	250	0	1
0.69-0.81	300	3	0
0.82-0.93	350	1	1
0.94-1.06	400	4	0
1.07-1.18	450	2	1
1.19-1.31	500	0	2
1.32-1.43	550	3	1
1.44-1.56	600	1	2
1.57-1.68	650	4	1
1.69-1.81	700	2	2
1.82-1.93	750	0	3
≥1.94	800	3	2

Dose Levels 3 to 6: Day 1 (Twice Daily)
BMN 673 Dose Assignment: 600 mcg/m^2/dose
Maximum Daily Dose is 1000 mcg/Day

BSA (m^2)	BMN 673 AM Day 1 Dose (mcg/dose)	BMN 673 PM Day 1 Dose (mcg/dose)	Number of 100 mcg capsules per dose	Number of 250 mcg capsules per dose	Total Dose (mcg/day)
0.42-0.45	250	250	0	1	500
0.46-0.54	300	300	3	0	600
0.55-0.62	350	350	1	1	700
0.63-0.70	400	400	4	0	800
0.71-0.79	450	450	2	1	900
≥0.80	500	500	0	2	1000

Dose Levels 3 to 6: Days 2-6 (Once Daily)

BSA (m^2)	Total Dose (mcg/day)	Number of 100 mcg capsules	Number of 250 mcg capsules
0.42-0.45	250	0	1
0.46-0.54	300	3	0
0.55-0.62	350	1	1
0.63-0.70	400	4	0
0.71-0.79	450	2	1
0.80-0.87	500	0	2
0.88-0.95	550	3	1
0.96-1.04	600	1	2
1.05-1.12	650	4	1
1.13-1.20	700	2	2
1.21-1.29	750	0	3
1.30-1.37	800	3	2
1.38-1.45	850	1	3
1.46-1.54	900	4	2
1.55-1.62	950	2	3
≥1.63	1000	0	4

APPENDIX II-B: TEMOZOLOMIDE DOSING NOMOGRAM

Note: Patients must have a BSA of ≥ 0.42 m^2 at the time of study enrollment.

Dose Level -1: Days 2-6 (Once Daily)
Temozolomide Dose Assignment: 15 mg/m^2/dose

BSA (m^2)	Total Daily Dose (mg/day)
0.42-0.62	5
0.63-0.87	10
0.88-1.16	15
1.17-1.50	20
1.51-1.83	25
1.84-2.16	30
2.17- ≥2.30	35

Dose Level 1, 2 and 3: Days 2-6 (Once Daily)
Temozolomide Dose Assignment: 20 mg/m^2/dose

BSA (m^2)	Total Daily Dose (mg/day)
0.42-0.62	10
0.63-0.87	15
0.88-1.12	20
1.13-1.37	25
1.38-1.62	30
1.63-1.87	35
1.88-2.12	40
2.13- ≥2.30	45

Dose Level 4: Days 2-6 (Once Daily)
Temozolomide Dose Assignment: 30 mg/m^2/dose

BSA (m^2)	Total Daily Dose (mg/day)
0.42-0.58	15
0.59-0.75	20
0.76-0.91	25
0.92-1.08	30
1.09-1.25	35
1.26-1.41	40
1.42-1.58	45
1.59-1.75	50
1.76-1.91	55
1.92-2.08	60
2.09-2.24	65
2.25- ≥2.30	70

Dose Level 5: Days 2-6 (Once Daily)
Temozolomide Dose Assignment: 40 mg/m^2/dose

BSA (m^2)	Total Daily Dose (mg/day)
0.42-0.56	20
0.57-0.68	25
0.69-0.81	30
0.82-0.93	35
0.94-1.06	40
1.07-1.18	45
1.19-1.31	50
1.32-1.43	55
1.44-1.56	60
1.57-1.68	65
1.69-1.81	70
1.82-1.93	75
1.94-2.06	80
2.07-2.18	85
2.19- ≥2.30	90

Dose Level 6: Days 2-6 (Once Daily)
Temozolomide Dose Assignment: 55 mg/m^2/dose

BSA (m^2)	Total Daily Dose (mg/day)
0.42-0.50	25
0.51-0.59	30
0.60-0.68	35
0.69-0.77	40
0.78-0.86	45
0.87-0.95	50
0.96-1.04	55
1.05-1.13	60
1.14-1.22	65
1.23-1.31	70
1.32-1.40	75
1.41-1.50	80
1.51-1.59	85
1.60-1.68	90
1.69-1.77	95
1.78-1.86	100
1.87-1.95	105
1.96-2.04	110
2.05-2.13	115
2.14-2.22	120
2.23- ≥2.30	125

APPENDIX III-A: PATIENT DIARY INSTRUCTIONS FOR BMN 673 AND TEMOZOLOMIDE (FOR DOSE LEVELS -1 TO 1)

COG Patient ID:_____ **Acc#**_____ **Institution:**_____
Please do not write patient names on this form.

Part of the Study (tick one): □ **A1** □ **A2** □ **B** □ **C** **Body Surface Area:** _____ m^2 **Cycle Start Date:** ___/___/___

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

Complete each day with the time BMN 673 and temozolomide are given. **Make note of other drugs and supplements taken under the Comments section below**.

On Days 2 to 6, BMN 673 should be taken immediately prior to temozolomide. Note the time you take the medication in the Time column next to the drug name.

The prescribed medication can be taken without food or drink restrictions**. The only exception to this instruction is during pharmacokinetic study days for Part A patients (Phase 1) during Cycle 1: Day 1, and Day 5 or 6 medication should be taken in the clinic on an empty stomach (1 hour before or 2 hours after food). Patients enrolled on Part A and who consent to Day 2 pharmacokinetic studies during Cycle 1 should take their medication in the clinic.**

The capsules should not be opened or crushed but should be swallowed whole. If the capsule is broken and the powder of the capsules gets on your skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse immediately for additional instructions.

If you vomit after taking BMN 673 and/or temozolomide within 30 minutes, that dose of BMN 673 and/or temozolomide may be repeated. You should contact your study doctor if you have vomiting and re-take the dose. If you vomit more than 30 minutes after taking either BMN 673 and /or temozolomide, that dose of BMN 673 and/or temozolomide will be missed.

If you miss a BMN 673 or temozolomide dose and less than 6 hours have passed since the scheduled dosing time, that dose should be taken immediately. If you miss a BMN 673 or temozolomide dose and more than 6 hours have passed since the scheduled dosing time, that dose of BMN 673 or temozolomide will be missed; wait and take the next regularly scheduled BMN 673 or temozolomide dose.

Add the dates to the calendar below and return the completed diary (Appx. III-B) to your institution after each treatment cycle. Your institution will upload this document into RAVE (the database to send it to the COG) after each treatment cycle.

EXAMPLE ********** *INSTITUTION USE ONLY* **********

# of prescribed BMN 673 capsules/ dose	
100 mcg	250 mcg
1	2

# of prescribed temozolomide capsules/ dose		
5 mg	20 mg	100 mg
2	1	

EXAMPLE	Date	Time		# of BMN 673 capsules taken		# temozolomide capsules taken			Comments
WEEK 1				100 mcg	250 mcg	5 mg	20 mg	100 mg	
Day 1 Wednesday	1/15/14	BMN 673	8:30 AM	1	2				He felt nauseated an hour after taking the drug but did not vomit.
Day 2 Thursday	1/16/14	BMN 673	8:30 AM	1	2				He felt the same as on Day 1.
		Temoz.	8.32 AM			2	1		

APPENDIX III-B: PATIENT DIARY FOR BMN 673 AND TEMOZOLOMIDE (FOR DOSE LEVELS -1 TO 1)

COG Patient ID:_____ **Acc#**_____ **Institution:**_____
Please do not write patient names on this form.

Part of the Study (tick one):□ **A1** □ **A2** □ **B** □ **C** **Body Surface Area:** _____ m^2 **Cycle Start Date:** ___/___/___

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

********** *INSTITUTION USE ONLY* **********

# of prescribed BMN 673 capsules/ dose	
100 mcg	250 mcg

# of prescribed temozolomide capsules/ dose		
5 mg	20 mg	100 mg

Cycle #: _____ **BMN 673 Dose Level:** _____mcg/m^2/dose
Temozolomide Dose Level: _____mg/m^2/dose

WEEK 1	Date	Time		# of BMN 673 capsules taken		# temozolomide capsules taken			Comments
				100 mcg	250 mcg	5 mg	20 mg	100 mg	
Day 1		BMN 673							
Day 2		BMN 673							
		Temozolomide							
Day 3		BMN 673							
		Temozolomide							
Day 4		BMN 673							
		Temozolomide							
Day 5		BMN 673							
		Temozolomide							
Day 6		BMN 673							
		Temozolomide							
Day 7									
WEEK 2 (Days 8-14)									
WEEK 3 (Days 15-21)									
WEEK 4 (Days 22-28)									

APPENDIX III-C: PATIENT DIARY INSTRUCTIONS FOR BMN 673 AND TEMOZOLOMIDE (FOR DOSE LEVELS 2 TO 6)

COG Patient ID:_____ **Acc#**_____ **Institution:**_____
Please do not write patient names on this form.

Part of the Study (tick one): □ A1 □ A2 □ B □ C **Body Surface Area:** _____ m^2 **Cycle Start Date:** ___/___/___

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

Complete each day with the time BMN 673 and temozolomide are given. **Make note of other drugs and supplements taken under the Comments section below**.

On Day 1, the first and second dose of BMN 673 should be taken 12 hours apart. On Days 2 to 6, BMN 673 should be taken immediately prior to temozolomide; note the time you take the medication in the Time column next to the drug name.

The prescribed medication can be taken without food or drink restrictions**. The only exception to this instruction is during pharmacokinetic study days for Part A patients (Phase 1) during Cycle 1: Day 1, and Day 5 or 6 medication should be taken in the clinic on an empty stomach (1 hour before or 2 hours after food). Patients enrolled on Part A and who consent to Day 2 pharmacokinetic studies during Cycle 1 should take their medication in the clinic.**

The capsules should not be opened or crushed but should be swallowed whole. If the capsule is broken and the powder of the capsules gets on your skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse immediately for additional instructions.

If you vomit after taking BMN 673 and/or temozolomide within 30 minutes, that dose of BMN 673 and/or temozolomide may be repeated. You should contact your study doctor if you have vomiting and re-take the dose. If you vomit more than 30 minutes after taking either BMN 673 and /or temozolomide, that dose of BMN 673 and/or temozolomide will be missed.

If **you miss a BMN 673 or temozolomide dose and less than 6 hours have passed since the scheduled dosing time, that dose should be taken immediately**. If you miss a BMN 673 or temozolomide dose and more than 6 hours have passed since the scheduled dosing time, that dose of BMN 673 or temozolomide will be missed; wait and take the next regularly scheduled BMN 673 or temozolomide dose.

Add the dates to the calendar below and return the completed diary (Appx. III-D) to your institution after each treatment cycle. Your institution will upload this document into RAVE (the database to send it to the COG) after each treatment cycle.

EXAMPLE ********** *INSTITUTION USE ONLY* **********

	# of prescribed BMN 673 capsules/ dose	
	100 mcg	250 mcg
Day 1	0	2
Days 2-6	0	3

# of prescribed temozolomide capsules/ dose		
5 mg	20 mg	100 mg
2	1	

EXAMPLE	Date	Time		# of BMN 673 capsules taken		# temozolomide capsules taken			Comments
WEEK 1				100 mcg	250 mcg	5 mg	20 mg	100 mg	
Day 1 Wednesday	1/15/14	BMN 673	8:30 AM	0	2				He felt nauseated an hour after taking the drug but did not vomit.
		BMN 673	8:30 PM	0	2				
Day 2 Thursday	1/16/14	BMN 673	8:30 AM	0	3				He felt the same as on Day 1.
		Temoz.	8.32 AM			2	1		

APPENDIX III-D: PATIENT DIARY FOR BMN 673 AND TEMOZOLOMIDE (FOR DOSE LEVELS 2 TO 6)

COG Patient ID:_____ **Acc#**_____ **Institution:**_____
Please do not write patient names on this form.

Part of the Study (tick one):□ **A1** □ **A2** □ **B** □ **C** **Body Surface Area:** _____ m^2 **Cycle Start Date:** ___/___/___

NOTE: BMN 673 dose and capsule strengths are in MICROGRAMS (mcg).

********** *INSTITUTION USE ONLY* **********

	# of prescribed BMN 673 capsules/ dose	
	100 mcg	250 mcg
Day 1		
Days 2-6		

# of prescribed temozolomide capsules/ dose		
5 mg	20 mg	100 mg

Cycle #: _____ **BMN 673 Dose Level:** _____mcg/m^2/dose
Temozolomide Dose Level: _____mg/m^2/dose

WEEK 1	Date	Time		# of BMN 673 capsules taken		# temozolomide capsules taken			Comments
				100 mcg	250 mcg	5 mg	20 mg	100 mg	
Day 1		BMN 673 (AM)							
		BMN 673 (PM)							
Day 2		BMN 673							
		Temozolomide							
Day 3		BMN 673							
		Temozolomide							
Day 4		BMN 673							
		Temozolomide							
Day 5		BMN 673							
		Temozolomide							
Day 6		BMN 673							
		Temozolomide							
Day 7									
WEEK 2 (Days 8-14)									
WEEK 3 (Days 15-21)									
WEEK 4 (Days 22-28)									

APPENDIX IV: CORRELATIVE STUDIES GUIDE

For Part A (Phase 1)

Correlative Study	Appendix	Blood Volume			Tube Type
		Volume per sample	Total Cycle 1 ≤ 10 kg	Total Cycle 1 > 10 kg	
Pharmacokinetics[a]	V	2-3 mL	36 mL	42 mL	K_3EDTA lavender top (BMN 673 PK studies) Heparinized containing sodium (temozolomide PK studies)
Pharmacokinetics[b]		3 mL	3 mL	3 mL	K_3EDTA lavender top (BMN 673 PK studies)
Total Blood Volume in Cycle 1			**39 mL**	**45 mL**	

[a] Required for all patients
[b] Optional for all patients

For Part B (Phase 2)

Correlative Study	Appendix
Tumor Tissue[a]	VIII

[a] Required from all Part B Patients

APPENDIX V: PHASE 1 PHARMACOKINETIC STUDY FORM FOR BMN 673 AND TEMOZOLOMIDE (PART A ONLY)

COG Pt ID # _____ **ACC #** _____ **Cycle 1, Day 1 Date:** ___/___/___ **Body Surface Area:** _____m^2

Please do not write patient names on this form or on samples. **Institution:** _____ **Weight:** _____kg

BMN 673 Dose Level: _____mcg/m^2/ dose **Temozolomide Dose Level:** _____mg/m^2/dose

Total Dose Day 1: _____mcg/day **BMN 673** **Total Dose Day 5 or 6:** _____mcg/day **BMN 673**

_____mg/day **Temozolomide**

Plasma samples (2-3 mL per sample) will be collected at the following time points during **Cycle 1**:

- **Day 1 (Required from all patients):** Pre-dose, and then at 1, 2, 4 and 8 hours after the first BMN 673 morning dose.
- **Day 2 (optional):** Pre-dose on Day 2 (24 hours after the first BMN 673 dose on Day 1) from consenting patients.
- **Day 5 or 6 (Required from all patients):** Pre-dose, and then at 1, 2, 4 and 8 hours after BMN 673 and temozolomide administration.
- **Day 8 and Day 15 (Required from patients > 10 kg):** These samples are collected at time of CBC evaluation.

Refer to Section 8.3.2 for detailed instructions regarding food and drink restrictions during pharmacokinetic study days. **Record the exact date and time each sample is drawn**. Sample handling and processing instructions for BMN 673 and temozolomide are in Section 8.3. **Note**: BMN 673 samples must be maintained at **room temperature** during collection and processing. Temozolomide samples should be maintained at 4 ºC during collection and processing.

Blood Sample No.	Time Point	Scheduled Collection Time	Scheduled Time Point	Actual Dose Administered To Patient	Actual Date Sample Collected or Dose Given	Actual Time Collected or Dose Given (24-hr clock)
1	Cycle 1, Day 1	Prior to Cycle 1, Day 1@			___/___/___	|__|__| : |__|__|
Cycle 1, Day 1			BMN 673 AM Dose	_____mcg	___/___/___	|__|__| : |__|__|
2	Cycle 1, Day 1	1 hr after 1st dose			___/___/___	|__|__| : |__|__|
3	Cycle 1, Day 1	2 hr after 1st dose			___/___/___	|__|__| : |__|__|
4	Cycle 1, Day 1	4 hrs after 1st dose			___/___/___	|__|__| : |__|__|
5	Cycle 1, Day 1	8 hrs after 1st dose			___/___/___	|__|__| : |__|__|
Cycle 1, Day 1			BMN 673 PM Dose +	_____mcg	___/___/___	|__|__| : |__|__|
6	Cycle 1, Day 2	24 hrs after 1st dose*			___/___/___	|__|__| : |__|__|
			Cycle 1, Day 5 or 6			
7	Cycle 1, Day 5 or 6	Prior to Cycle 1, Day 5 or 6 dose of BMN 673@			___/___/___	|__|__| : |__|__|
Cycle 1, Day 5 or 6			BMN 673 Dose	_____mcg	___/___/___	|__|__| : |__|__|
			Temozolomide Dose	_____mg	___/___/___	|__|__| : |__|__|
8	Cycle 1, Day 5 or 6	1 hr after dose@			___/___/___	|__|__| : |__|__|
9	Cycle 1, Day 5 or 6	2 hr after dose@			___/___/___	|__|__| : |__|__|
10	Cycle 1, Day 5 or 6	4 hrs after dose@			___/___/___	|__|__| : |__|__|
11	Cycle 1, Day 5 or 6	8 hrs after dose@			___/___/___	|__|__| : |__|__|
12^	Cycle 1, Day 8				___/___/___	|__|__| : |__|__|
13^	Cycle 1, Day 15				___/___/___	|__|__| : |__|__|

@ Two consecutive 2 mL blood samples will be collected (a total of 4 mL). **Sample 1:** Follow BMN 673 PK processing and shipping requirements in Section 8.3.4.1. **Sample 2:** Follow temozolomide PK processing and shipping requirements in Section 8.3.4.2.

\+ Only applicable for Dose Levels 2 to 6. The 2nd dose of BMN 673 on Day 1 of Cycle 1 should be administered 12 hours after the first dose of BMN 673.

* Optional pre-dose sample on Day 2.

^ Patients > 10 kg only.

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. Another copy should be sent with the samples to the address listed in Appendix VI and Appendix VII. See Appendix VI and Appendix VII for detailed guidelines for packaging and shipping PK samples to Alliance Pharma and the Mayo Clinic, respectively.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____

(site personnel who collected samples)

APPENDIX VI: GUIDELINES FOR SHIPPING PK SAMPLES TO ALLIANCE PHARMA

1. Ship PK plasma samples to Alliance Pharma when requested (see Step 6 below). The PK samples should be batched for shipping at the end of Cycle 1.
2. Place samples grouped by patient in a cryobox. Ensure the cryobox is closed and remains so in transit using shipping tape. Place the cryobox in a shipping container with sufficient dry ice to maintain samples at -20 ºC for at least 72 hours.
3. Each shipment should be prepared in accordance with IATA regulations.
4. Samples must be shipped at least 3 days prior to US National Holiday. A holiday schedule will be provided.
5. Frozen samples should be shipped via **overnight FedEx, Monday through Wednesday**. **No shipments should be made later than Wednesday of any given week**.
6. **Before shipment:** Clinical sites will arrange for the timing of the shipment with Alliance Pharma. For questions regarding sample shipment, contact Lara Graham via email (lgraham@alliancepharmaco.com) or by phone (610-296-3152).
7. **On the day of shipment**: Email a copy of the completed pharmacokinetic study form (Appendix V) and the tracking number to **Lara Graham** (lgraham@alliancepharmaco.com) and copy the **ADVL1411COG Study Assigned Research Coordinator** on the email.
8. Ship the PK samples to the following address and include a completed copy of Appendix V with the shipment:

Attention: Lara Graham
Sample Management
Alliance Pharma
17 Lee Blvd.
Malvern, PA19355
Phone: 610-296-3152
Email: lgraham@alliancepharmaco.com

Email the sample information and tracking # to lgraham@alliancepharmaco.com and linh.nguyen@medivation.com at time of shipment. Use FedEx Account# 2919-4462-0 for these shipments.

APPENDIX VII: GUIDELINES FOR SHIPPING PK SAMPLES TO THE MAYO CLINIC

1. Day 1 pre-dose, and Day 5 or 6 PK samples should be batched, maintained at -70 ºC until shipment, and shipped together for each patient at the end of Cycle 1.
2. Place samples in a cryobox. Ensure the cryobox is closed and remains so in transit using shipping tape. Place the cryobox in a shipping container with sufficient dry ice to maintain samples at -20 ºC for at least 72 hours.
3. Each shipment should be prepared in accordance with IATA regulations.
4. Frozen samples should be shipped via **overnight FedEx, Monday through Wednesday**. **No shipments should be made later than Wednesday of any given week**.
5. **On the day of shipment**: Email a copy of the completed pharmacokinetic study form (Appendix V) and the tracking number to **Dr. Joel Reid** (reid.joel@mayo.edu) and copy the **ADVL1411 COG Study Assigned Research Coordinator** on the email.
6. Ship the PK samples to the following address and include a completed copy of Appendix V with the shipment:

Attention: **Dr. Joel M. Reid**
Department of Oncology
Mayo Clinic
Room 19-151, Gonda Building
200 First Street SW
Rochester, MN 55905.
Phone (507) 284-0822
Fax (507) 284-3906
Email: reid.joel@mayo.edu

APPENDIX VIII: PHASE 2 TUMOR TISSUE STUDY FORM (PART B ONLY)

COG Pt ID # _____ **ACC #** _____ **Cycle 1, Day 1 Date:** ___/___/___ **Institution:** _____

Please do not write patient names on this form or on samples.

BMN 673 Dose Level: _____mcg/m^2/ dose **Total Dose Day 1:** _____**mcg/day BMN 673** **BSA:** _____ m^2

Temozolomide Dose Level: _____mg/m^2/dose **Total Dose Days 2-6:** _____**mcg/day BMN 673**

_____**mg/day Temozolomide**

Tumor sample scheduling and collection:

See Section 8.4 for schedule details. A paraffin-embedded tissue block should be submitted. If a tissue block is unavailable, at least 10 unstained standard sections of 3 to 4 µM thickness must be sent (15 slides are recommended).

Tumor sample labeling

Samples should be labeled with the following information:

Protocol Number:	**ADVL1411**
Institution:	
COG Patient ID #:	
Accession #:	
Sample Date:	
Site of Acquired Tissue:	
Time tissue obtained at (check one option): □ Diagnosis □ Relapse □ After the start of ADVL1411 treatment	

On the day of shipment:

Email shipment notifications (including the FedEx tracking number) along with a completed copy of this form to the laboratory manager, Eva Loranc (Loranc@uthscsa.edu). Dr. Alex Bishop (bishopa@uthscsa.edu) and **the ADVL1411 COG Study Assigned Research Coordinator** should also be copied on this email.

For questions regarding sample shipments sites may contact Eva Loranc by phone (business hours: 210-562-9066; after hours: 210-364-7900) or by email (Loranc@uthscsa.edu).

Shipment of tumor tissue (Monday through Thursday via overnight FedEx):

Please indicate above the date of the sample, site of tissue acquisition and whether it was obtained at diagnosis, relapse, or after the start of ADVL1411 treatment. Paraffin embedded tumor specimens must be packaged appropriately and shipped at room temperature to Dr. Alex Bishop's laboratory as stated below.

Attention: Eva Loranc
Dr. Alex Bishop Laboratory
Greehey Children's Cancer Research Institute
The University of Texas Health Science Center
8403 Floyd Curl Dr.
San Antonio TX, 78229
Phone: 210-562-9066

This form must accompany the patient samples at time of shipment, and one copy of the form should be uploaded into RAVE. Please include one form per patient per time point in each shipment.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel who collected samples).

APPENDIX IX: PREGNANCY INFORMATION FORM

Attach to CTEP-AERS 5-Day Report

PREGNANCY INFORMATION FAX
FACSIMILE TRANSMISSION
Ticket Number:_____

Study #:
SAF FAX NO: (301) 230-0159
ALTERNATE FAX NO: (301) 897-7404

Initial Report Date: ___ - ___ - ___ (DD MMM YY)
Follow-up Report Date: ___ - ___ - ___ (DD MMM YY)

Principal Investigator:
Reporter:

Reporter Telephone #:
Reporter FAX #:

Investigator Number [ ][ ][ ][ ][ ]
Subject Number [ ][ ][ ][ ][ ]

Complete all of the investigator and subject number boxes provided. Use leading zeros, when necessary, to complete all expected boxes.

Example: Investigator #407 would be filled in as: 0 0 4 0 7

Subject Initials [ ][ ][ ]

Record the first letter of the subject's first, middle and last name, in that sequence. If the subject has no middle name, enter a dash.

Example: A - C

Subject's Sex: ☐ Female ☐ Male

Subject's Weight: _____ kg

Subject's Date of Birth: ___ - ___ - ___ (DD MMM YYYY)

Subject's Ethnicity (check one only): ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Not Available

Subject's Race (check all that apply): ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Not Available

Study Drug:
Study Drug Start Date: ___ - ___ - ___ (DD MMM YY)
Study Drug Stop Date: ___ - ___ - ___ (DD MMM YY) OR ☐ Study Drug Continuing

Dose:
Route: **ORAL**
Frequency: **QD**
Kit #:

First Day of Last Menstrual Period: ___ - ___ - ___ (DD MMM YY)
Estimated Date of Delivery: ___ - ___ - ___ (DD MMM YY)

Method of Contraception (check all that apply):
☐ Oral Contraceptive Pills ☐ Condoms ☐ Periodic Abstinence ☐ Progestin Injection or Implants ☐ Spermacide
☐ Diaphragm ☐ Intrauterine Device (IUD) ☐ Tubal Ligation ☐ Other, specify:_____

Reproductive History: ☐ Gravida _____ ☐ Para _____

Tests performed during pregnancy: ☐ None ☐ Unknown
☐ CVS Results: ☐ Normal ☐ Abnormal
☐ Amniocentesis Results: ☐ Normal ☐ Abnormal
☐ Ultrasound Results: ☐ Normal ☐ Abnormal

Pregnancy Outcome
Was pregnancy interrupted? ☐ Yes ☐ No
If yes, specify: ☐ Elective Termination ☐ Spontaneous Abortion ☐ Ectopic
Date of Termination: ___ - ___ - ___ (DD MMM YY)
If pregnancy was **not** terminated, specify pregnancy outcome (and provide infant outcome information)
☐ Vaginal Birth: ☐ Premature ☐ Term
OR
☐ C-Section: ☐ Scheduled ☐ Emergency
Date of Delivery: ___ - ___ - ___ (DD MMM YY)
Infant outcome information: ☐ Normal ☐ Abnormal

Additional Case Details (if needed):

NOTE: For an initial reporting fax both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form. For follow-up reporting, fax only this Pregnancy Information Form (See Section 13.7). Copies of all documents that are faxed to the NCI during initial and follow-up reporting must also be sent via email to the ADVL1411 Study Assigned Research Coordinator.