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CHILDREN'S ONCOLOGY GROUP

ADVL1514

A PHASE 1 STUDY OF ABI-009 (NAB-RAPAMYCIN) [redacted] IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS, INCLUDING CNS TUMORS AS A SINGLE AGENT AND IN COMBINATION WITH TEMOZOLOMIDE AND IRINOTECAN

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

[redacted]

For COG PEP-CTN Operations Contacts see: http://members.childrensoncologygroup.org

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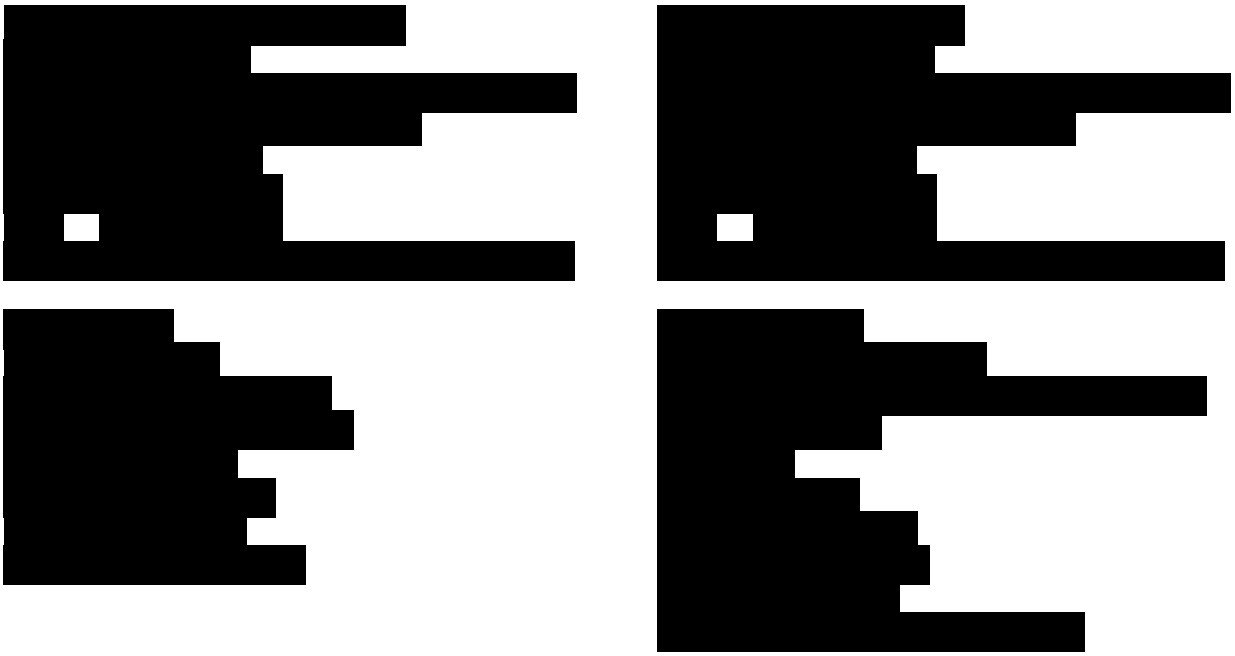
STUDY COMMITTEE, CONT.



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AGENT NSC# AND IND#'s

Agent Supplied by AADi:
ABI-009 (*nab*-rapamycin; *nab*-sirlolimus) (NSC# 791518, [redacted]

Commercial Agents:
Temozolomide (Temodar®, Temodal®; NSC# 362856)
Irinotecan (Camptosar®; NSC# 616348)
Cefixime (Suprax®) NSC# NA

IND Sponsor: COG

SEE SECTIONS 8.3.6 AND 8.4.2 FOR SPECIMEN SHIPPING ADDRESSES

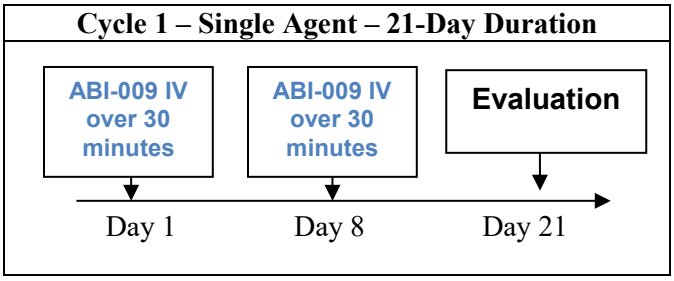
This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers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

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

ABSTRACT

Relapsed/refractory pediatric solid and CNS tumors are a major cause of morbidity and mortality in pediatric oncology with few effective treatment options. Both preclinical and clinical studies involving pediatric solid and CNS tumors have shown an aberration of the mammalian target of rapamycin (mTOR) pathway. In addition, these studies have demonstrated that inhibition of the mTOR pathway has significant efficacy impeding growth of these tumors. ABI-009, also known as nab-Rapamycin, is a novel human albumin-bound preparation of rapamycin, a potent mTOR inhibitor. Albumin nanoparticle technology encapsulates lipophilic drugs into nanoparticles by combining drug and human serum albumin in a water-based solvent under high pressure. This technology enhances permeability and retention (EPR), allowing accumulation of macromolecules in solid tumors. In the adult phase 1 trial, ABI-009 was well tolerated with the most common toxicities including thrombocytopenia, mucositis, fatigue, rash, diarrhea, and hypertriglyceridemia. We will conduct a phase 1 trial of ABI-009 in combination with irinotecan and temozolomide in children with recurrent solid and CNS tumors using the Rolling Six design. The aims of the trial will be to establish the maximum tolerated pediatric dose of ABI-009, and to investigate the toxicities, pharmacokinetics, and pharmacodynamics of ABI-009 in children with these tumors.

EXPERIMENTAL DESIGN SCHEMA



Cycle 2+ Combination Therapy 21 Day Duration					
Day -2	Cefixime				PJP Prophylaxis
Day -1					
Day 1		TEMO	IRIN	ABI-009	
Day 2		TEMO	IRIN		
Day 3		TEMO	IRIN		
Day 4		TEMO	IRIN		
Day 5		TEMO	IRIN		
Day 6					
Day 7					
Day 8				ABI-009	
Day 9-19					
Day 20[1]	Cefixime				
Day 21[2]		**Evaluation**			

TEMO: Temozolomide
IRIN: Irinotecan
PJP: Pneumocystis pneumonia

[1] Day 20 equals Day -2 of the following cycle.
[2] Day 21 equals Day -1 of the following cycle.

Treatment will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Patients with stable disease or greater response may continue receiving protocol therapy provided that 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

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ABI-009 administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle, in combination with temozolomide and irinotecan (administered on Days 1-5) in pediatric patients with recurrent or refractory solid tumors, including CNS tumors.

1.1.2 To define and describe the toxicities of single-agent ABI-009 administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle in pediatric patients with recurrent or refractory solid tumors, including CNS tumors.

1.1.3 To define and describe the toxicities of ABI-009 administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle in combination with temozolomide and irinotecan (administered on Days 1-5) in pediatric patients with recurrent or refractory solid tumors, including CNS tumors.

1.1.4 To characterize the pharmacokinetics of ABI-009 in pediatric patients with recurrent or refractory solid tumors, including CNS tumors.

1.2 Secondary Aim

1.2.1 To preliminarily define the antitumor activity of ABI-009 in combination with temozolomide and irinotecan within the confines of a Phase 1 study.

1.3 Exploratory Aim

1.3.1 To assess the biologic activity of ABI-009 by examining SK61 and 4E-BP1 expression status in archival tumor tissue from solid tumor pediatric patients using immunohistochemistry.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 ABI-009 and the mTOR Pathway

ABI-009, also known as *nab*-Rapamycin, is a novel human albumin-bound preparation of rapamycin, a potent mammalian target of rapamycin (mTOR) inhibitor. Rapamycin interacts with the 12 kDa FK506-binding protein (FKBP12) and forms a gain-of-function complex, resulting in inhibition of mTOR function.[1] Aberration of the mTOR pathway occurs in numerous adult and pediatric cancers as a result of gain-of-function mutations in oncogenes and/or loss-of-function mutations in tumor suppressors.[1] The deregulation of the mTOR pathway is not only confined to cancer, but also observed in obesity, type 2 diabetes, and neurodegeneration.[2]

mTOR, a serine/threonine protein kinase, belongs to the phosphoinositide 3-kinase (PI3K)-related protein kinase family because of the homology its C-terminus shares with the catalytic domain of PI3K.[2] It is composed of two functionally separate protein complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2), that have varying upstream inputs and downstream outputs as well as sensitivity to rapamycin, with mTORC1 being the more sensitive complex.[3] Once activated, mTORC1 directly phosphorylates the translation regulators p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic inhibition factor eIF4E binding protein 1 (4E-BP1) resulting in nucleotide and protein synthesis.[4] Additionally, phosphorylation status of S6K and 4E-BP1 are frequently used to assess mTORC1 activity *in vivo.*[3] Conversely, the underpinnings of mTORC2 role and function are yet to be fully understood. mTORC2 is thought to be rapamycin insensitive; however, long-term exposure in certain cell types reduces mTORC2 signaling.[5]

2.1.2 mTOR Signaling in Cancer

The mTOR pathway has numerous roles in cancer pathogenesis. Aberrant activation of this pathway, either by gain-of-function mutations in oncogenes and/or loss-of-function mutations in tumor suppressors, results in tumor growth, angiogenesis, resisting cell death, and metastasis.[6] One signaling pathway altered in multiple cancer types is the PI3K/AKT kinase cascade, which is the key kinase acting upstream of both mTORC1 and mTORC2. The PI3K/AKT signaling cascade is deregulated by multiple mechanisms some which include mutations in PI3K, mutations or amplifications of AKT, overexpression of growth factor receptors human epidermal growth factor receptor 2 (HER-2), insulin-like growth factor receptor (IGFR), and platelet-derived growth factor receptor (PDGFR), or loss of phosphatase and tensin homolog (PTEN) function.[3,6] mTOR downstream effectors S6K1, 4EBP1, and eIF4E are also implicated in tumorigenesis; however, their exact mechanisms of tumorigenesis are yet to be elucidated. Tumor formation is not only a consequence of aberrant activation of the mTOR pathway, but is also a result of familial cancer syndromes that interact upstream from this pathway; specifically, Peutz-Jeghers syndrome (mutation of the serine threonine kinase 11 (Lkb1)), Tuberous Sclerosis (mutations in the TSC1 or TSC2), and Cowden disease (loss of PTEN function).[3]

The overall survival for advanced stage or refractory pediatric intracranial and extra-cranial solid tumor malignancies remains dismal.[7] The PI3K/AKT/mTOR pathway has been implicated in several pediatric solid tumor malignancies. These findings are outlined below:

- **Neuroblastoma (NB):** Overexpression of PI3K p85, PI3K p110, p-Akt, and p-mTOR, and decreased PTEN expression, as well as, Akt activation have been identified as poor prognostic indicators.[8,9]

- **Osteosarcoma (OS):** The PI3K/AKT pathway has been shown to be deregulated in a majority of localized OS and in 100% of advanced-stage disease.[10] In addition amplification of the oncogene c-Myc is seen in approximately 10% of OS and upregulated by Akt phosphorylation, while cyclin D1 is overexpressed in 20% of OS and is a downstream target of mTORC1.[11] Investigators have also shown that *in vitro* mTOR inhibition decreases proliferation, while *in vivo* delays tumor progression and pulmonary metastasis.[12]

- **Ewing Sarcoma (EWS):** EWS has a distinctive karyotypic abnormality involving the EWSR1 locus forming a fusion product with Fli-1, ERG, ETV1, or E1AF. These fusion proteins act as aberrant transcription factors and in *in vitro* studies have been shown to interact with insulin like growth factor 1 (IGF-1). IGF-1 indirectly activates PI3K through Ras signaling and via insulin receptor substrate 1 (IRS-1) leading to downstream activation of mTOR signaling.[13] All EWS family of tumors express the IGF-1 receptor and this suggests a potential role for IGF-1 in tumorigenesis.[13]

- **Rhabdomyosarcoma (RMS):** The chromosomal translocation involving the FOXO1 gene and the PAX3 or PAX7 gene occur in approximately 80% of alveolar RMS (ARMS), and are known to play a vital role in cell cycle dysregulation and tumorgenesis.[14] The PAX3-FOXO1 translocation decreases PTEN expression resulting in PI3K/Akt activation.[13] The Children's Oncology Group analyzed 64 primary RMS tumors via microarray and noted phosphorylated mTOR levels were increased in 60% of ARMS and 68% of embryonal RMS (ERMS) cases.[13]

- **Medulloblastoma (MB):** Recent studies have linked the sonic hedgehog (SHH) signaling pathway as an important mediator in the activation of the mTOR pathway and its downstream effectors S6K and eIF4E.[15]

- **Gliomas:** The signaling pathways that trigger the pathogenesis of pediatric gliomas have yet to be understood. Mueller et al. investigated the PI3K/Akt/mTOR pathway in low- and high-grade pediatric gliomas. Their study revealed that 80% of high-grade pediatric gliomas and 40% of low-grade gliomas showed activation of the PI3K/Akt/mTOR pathway and also suggested the tumor grade correlated negatively with PTEN expression.[16]

- **Renal Tumors:** Currently, initial treatment for metastatic renal cell carcinoma involves mTOR inhibition.[17] mTOR's role in Wilms' tumor is less defined; however, one study did reveal activation of the mTOR-signaling pathway in a metastatic lung lesion in a patient with Wilms' tumor.[18]

- **Hepatic Tumors:** Both hepatoblastoma and hepatocellular have deregulation of PI3K/Akt/mTOR signaling pathways resulting in tumorgenesis.[19,20]

2.1.3 Rapamycin *vs.* ABI-009 (*nab*-Rapamycin)

Rapamycin (sirolimus) is a potent allosteric inhibitor of mTORC1; yet, it has low oral bioavailability, poor solubility, and dose-limiting intestinal toxicity.[1,21] Temsirolimus, a prodrug of rapamycin and the only current intravenous "rapalog" preparation, has low water-solubility requiring formulation in surfactants and solvents; when infused, temsirolimus can potentially cause hypersensitivity reactions and decreased drug efficacy.[21] ABI-009, *nab*-Rapamycin, is a novel human albumin-bound intravenous preparation of rapamycin. Albumin nanoparticle technology encapsulates lipophilic drugs into nanoparticles by combining drug and human serum albumin in a water based solvent under high pressure, resulting in nanoparticle size in the range of 100-200 nM.[22] This technology enhances permeability and retention (EPR) allowing accumulation of macromolecules (*i.e.* drug albumin nanoparticles) in solid tumors.

This increased permeability and retention is important due to the underlying pathophysiology of tumor tissue defined by angiogenesis, defective lymphatic drainage, and abnormal vascular architecture.[22] ABI-009 is formulated in saline, has low anaphylaxis potential, and may improve drug delivery and efficacy.[21]

Proof of this concept has been demonstrated in preclinical studies comparing albumin-bound paclitaxel nanoparticles (nab- paclitaxel or ABI-007) *vs.* paclitaxel. Improved drug accumulation and antitumor response, as well as, enhanced biodistribution and increase in the maximum tolerated dose (MTD) was observed in the ABI-007 treated mice compared to those treated with paclitaxel.[22] Adult phase 1, 2 and 3 clinical studies of ABI-007 showed no hypersensitivity reactions when compared to paclitaxel; ABI-007 showed increased response rates (33% *vs.* 19%) and prolonged tumor progression (22 *vs.* 16.9 weeks) in patients with metastatic breast cancer.[22]

2.1.4 Rationale for Combination Therapy and Starting Dose

There have been numerous clinical trials evaluating mTOR inhibition in combination with a variety of chemotherapy backbone regimens in both adult and pediatric trials. Specifically, COG has investigated mTOR inhibition in combination with cyclophosphamide and vinorelbine (ARST0921) and in combination with irinotecan (IRN) and temozolomide (TMZ) (ADVL0918).[23,24] Of the combinations noted above, IRN and TMZ is of most interest due to its activity in heavily pretreated patients. The COG study ANBL0421, evaluated this backbone in patients with recurrent or refractory neuroblastoma. In this cohort, eight of the first 50 evaluable patients had objective responses to treatment.[25] In addition to evaluating this combination in neuroblastoma, other studies have investigated this backbone in relapsed Ewing sarcoma, rhabdomyosarcoma, and other difficult to treat solid tumors suggesting its feasibility in children.

These studies contributed to the development of a COG Phase 1 trial (ADVL0918) evaluating temsirolimus (TEM) in combination with IRN and TMZ. This was a dose finding study evaluating escalating doses of intravenous TEM, oral TMZ, and oral IRN. Seventy-one eligible patients were enrolled with a variety of solid tumor diagnoses, including CNS. Dose limiting toxicities included elevated serum alanine aminotransferase and triglycerides, anorexia, and thrombocytopenia. The MTD was identified as TEM 35 mg/m^2 weekly on Days 1, 8, and 15 with IRN 90 mg/m^2 and TMZ 125 mg/m^2 on Days 1-5 of a 21-day cycle. Of the seventy-one patients enrolled, six patients had objective responses with three of those having sustained responses for ≥ 14 cycles of therapy.[23]

To further delineate a starting dose of ABI-009, a review of published adult PKs of temsirolimus[26] and ABI-009[21] noted a starting dose of 45 mg/m^2. When administered temsirolimus produces the sirolimus metabolite, and the AUC of temsirolimus + sirolimus metabolite from temsirolimus at a dose of 45 mg/m^2 is 3414 + 11740 = 15,154 ng•h/ml. Since the molecular weight of temsirolimus (1030 g/mol) is similar to the molecular weight of sirolimus (914 g/mol), AUCs were summed without adjustment. The AUC of sirolimus from ABI-009 at 45 mg/m^2 is 24,564 (ng•h/ml) which is at least twice the total exposure compared to temsirolimus based on sirolimus alone. Thus the AUC of sirolimus from ABI-009 is substantially higher than that from temsirolimus at an equal dose (45 mg/m^2) of both drugs. A similar higher exposure of sirolimus with ABI-009 compared to temsirolimus would be expected at the lower dose

of 35 mg/m^2. Given that in the ADVL0918 study, the dose of 35 mg/m^2 of temsirolimus was well tolerated in combination, the starting dose for ABI-009 was extrapolated to start at 35 mg/m^2, understanding that this would roughly double the exposure of temsirolimus.

Furthermore, the phase 1 trial evaluating ABI-009, determined that the majority of missed doses (83%) occurred on day 15 (the 3rd dose of every 4-week schedule) (data unpublished). As a result, AADi has recently started two new phase 2 studies that incorporate the 2-dose, 3-week schedule. Based upon this information, the starting dose for this pediatric trial will mimic ADVL0918 on a Day 1 and Day 8 schedule. This will allow for rapid translation of the results of this trial into disease specific studies within COG.

2.2 Preclinical Studies

The activity of the combination of chemotherapy and mTOR inhibition was studied in preclinical models.

2.2.1 Antitumor Activity

Biochemical and functional characterization of ABI-009 has been undertaken in preclinical studies. These studies have suggested exceptional drug efficacy and safety, as well as decreased cancer cell viability and downstream signaling in several xenograft cancer models, including pancreatic, colorectal, breast cancer, and multiple myeloma.[27-30] Significant antitumor activity was observed across all tumor models tested at 40 mg/kg.[28]

Increased antitumor activity was noted when ABI-009 was used in combination with either ABI-007, doxorubicin, SAHA, erlotinib or perifosine.[27-30]

2.2.2 Animal Toxicology

One study evaluated overall toxicity of ABI-009 in breast and colon xenograft models at dose levels of 0, 15, 30, 45, 90 and 180 mg/kg on an every 4 days times 3 schedule; pharmacokinetic properties were evaluated at dose levels of 1, 15, 30, and 45 mg/kg, and antitumor activity was evaluated at 40 mg/kg with a 3 times weekly for 4 weeks schedule. The investigators noted that ABI-009 was non-toxic at the dose level of 180 mg/kg; no changes were noted in blood chemistry, CBC, hypercholesterolemia, or hypertriglyceridemia. ABI-009 showed no CNS side effects in xenograft models tested.[27-30]

2.2.3 Preclinical Pharmacokinetic Studies

With respect to dose, ABI-009 exhibited linear Pharmacokinetics.[28]

2.3 Adult Studies

2.3.1 Phase 1 Studies

The first in-human trial of ABI-009 administered at 5 dose levels (45, 56.25, 100, 125, and 150 mg/m^2) on a weekly schedule for 3 weeks followed by 1 week of rest in patients with advanced solid tumors. The maximum tolerated dose (MTD) was 100 mg/m^2 with the most common toxicities including thrombocytopenia (58%), hypokalemia (23%), mucositis (38%), fatigue (27%), rash (23%), diarrhea (23%),

nausea (19%), anemia (19%), hypophosphatemia (19%), neutropenia (15%), and hypertriglyceridemia (15%). The study initially dose escalated from 100 mg/m^2 to 150 mg/m^2 which resulted in 4 dose-limiting toxicities (DLTs), two at 150 mg/m^2 and two at 125 mg/m^2; these were grade 3 AST elevation and grade 4 thrombocytopenia and grade 3 suicidal ideation and grade 3 hypophosphatemia, respectively (CTCAE v.4). The MTD had only 1 grade 3 non-hematologic event (dyspnea) and 1 grade 3 hematologic event (anemia) after cycle 1 (CTCAE v4). Twenty-seven patients were enrolled on this trial; however, only 19 were evaluable for efficacy. There was 1 patient with adenocarcinoma of the kidney with a partial response, two patients with stable disease (mesothelioma and neuroendocrine tumor) with prolonged stabilization for 1 year and 238 days, respectively.[21]

2.3.2 Phase 2 Studies

No Phase 2 studies have been conducted to date.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

The pharmacokinetic analysis showed an almost proportional increase of the maximum concentration (C_{max}) and area under the curve (AUC) with the outlier being a moderately low AUC at 125 mg/m^2. The C_{max} of ABI-009 was 3227.61 ng/mL that is significantly higher than levels achieved in other studies evaluating oral rapamycin and intravenous temsirolimus.[31,32] The half-life was 40–91 hours across the tested dose range and was 63 hours at the MTD of 100 mg/m^2. Circulating levels of the biomarkers S6K1 and 4EBP1 were significantly inhibited by ABI-009 and inhibition was maintained for several days after administration at dose levels greater than 56.25 mg/m^2.

2.4 Pediatric Studies

No pediatric studies of ABI-009 have been conducted. The Pediatric Preclinical Testing Program (PPTP) evaluated rapamycin in their xenograft models and noted a broad antitumor activity, with a significant activity in sarcoma models.[33] The Children's Oncology Group (COG) evaluated, in a Phase 2 trial (ARST0921), bevacizumab and temsirolimus in combination with vinorelbine (V) and cyclophosphamide (C) for initial relapse/progression for patients with RMS. Patients were randomized between the bevacizumab plus VC arm *vs.* temsirolimus plus VC arm. Patients that were randomized to the temsirolimus arm had a significantly improved EFS compared to the bevacizumab arm, 65% *vs.* 50%, respectively.[24] In addition, there have been multiple Phase 1 and 2 trials evaluating mTOR inhibitors including oral rapamycin, everolimus and temsirolimus alone or in combination in pediatric patients.[13]

2.4.1 Prior Experience in Children

There have been no pediatric studies of ABI-009.

2.5 Overview of Proposed Pediatric Study

We propose to conduct a Phase 1 study of ABI-009 in children with relapsed/refractory solid tumors using the rolling 6 design. Cycle 1 will aim to establish tolerability and safety and to

obtain pharmacokinetics of ABI-009 as a single agent dosed on days 1 and 8 of a 21-day cycle. Additionally, Cycle 2+ will aim to determine the MTD and/or RP2D of ABI-009 in combination with temozolomide and irinotecan. The ABI-009 starting dose will be 35 mg/m^2 as a single agent during Cycle 1, while Cycle 2+ dosing and scheduling in combination with irinotecan (90 mg/m^2) and temozolomide (125 mg/m^2) will mimic the Phase 1 pediatric trial ADVL0918.[23]

2.6 **Rationale for Amendment #4 (Addition of Dose Level -2 and modification of the definition of hematological DLT)**

With Amendment #4, an additional Dose Level -2 of 15 mg/m^2 has been added. To date (08/21/19), 18 patients have enrolled onto the study. Five patients enrolled at Dose Level 1 (35 mg/m^2); two of these patients experienced a DLT of platelet count decrease within the first one to three cycles of protocol therapy. An additional 13 patients enrolled at Dose Level -1 (20 mg/m^2) of which 7 patients are inevaluable. There were 2 DLTs (platelet count decrease) observed among the 6 evaluable patients. This amendment will provide a dose reduction to 15 mg/m^2 (Dose Level -2). We have reviewed our PK data for both Dose Level 1 (35 mg/m^2) and Dose Level -1 (20 mg/m^2). The data notes the median AUC for Dose Level 1 and Dose Level -1 to be 11,561 (ng•h/mL) and 8,599 (ng•h/mL), respectively. These median AUCs at these dose levels are well above the published AUCs for both temsirolimus and sirolimus. A Pediatric phase 1 trial evaluated weekly temsirolimus in refractory/recurrent solid tumors at doses of 10, 25, 75, and 150 mg/m^2 on days 1, 8, and 15.[34] The reported PK data indicates a median AUC for temsirolimus at doses of 10, 25, 75, and 150 mg/m^2 to be 1670, 3570, 2810, and 5190 (ng•h/mL), respectively.[34] In addition, sirolimus PK data was also investigated in this trial as following administration temsirolimus produces the sirolimus metabolite.[34] The median AUCs for sirolimus in this study at the above doses were 2560, 4520, 7670, and 8660 (ng•h/mL), respectively.[34] Review of the nab-rapamycin pharmacokinetics in adults demonstrates high variability (% coefficient of variation (CV), up to 40%) in both C_{max} and AUC.[21] In addition, for children and adolescent who received nab-rapamycin on this trial, PK parameters also had significantly variability (CV at least 35%). At Dose Level -1 (20mg/m2): C_{max} (mean 374 µg/L, median 368 µg/L, CV 39%); AUC_{inf} (mean 10113 µg•h/L, median 9749 µg•h/L, CV 37%); Clearance (mean 2.2 L/h/m^2, median 2 L/h/m^2, CV 35%). As noted previously, initial dosing for this study mimic the MTD in ADVL0918.[23] This study evaluated temsirolimus at 15mg/m^2 in combination with irinotecan and temozolomide, thus further validating this suggested dose reduction.[23] In addition, Raymond et al, noted in their trial evaluating the safety and efficacy of CCI-779, a novel mTor inhibitor, a partial response in a patient with renal cell carcinoma at a dose of 15 mg/m^2. Thus, based upon the information, above, a dose reduction of ABI-009 to 15 mg/m^2 is likely to yield a higher AUC then noted in the previous pediatric phase 1 trial of temsirolimus and that this dose would be in the therapeutic range. Given the significant variability in exposures as dose reduction to 15 mg/m^2 (Dose Level -2) ensures an adequate margin of safety with potential for clinical benefit.

In addition, careful review of the dose limiting thrombocytopenia experienced during the trial to date, indicates that the platelet threshold (>75,000/mm^3) for administration of day 8 protocol therapy is the primary reason for declaration of DLT. Based on the platelet nadir and recovery of patients with dose limiting thrombocytopenia, the platelet threshold for administration of day 8 protocol therapy has been modified to platelet count > 50,000/mm^3. In addition, grade 4 thrombocytopenia (<25,000/mm^3) ≥ 7 days duration and grade 3 thrombocytopenia (platelet count > 25,000/mm^3 and <50,000/mm^2) with clinically

significant bleeding, petechiae or purpura, or that persists for ≥ 7 days, and/or that requires platelet transfusion are considered dose limiting.

Acc #	Stratum	Dose Level	DLT Criteria	DLT Cycle	Subject Summary	DLT Details
1	Stratum 1	DL1	Gr. 4 Platelet count	2	Completed courses 1 and 2; evaluable for DLT, and experienced DLT.	Cycle 2, Day 8 platelet count was 78,000; Gr 3 plt started Cycle 1, Day 13; plt nadir 22,000, Gr 4, (Cycle 2 Day 31). Transfused x 3 in 7 day period (2 on Cycle 2, Day 15 and 1 on Cycle 2, Day 22); 100,000 by Cycle 2, Day 41.
4	Stratum 1	DL1	Gr. 3 Platelet count day 8, not resolve to grade ≤2 by day 11	1	Completed course 1. evaluable for DLT, and experienced DLT	Cycle 1, Day 8 platelets were 63,000, platelet nadir 35,000 on Cycle 1 Day 11; recovered to 118,000 by Cycle 1, Day 15; no transfusion given.
8	Stratum 1	DL-1	Gr. 3 Platelet count day 8 not resolve grade≤ 2 by day 11	1	Patient received one dose of study drug during Cycle 1 experienced DLT. Removed from protocol therapy at the end of C1.	Cycle 1, Day 8 platelets were 68,000; nadir platelet 32,000 on (Cycle 1, Day 13), platelet transfusion was given; Cycle 1, Day 21 platelet count was 65,000.
18	Stratum 1	DL-1	Gr. 3 Platelet count day 8, not resolved grade ≤ 2 by day 11	1	Patient received one dose of study drug during Cycle 1, experienced DLT. Removed from protocol therapy during C1.	Cycle 1, Day 8 platelets were 49,000; nadir platelet 35,000 on (Cycle 1, Day 11), platelet transfusion was given; Cycle 1, Day 11.

Due to the fact that all of the DLTs experienced thus far in this study have been hematologic DLTs, no patients with known bone marrow involvement will be enrolled (Stratum 2). Therefore, all enrolled participants will be evaluable for hematological toxicity. DL-2 will be evaluated with modified definitions of hematological DLT. Based on experience to date and the DLT evaluation period including both cycle 1 and cycle 2, we have increased the accrual ceiling to include a 30% rate of patients who are not evaluable for toxicity, rather than 20%.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at < https://ctepcore.nci.nih.gov/iam/index.jsp>). This is the same account (user id and password) used for credentialing in the CTSU members web site (refer to Appendix XVI for CTEP and CTSU registration procedures). To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

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 Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations 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

NCI Pediatric CIRB approval or local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit CIRB/IRB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. 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 Regulatory Tab.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission
When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.
For general (non-regulatory) questions, call the CTSU General Helpdesk at 1-888-823-5923 or contact CTSU by e-mail at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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 in the OPEN 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 through the OPEN website 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 COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. 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. 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: Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Body Surface Area: Patients must have a BSA of ≥ 0.2 m^2 at the time of study enrollment.

4.1.3 Diagnosis: Patients with recurrent or refractory solid tumors, including CNS tumors, 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.

4.1.4 Disease Status:
Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

4.1.5 Therapeutic Options: Patient's current disease state must be one for which there is

no known curative therapy.

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 must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the Study Chair and the study-assigned Research Coordinator prior to enrollment.
   - ≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) 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 and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoetic Growth Factors): ≥ 21 days after the completion of interleukins,

interferon or cytokines (other than Hematopoetic Growth Factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

k. Irinotecan, temozolomide and mTOR inhibitor exposure:
i. Patients who have received prior single agent therapy with irinotecan, temozolomide, or an mTOR inhibitor, excluding ABI-009, are eligible.
ii. Patients who have received prior therapy with ABI-009 are not eligible.
iii. Patients who have previously received irinotecan and temozolomide in combination without progressive disease while on therapy are eligible.
iv. Patients who have previously received irinotecan and temozolomide in combination and had significant toxicity with these two drugs are not eligible.
v. Patients who have received prior therapy with all three agents in combination (i.e. irinotecan, temozolomide, and an mTOR 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 at baseline (may receive RBC transfusions)

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:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 3 × ULN = 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.8.4 Adequate Pulmonary Function Defined as:

- Pulse oximetry > 94% on room air if there is clinical indication for determination (e.g. dyspnea at rest).

4.1.8.5 Adequate Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants (see Appendix X) and well controlled.
- Nervous system disorders (NCI CTCAE version 5.0) resulting from prior therapy must be ≤ Grade 2 with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

4.1.8.6 Adequate Metabolic Function Defined as:

- Serum triglyceride level ≤ 300 mg/dL
- Serum total cholesterol level ≤ 300 mg/dL
- Random or fasting blood glucose ≤ the upper normal limits for age. If the initial blood glucose is a random sample that is outside of the normal limits, then follow-up fasting blood glucose can be obtained and must be ≤ the upper normal limits for age.

4.1.8.7 Adequate Coagulation Defined as:

- INR ≤ 1.5
- Not currently receiving anticoagulation therapy

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 Tissue blocks or slides must be sent for all patients 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. 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 both during and for 6 months after participation in this study. Abstinence is an acceptable method of contraception.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids:
Patients receiving corticosteroids must have been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.7.1.d).

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.

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.

4.2.2.5 Anticonvulsants: Patients must not have received enzyme-inducing anticonvulsants for at least 7 days prior to enrollment (see Appendix X for a list of enzyme-inducing and non enzyme-inducing anticonvulsants).

4.2.2.6 Anticoagulants: Patients who are currently receiving therapeutic anticoagulants (including aspirin, low molecular weight heparin, and others) are not eligible.

4.2.2.7 CYP3A4 or P-gp-active agents: Patients must not be receiving any **strong** CYP3A4 or P-gp inducers or inhibitors within 7 days prior to enrollment (see Appendix XIV). Moderate inducers or inhibitors of CYP3A4 and P-gp should also be avoided during ABI-009 treatment, if possible.

4.2.3 Study Specific:

a. Pulmonary Dysfunction:
- Patients with interstitial lung disease and/or pneumonitis are not eligible.

b. Allergic reactions:
- Patients with a history of allergic reactions attributed to compounds of similar composition, including macrolide and ketolide antibiotics, temsirolimus/other mTOR inhibitors, temozolomide or irinotecan are not eligible.
- Patients with hypersensitivity to albumin are not eligible.

c. Surgery:
- Patients who have had or are planning to have the following invasive procedures are not eligible:
  - Major surgical procedure, laparoscopic procedure, open biopsy or significant traumatic injury within 28 days prior to enrollment.
  - Subcutaneous port placement or central line placement is not considered major surgery. External central lines must be placed at least 3 days prior to enrollment and subcutaneous ports must be placed at least 7 days prior to enrollment.
  - Core biopsy within 7 days prior to enrollment.
  - Fine needle aspirate within 7 days prior to enrollment.

  NOTE: For purposes of this study, bone marrow aspirate and biopsy are not considered surgical procedures and therefore are permitted within 14 days prior to start of protocol therapy.

d. Coagulation:
- Patients with current deep vein thrombosis or deep vein thrombosis within the past 6 months are not eligible.

e. Psychiatric Disorders:
- Patients with a history of, or current grade 4 depression are not eligible.

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

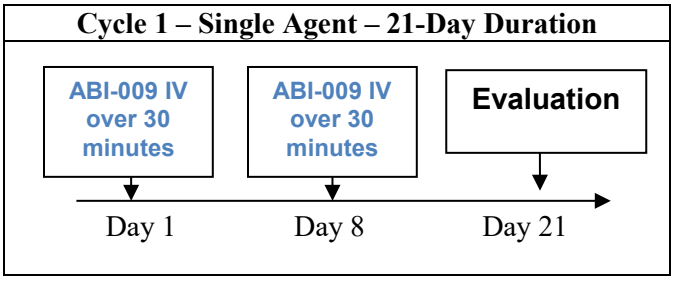
4.2.5 Patients who have received a prior solid organ transplantation are not eligible.

4.2.6 Patients who have known bone marrow involvement are not eligible.

4.2.7 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.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan



Cycle 2+ Combination Therapy 21 Day Duration					
Day -2	Cefixime				PJP Prophylaxis
Day -1					
Day 1		TEMO	IRIN	ABI-009	
Day 2		TEMO	IRIN		
Day 3		TEMO	IRIN		
Day 4		TEMO	IRIN		
Day 5		TEMO	IRIN		
Day 6					
Day 7					
Day 8				ABI-009	
Day 9-19					
Day 20[1]	Cefixime				
Day 21[2]		**Evaluation**			

TEMO: Temozolomide
IRIN: Irinotecan
PJP: Pneumocystis pneumonia

[1] Day 20 equals Day -2 of the following cycle.
[2] Day 21 equals Day -1 of the following cycle.

A cycle of therapy is considered to be 21 days. A cycle may be repeated for a total of 35 cycles, 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.

5.1.1 Cycle 1

Pre-Amendment #4: ABI-009 will be administered intravenously over 30 minutes on Days 1 and 8 of Cycle 1 (beginning at Dose Level 1 = 35 mg/m^2/dose; see dose escalation table in Section 5.3.1). The use of in-line filters is NOT necessary. Upon completion of infusion, the infusion catheter should be flushed with normal saline.

Amendment #4: ABI-009 will be administered intravenously over 30 minutes on Days 1 and 8 of Cycle 1 (beginning at Dose Level -2 = 15 mg/m^2/dose; see dose escalation table in Section 5.3.1). The use of in-line filters is NOT necessary. Upon completion of infusion, the infusion catheter should be flushed with normal saline.

5.1.2 Cycle 2 and subsequent cycles

Temozolomide will be administered orally at 125 mg/m^2/dose (maximum 250 mg/dose) once daily x 5 on Days 1-5 of each cycle. The dosing nomogram is included in Appendix IV. If emesis occurs within 30 minutes of taking a dose of temozolomide, then the dose may be repeated once. If emesis occurs after 30 minutes, the dose should not be repeated. Instructions for administration of oral temozolomide to young children are included in Appendix V.

Irinotecan will be administered orally at 90 mg/m^2/dose once daily x 5 on Days 1-5 of each cycle. Irinotecan should be administered one hour after the administration of temozolomide. If emesis occurs within 30 minutes of taking a dose of irinotecan, then the dose may be repeated once. If emesis occurs after 30 minutes, the dose should not be repeated. Guidelines for the administration of oral irinotecan are included in Appendix VI. Instructions for the preparation and administration of oral irinotecan are included in Appendix VII.

If a dose of temozolomide or irinotecan is missed and less than 6 hours have passed since the scheduled dosing time, the 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.

Aprepitant is a substrate and moderate inhibitor of CYP3A4. Single aprepitant or fosaprepitant doses appear to only weakly inhibit CYP3A4 and are permitted. However, longer regimens (aprepitant administered on 2 or more consecutive days) may cause moderate CYP3A4 inhibition and should be avoided if reasonable alternatives exist.

Pre-Amendment #4: ABI-009 will be administered intravenously over 30 minutes on Day 1 and Day 8 of each cycle (beginning at Dose Level 1 = 35 mg/m^2/dose; see dose escalation table in Section 5.3.1). ABI-009 should be given within 8 hours following administration of temozolomide and irinotecan. The use of in-line filters is NOT necessary. Upon completion of infusion, the infusion catheter should be flushed with normal saline.

Amendment #4: ABI-009 will be administered intravenously over 30 minutes on Day 1 and Day 8 of each cycle (beginning at Dose Level -2 = 15 mg/m^2/dose; see dose escalation table in Section 5.3.1). ABI-009 should be given within 8 hours following administration of temozolomide and irinotecan. The use of in-line filters is NOT necessary. Upon completion of infusion, the infusion catheter should be flushed with normal saline.

Cefixime or an available equivalent antibiotic will be used as diarrheal prophylaxis for cycles 2+. Initiation of antibiotic treatment two days prior to the start of irinotecan is required, and will continue during, and 3 days after the last dose of irinotecan of each cycle. This antibiotic therapy will continue throughout protocol therapy. Cefixime will be dosed at 8 mg/kg PO once daily (max: 400 mg/day). If cefixime is not available, cefpodoxime can be used as an alternative at 5 mg/kg/dose PO twice daily (10 mg/kg/day in two divided doses; max: 200 mg/dose).

Note: Patients **must** also receive pneumocystis prophylaxis during study therapy for cycles 2+.

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 21 days if the patient has again met laboratory parameters as defined in the eligibility section, Section 4.0, or is eligible to continue agent administration per the requirements in Section 6.0. For cycles 3 and later, patients must also have at least stable disease while meeting the criteria established in Section 4.0 and meets the requirements presented in Section 6.0.

5.3 Dose Escalation Schema

5.3.1 Inter-Patient Escalation

The starting dose of ABI-009 will be 35 mg/m^2 (dose level 1) with dose levels for subsequent groups of patients as follows.

Dose Level	Cycle 1	Cycle 2+		
	ABI-009 (mg/m^2)	**ABI-009 (mg/m^2)**	**Irinotecan (mg/m^2)**	**Temozolomide ** (mg/m^2)**
-2^	**15**	**15**	**90**	**125**
-1	20	20	90	125
1*	35	35	90	125
2	45	45	90	125
3	55	55	90	125

* Pre-Amendment #4: Starting dose level is the RP2D from COG study ADVL0918.
** Maximum temozolomide dose = 250 mg/dose
^ Amendment #4: Starting dose level

There will be no planned escalations beyond dose level 3 (55 mg/m^2), as previous pediatric Phase 1 studies have rarely defined an MTD greater than 160% of the adult MTD. However, if evaluation of PK and toxicity data as well as additional data from adult studies suggest higher doses are required to achieve maximal potential benefit, an amendment to the trial will be considered to add additional dose levels.

Amendment #4:
DL- 2 will be evaluated with modified definitions of hematological DLT, and there will be no planned escalations beyond dose level -2. If DL -2 is not well tolerated further de-escalation will not occur. The study will be closed to accrual.

5.3.2 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 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 Cycles 1 and 2 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 greater non-hematological toxicity attributable to the protocol therapy with the specific exclusion of:

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT, 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 and the ULN for AST is defined as 50 U/L, regardless of baseline. See Appendix XV for values that represent thresholds between CTCAE grades for ALT, AST, GGT and bilirubin.
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Grade 3 or 4 hypertriglyceridemia that returns to Grade ≤ 2 prior to the start of the next treatment cycle. The severity (grade) of hypertriglyceridemia is based upon fasting levels. If Grade 3 or 4 triglycerides are detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading (see Section 6.4).
- Grade 3 hyperglycemia that returns to a fasting glucose value ≤ 250 mg/dL or a fasting glucose of value ≤ 13.9 mmol/L (with or without the use of insulin or oral diabetic agents) prior to the start of the next treatment cycle. Medical management of hyperglycemia should be based on fasting levels. If routine (non-fasting) laboratory studies are performed and indicate the potential for intervention, the test should be repeated within 3 days in the fasting state to permit accurate medical management and grading (see Section 6.6).
- Grade 3 or 4 hypercholesterolemia that returns to ≤ Grade 2 after initiation of lipid lowering medication prior to the next treatment cycle. The severity (grade) of hypercholesterolemia is based upon fasting levels. If Grade 3 or 4 hypercholesterolemia is detected when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading (see Section 6.5).

5.5.1.2 Non-hematological toxicity that causes a delay of > 21 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

In patients evaluable for hematological toxicity (see Section 4.1.8.1), hematological dose-limiting toxicity is defined as:

- Day 8:
  - Grade 4 neutropenia or platelets < 50,000/mm^3 on Day 8 that does not resolve to ANC ≥ 750/mm^3 and platelets ≥ 50,000/mm^3 (transfusion independent) by Day 11 will be considered dose-limiting (see Section 6.1).
- Grade 4 thrombocytopenia (platelet count < 25,000/mm^3) for ≥ 7 days
- Grade 4 anemia, not due to malignant infiltration.
- Grade 4 neutropenia that lasts for > 7 days
- Grade 3 thrombocytopenia with clinically significant bleeding, petechiae or purpura, or that persists for ≥ 7 days, and/or that requires platelet transfusion.
- Myelosuppression that causes a delay of > 21 days between treatment cycles.

Note: Grade 3 or 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.

6.1 Dose Modification Guidelines for Cycle 1, Day 8

For Patients Evaluable for Hematological Toxicity:

Hematological Toxicity on Day 8: Thrombocytopenia	**Action**
Platelets ≥ 50,000/mm^3	• Continue protocol therapy.

Platelets < 50,000/mm^3 without clinically significant bleeding, petechial or purpura	• Patients who have platelets < 50,000/mm^3 on Day 8 will have the dose of ABI-009 withheld. • If the toxicity resolves to platelets ≥ 50,000/mm^3 (transfusion independent) by Day 11, the Day 8 dose of ABI-009 may be given. • If the toxicity does not resolve to platelets ≥ 50,000/mm^3 by Day 11, the Day 8 dose of ABI-009 will be omitted and this will be considered a DLT. Patients should receive subsequent cycles of ABI-009 but at the next lower dose level or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued.
Platelets < 50,000/mm^3 with clinically significant bleeding, petechial or purpura	• If Grade 3 thrombocytopenia with clinically significant bleeding, petechial or purpura, omit Day 8 dose of ABI-009, and this will be considered a DLT. Patients should receive subsequent cycles of ABI-009 but at the next lower dose level or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • If persists for ≥ 7 days, patients should receive subsequent doses of ABI-009 at the next lower dose level or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued.
Other thrombocytopenia DLTs per Section 5.5.2 on Day 8	• As above, per platelet grade and bleeding.

Hematological Toxicity on Day 8: Neutropenia	**Action**
Grade 1-3	• Continue protocol therapy.

Grade 4	• Patients who have Grade 4 neutropenia on Day 8 will have the dose of ABI-009 withheld. If the toxicity resolves to ANC ≥ 750/mm^3 by Day 11, the Day 8 dose of ABI-009 may be given. • If the toxicity does not resolve to ANC ≥ 750/mm^3 by Day 11, the Day 8 dose of ABI-009 will be omitted and this will be considered a DLT. Patients should receive subsequent cycles of ABI-009 but at the next lower dose level or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • Patients who require that their Day 8 dose of ABI-009 be omitted for Grade 4 neutropenia after one dose reduction (if starting at DL -1) or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued.
Other neutropenia DLTs per Section 5.5.2 on Day 8	• As above in Grade 4 neutropenia.

Non-Hematological Toxicity on Day 8	**Action**
Grade 1-2	• Continue protocol therapy.
Grade 3-4	• Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 8 dose (with the exception of the DLT exclusions in Section 5.5.1.1) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 8, the dose of ABI-009 may be given but at the next lower dose level. • Patients who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug on Day 8 prior to dosing (with the exception of the DLT exclusions in Section 5.5.1.1) will have their dose of ABI-009 withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤ Grade 2 (if not part of eligibility criteria) by Day 11, the Day 8 dose of ABI-009 may be given but at the next lower dose level. If the toxicity does not resolve by Day 11, the Day 8 dose of ABI-009 will be omitted. Patients should receive subsequent cycles of ABI-009 but with dose modifications according to Section 6.2 and Section 6.3.

6.2 Dose Modification Guidelines for Cycle 1

Hematological Toxicity: Thrombocytopenia	**Action**
Thrombocytopenia DLTs per Section 5.5.2	• Patients who have dose-limiting thrombocytopenia as defined in Section 5.5.2 should receive subsequent cycles at the next lower dose level of ABI-009; if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • Patients who experience dose-limiting thrombocytopenia after one dose reduction (if starting at DL -1) or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • Patients who require that their Day 8 dose of ABI-009 be omitted for platelets < 50,000/mm^3 (Section 6.1) after one dose reduction (if starting at DL -1) or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued.

Hematological Toxicity: Neutropenia	**Action**

Neutropenia DLTs per Section 5.5.2	• Patients who have dose-limiting neutropenia as defined in Section 5.5.2 with no other dose-limiting toxicity should receive the same dose of ABI-009 in the next cycle with myeloid growth factor support administered the next day after the Day 8 dose of ABI-009 is given during subsequent cycles (See Section 7.4). [Note: Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy (See Section 7.4).] • If dose-limiting neutropenia recurs after myeloid growth factor is added, then the patient should be given the next lower dose level of ABI-009 followed by myeloid growth factor support beginning the next day after the Day 8 dose of ABI-009 is given for subsequent cycles (See Section 7.4). • Patients who experience dose-limiting neutropenia after the addition of myeloid growth factor and one dose reduction of ABI-009 must be removed from protocol therapy. • Patients who experience early dose-limiting neutropenia requiring the omission of the Day 8 dose of ABI-009 (as defined in Section 6.1) should receive subsequent cycles of protocol therapy but at the next lower dose level of ABI-009 or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • Patients who require that their Day 8 dose of ABI-009 be omitted for Grade 4 neutropenia after one dose reduction (if starting at DL -1) or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued.

Other Hematological Toxicity	**Action**
Other hematologic DLTs per Section 5.5.2	• 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.

Non-Hematological Toxicity	**Action**

Non-hematological DLTs per Section 5.5.1	• 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 but should receive subsequent doses at the next lower dose level of ABI-009. • If any non-hematological dose-limiting toxicity recurs after one dose reduction of ABI-009, the patient must be removed from protocol therapy. • Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.3 Dose Modification Guidelines for Cycle 2 or greater

Hematological Toxicity: Thrombocytopenia	**Action**
Platelets ≥ 75,000/mm^3	• Continue protocol therapy.
Platelets < 75,000/mm^3	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.
Platelets < 50,000/mm^3	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.
Other thrombocytopenia DLTs per Section 5.5.2 on Day 8	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.

Hematological Toxicity: Neutropenia	**Action**
Grade 1-3	• Continue protocol therapy.
Grade 4	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.
Other neutropenia DLTs per Section 5.5.2 on Day 8	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.

Non-Hematological Toxicity	Action
Grade 1-2	• Continue protocol therapy.
Grade 3-4	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose.

Non-Hematological Toxicity	Action
Non-hematological DLTs per Section 5.5.1	• ABI-009 as per Section 6.1 & Section 6.2. • Irinotecan & temozolomide will be continued at full dose. • Patients who experience dose-limiting non-hematological dose-limiting toxicity after one dose reduction (if starting at DL -1) or if the patient is being treated on the lowest dose level, protocol therapy should be discontinued. • Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.4 Dose Modifications for Elevated Fasting Triglycerides

The following guidelines should be used for patients who develop elevated fasting triglycerides.
Continue irinotecan and temozolomide at full dose for cycles 2 or greater.

Grade	Action
Grade 2	• Continue ABI-009; if triglycerides are between 301 and 400 mg/dL consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants. HMG-CoA reductase inhibitor is recommended if triglycerides are between 401 and 500 mg/dL
Grade 3-4	• Hold ABI-009 until recovery to ≤ Grade 2 • An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants • Upon retreatment at the same dose level, if Grade 3 or 4 toxicity recurs, lipid lowering medication should be adjusted in consultation with institutional hyperlipidemia consultants. ABI-009 should be held until recovery to ≤ Grade 2. • Upon retreatment with ABI-009 concurrent with an HMG-CoA reductase inhibitor, if Grade 3 or 4 elevations recur, ABI-009 should be held until recovery to ≤ Grade 2. Further lipid lowering

	medication options should be discussed with institutional hyperlipidemia consultants. Upon recovery to ≤ Grade 2, ABI-009 should be restarted at the next lower dose level. If the patient is being treated on the lowest dose level, protocol therapy should be discontinued.

6.5 Dose Modifications for Elevated Fasting Cholesterol

The following guidelines should be used for patients who develop elevated fasting cholesterol.

Continue irinotecan and temozolomide at full dose for cycles 2 or greater.

Grade	Action
Grade 2	• Continue ABI-009; consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants.
Grade 3	• An HMG-CoA reductase inhibitor should be started, and dosages adjusted based upon recommendations of institutional hyperlipidemia consultants. • It is expected that optimal effects of the lipid lowering medication will be observed 2-4 weeks after its initiation. Treatment with ABI-009 is to be restarted at the same dose level when recovery of hypercholesterolemia to ≤ Grade 2 is observed.
Grade 4	• Hold ABI-009. • An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants. • It is expected that optimal effect of the lipid lowering medication will be observed 2-4 weeks after initiation. ABI-009 is to be restarted at the same dose level when recovery to ≤ Grade 2 cholesterol is observed. • Upon retreatment with ABI-009 concurrent with an HMG-CoA reductase inhibitor, if Grade 4 elevations recur, ABI-009 should be held until recovery to ≤ Grade 3. Further lipid lowering medication options should be discussed with institutional hyperlipidemia consultants. Upon recovery to ≤ Grade 3 cholesterol, ABI-009 should be restarted at the next lower dose level. If the patient is being treated on the lowest dose level, protocol therapy should be discontinued.

6.6 Dose Modifications for Hyperglycemia

The following guidelines should be used for patients who develop hyperglycemia based on fasting glucose levels.

Grade	Action
Grade 1-2	• Continue ABI-009. Grade 2 may initiate oral antiglycemic agent*.
Grade 3	• Initiate insulin therapy as indicated. • Hold ABI-009 until fasting serum glucose is consistently ≤ 250

	mg/dL or ≤ 13.9 mmol. • Resume ABI-009 at same dose IF patient is asymptomatic, AND fasting serum glucose is consistently ≤ 250 mg/dL or ≤ 13.9 mmol) without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ABI-009. • If the fasting serum glucose value of ≥ 250 – 500 mg/dL or > 13.9 – 27.8 mmol/L recurs and does not return to a fasting value ≤ 250 mg/dL or ≤ 13.9 mmol/L despite a stable dose of insulin and an oral diabetic agent Insulin and anoral diabetic agents should be tried before declaring a patient's hyperglycemia refractory to therapy. If the fasting serum glucose value of ≥ 250 mg/dL or > 13.9 mmol/L recurs and does not return to a fasting value ≤ 250 mg/dL or ≤ 13.9 mmol/L despite the use of insulin and an oral diabetic agent, subsequent doses of ABI-009 should be decreased to the next lower dose level. • If a patient experiences recurrence of a fasting serum glucose ≥ 250 mg/dL or > 13.9 mmol/L which does not return to ≤ 250 mg/dL or ≤ 13.9 mmol despite insulin, an oral diabetic agent AND the dose reduction, patient should be taken off protocol therapy. If the patient was already being treated at the lowest dose level, or if hyperglycemia > 250 mg/dL or > 13.9 mmol/L has recurred despite reduction of ABI-009 to the lowest dose level, the patient should be taken off protocol therapy.
Grade 4	• Hold ABI-009 until resolution to fasting serum glucose is consistently ≤ 250 mg/dL or ≤ 13.9 mmol. • Resume ABI-009 with one dose level reduction IF patient is asymptomatic AND serum glucose is consistently consistently ≤ 250 mg/dL or ≤ 13.9 mmol without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving ABI-009. • If Grade 4 hyperglycemia recurs and does not return to consistently ≤ 250 mg/dL or ≤ 13.9 mmol (despite a stable dose of insulin, an oral diabetic agent, and dose reduction to the next lower dose level, then subsequent doses of ABI-009 should be reduced again so that the new dose is two dose levels below the patient's starting dose. If the patient was already being treated at the lowest dose level, or if the fasting serum glucose is > 250 mg/dL or > 13.9 mmol has recurred despite reduction of ABI-009 to the lowest dose level, the patient should be taken off protocol therapy.

***Recommended guidelines for use of oral diabetic agents:**
Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist at the local institution. Metformin or other oral anti-hyperglycemia agent may be used per local endocrinologist's recommendations. Insulin therapy should be directed by specialists in pediatric diabetes, with the goal of normal fasting blood sugars < 126 mg/dL and HgbA1C < 8%.

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.

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 (except aprepitant), fluids, electrolytes and general supportive care are to be used as necessary. See Appendix VIII for information on management of irinotecan-induced diarrhea. See Appendix X, Appendix XIII, and Appendix XIV for drugs that should not be used concomitantly due to potential interactions with ABI-009, irinotecan, or temozolomide.

Please refer to COG Supportive Care Guidelines found under the Protocol Reference Materials tab under Standard Sections for Protocols at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines.

7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered in accordance with Section 6.2 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications (Study Specific)

a. HMG-CoA reductase inhibitors may be used to treat elevated fasting triglycerides and cholesterol. See Section 6.4 and Section 6.5.

While on study, the following BCRP inhibitors (cyclosporine, eltrombopag, gefitinib) should be avoided if possible, and concomitant use of UGT1A1 inhibitors, such as diclofenac, ketoconazole, probenecid, silibinin, nilotinib and atazanavir, should be avoided because of potential for increased irinotecan toxicity.

Because rapamycin is a substrate for both CYP3A4 and P-gp, concomitant administration with inhibitors or inducers of CYP3A4 and P-gp may alter the pharmacokinetics of ABI-009. Inhibitors of CYP3A4 may decrease the metabolism of rapamycin and increase rapamycin concentrations, while inducers of CYP3A4 may increase the metabolism of rapamycin and decrease rapamycin concentrations. Drugs that may increase rapamycin blood concentrations include antifungal agents (e.g., voriconazole, itraconazole, posaconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), and other drugs (e.g., HIV-protease inhibitors). Drugs that may decrease rapamycin concentrations include anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin), and antibiotics (e.g., rifabutin, rifampin). See Appendix XIV for more information on CYP3A4 inducers and inhibitors.

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. 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	Cycles 1 & 2	Prior to Subsequent Cycles^
History	X	Weekly	X
Physical Exam with vital signs	X	Weekly	X
Height, weight, BSA	X	Prior to Cycle 2	X
Performance Status	X	Prior to Cycle 2	X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	Weekly[4]
Pharmacokinetics[1]	X	X	
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4^{3-}, Mg^{++}, glucose[11]	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Albumin	X	Prior to Cycle 2	X
INR	X		
Total Cholesterol, Triglycerides[10]	X	Weekly	X
Amylase, Lipase	X	Prior to Cycle 2	X
Pregnancy Test[2]	X		
Tumor Disease Evaluation	X	End of Cycles 1[12] & 2	Every other cycle x 2 then q 3 cycles[5]
Bone Marrow Evaluation[7]	X		
Medication Diary[6]		Cycle 2	X
Oxygen Saturation	X	Weekly	X[8]
Tumor Tissue Studies[9]	X		

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

1 See Section 8.3 for timing of PK studies.

2 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.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every 2-3 days until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

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

5 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. 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] Medication diary (see Appendix IX) should be reviewed after completion of each treatment cycle and uploaded into RAVE.

[7] As appropriate for disease, to confirm bone marrow involvement at enrollment, or as clinically indicated.

[8] Required prior to each cycle; weekly for subsequent cycles only if clinically indicated.

[9] See Section 8.4 and Appendix XII for details of Tumor Tissue studies.

[10] If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading.

[11] If the initial blood glucose is a random sample that is outside of the normal limits, then follow-up fasting blood glucose can be obtained and must be within the upper normal limits for age. If blood glucose is ≥ 250 – 500 mg/dL or > 13.9 – 27.8 mmol/L when routine (non-fasting) laboratory studies are performed, the test should be repeated within 3 days in the fasting state to permit accurate grading.

[12] Patients experiencing progressive disease (defined in Section 12.6.4) in Cycle 1 can continue to Cycle 2 as long as 1) they have not experienced a DLT in Cycle 1, 2) they have not met any off study criteria listed in section 10.2, and 3) they meet all guidelines established in section 5.2. Patients must have at least stable disease to continue to Cycles 3 and later.

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 CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1514) and date and shipped to Syed Aamer at the address below:

8.3 Pharmacology (required)

8.3.1 Description of Studies and Assay

- ABI-009 concentrations will be determined by a validated LC/MS/MS method (AADi).
- Irinotecan and SN-38 concentrations will be determined using a validated HPLC assay with fluorescence detection (Dr. Joel Reid/Mayo Clinic).

8.3.2 Sampling Schedule (See Appendix XI-A and Appendix XI-B)
Whole blood samples (2 ml) will be obtained prior to drug administration and at the following time points:

8.3.2.1 ABI-009 Sampling Schedule during Cycle 1 (Single Agent) and Cycle 2 (Combination Therapy):

- Day 1: Pre-dose, end of infusion, and then 1, 2, 4, and 8 hrs after beginning of infusion.
- Day 2: 24 hours post-Day 1 ABI-009 dose.
- Day 4 (± 1 day): 72 hours (± 24 hours) post- Day 1 ABI-009 dose
- Day 8: Pre-ABI-009 dose.

8.3.2.2 Irinotecan/SN-38 Sampling Schedule during Cycle 2 (Combination Therapy):

- Day 1: Pre-dose, and then 10 min, 1 hr, 3 hrs, and 6 hrs post-irinotecan dose.
- Day 2: Pre-Day 2 irinotecan dose (24 hours after Day 1 irinotecan dose).

8.3.3 Sample Collection and Handling Instructions

8.3.3.1 ABI-009
Blood samples (2 ml) will be collected in EDTA tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the infusion is started and stopped.
If the duration of infusion is changed, the sample should be collected immediately before termination of the infusion.

8.3.3.2 Irinotecan
Blood samples (2 ml) will be collected in heparinized tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.3.4 Sample Processing

8.3.4.1 ABI-009

- After drawing blood into EDTA tubes, gently mix by inversion 8-10 times.
- Keep on wet ice until frozen; freeze as soon as possible.
- Samples can be placed on dry ice for short-term storage; however, must be placed in the appropriate freezer within 24 hours of the draw-time (storage in -80 °C is preferred; storage at -20 °C for no more than 60 days is acceptable).

8.3.4.2 Irinotecan

Blood collected into sodium heparin tubes should be gently mixed by immediately inverting the tubes. Blood samples will then be centrifuged immediately for 15 minutes in a refrigerated centrifuge set at 805 g. Next, remove the plasma using a transfer pipette and transfer the plasma into two separate 3.5 mL polypropylene tubes. Next, immediately freeze the tubes at -80 °C and store until delivery to the Mayo Clinic (see Section 8.3.6 for shipping instructions).

8.3.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and exact time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions

8.3.6.1 ABI-009

Samples should be batched per patient and shipped frozen on dry ice in opaque containers at the end of Cycle 2.

Samples should be shipped using FedEx priority overnight to:

AIT Bioscience
Attn: Sample Receipt
7840 Innovation Blvd.
Indianapolis, IN 46278

On the day of each shipment, notify samples@aitbioscience.com of the pending shipment, including tracking information.

8.3.6.2 Irinotecan

Samples will be held until all samples have been obtained and then sent as a single batch. Batched samples should be sent frozen on dry ice by FedEx priority overnight to:

[redacted]

A copy of the irinotecan pharmacokinetics specimen transmittal form should accompany the shipment and another copy should be faxed to 507-293-0107. Samples should only be shipped on a Monday-Thursday to allow for weekday delivery. Avoid holiday shipments. Email [redacted] ([redacted]) with the tracking number at the time of sample shipment.

8.4 **Tissue Studies (required)**

The key objective of the tumor molecular profiling is to identify specific markers related to the mTOR pathway that may be predictive of response to ABI-009.
Archival tumor tissue (or unstained tissue slides) should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.4.1 Description of Studies

8.4.1.1 Study of S6K1

Tumor tissue will be analyzed by immunohistochemistry. Antibody to be used for pS6(S235) is obtained from Cell Signaling, Catalog #2211S.

8.4.1.2 Study of 4E-BP1

Tumor tissue will be analyzed by immunohistochemistry. Antibody to be used for p4EBP1 is obtained from Cell Signaling, Catalog #2855S.

8.4.2 Sample Collection, Handling, and Shipment

Paraffin-embedded tissue blocks or slides will be shipped to the Histopathology Core of the Brigham and Women's Hospital. If sending tissue slides, it is preferred that 8-10 unstained slides (minimum: 6) are being sent. Detailed instructions regarding collection, handling, and shipping of tissue samples are located in the Tissue Study Form (Appendix XII).

8.4.2.1 Tumor Block Instructions

- Paraffin-embedded tumor specimens must be packaged appropriately and shipped at room temperature in the tumor block bags provided.
- Ensure that the specimen is labeled with the subject ID, both on the block and on the block bag.

8.4.2.2 Tumor Slides Instructions

- Cut 8-10 (minimum: 6) tissue sections 4-5 microns thick and mount on positively charged slides.
- Number sequentially; write the subject ID and original block ID on frosted end of slide.
- Place the slides in the pre-labeled slide holders provided and write the subject ID on the label.

All samples must be shipped under ambient conditions, Monday – Thursday ONLY with a corresponding pathology report containing the subject ID and the block ID. Ensure to de-identify the pathology report.

Before shipping, a "Work Request for Processing, Sectioning & Staining" and a "Work Request for Standardized Immunohistochemistry Services" must be submitted online at http://pathcore.hms.harvard.edu. Please follow the instructions posted on the protocol page of the COG website.

Samples should be shipped to:

Specialized Histopathology Core
Brigham and Women's Hospital
20 Shattuck Street
Thorn Building, Rm 603C
Boston, MA 02115
[redacted]

Please contact phase1@childrensoncologygroup.org or the COG study-specific research coordinator with protocol or work order related questions.

8.4.3 Sample Labeling

Each sample must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was taken. Data should be recorded on the Tissue Study Form, which must accompany the sample(s).

9.0 AGENT INFORMATION

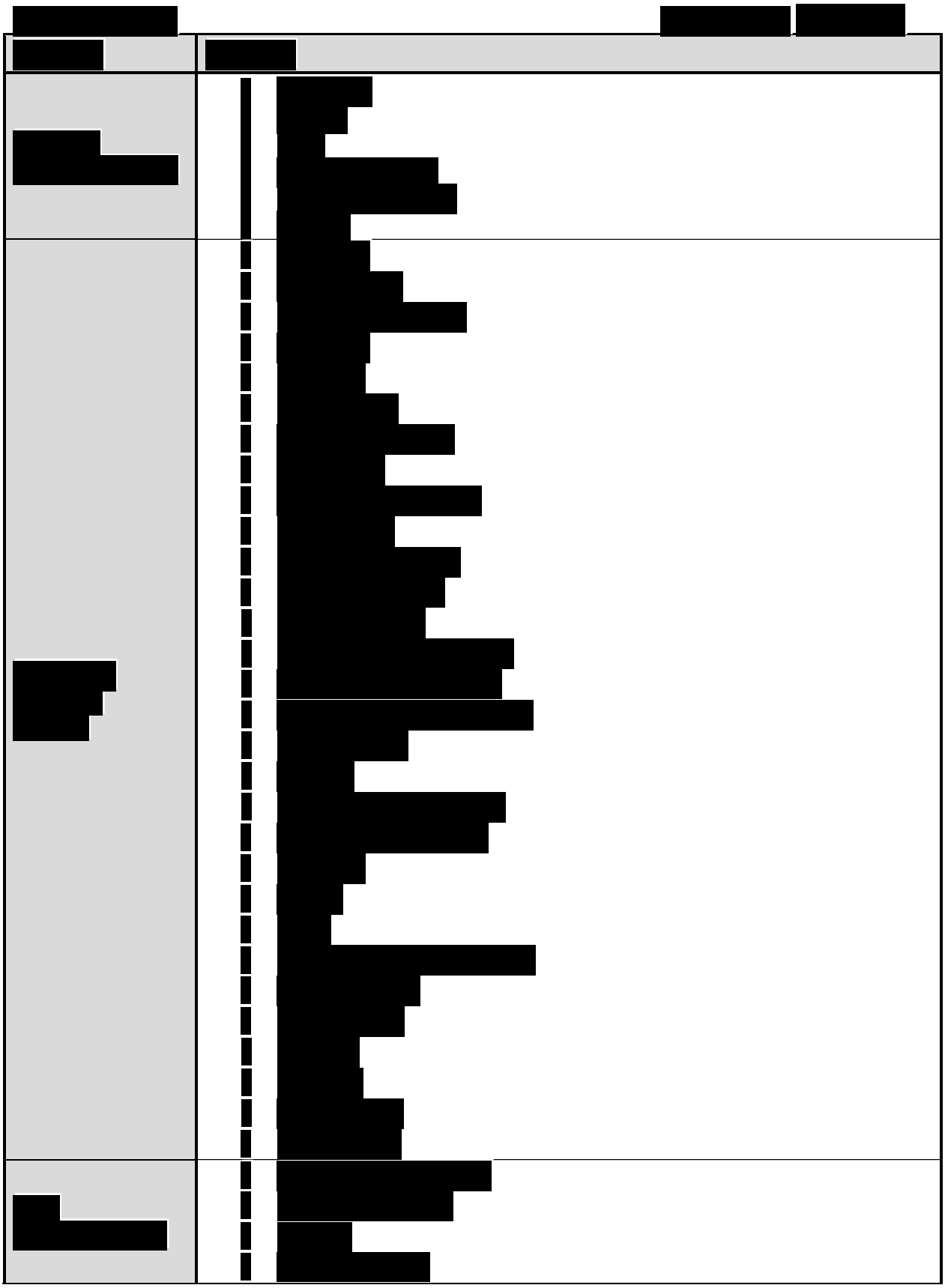
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

[redacted]

9.2 **CEFIXIME**
(Suprax®) NSC# NA (11/17/17)

9.2.1 Source and Pharmacology

Cefixime is a third generation cephalosporin antibiotic for oral administration that inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins and interfering with the final transpeptidation step of peptidoglycan synthesis. Its spectrum of activity is similar to other third-generation agents, including Enterobacteriaceae, and β-lactamase producing *H. influenzae* and *N. gonorreae*, and *Staph. aureus.* When taken orally, it is about 40%-50% absorbed whether administered with or without food. The area under the time versus concentration curve is greater by approximately 10%-25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Cefixime serum half-life is approximately 3-4 hours. It is excreted primarily by the kidney. There is no evidence of metabolism of cefixime *in vivo*.

9.2.2 Toxicity

Incidence	**Toxicities**
Common (>20% of patients)	*None known*
Occasional (4-20% of patients)	Diarrhea, nausea, flatulence, loose or frequent stools

Incidence	Toxicities
Rare (≤3% of patients)	Erythema multiforme, pruritus, rash maculo-papular, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, angioedema, abdominal pain, pseudomembranous colitis, dyspepsia; transient white blood cell decrease, neutrophil count decreased, platelet count decreased; transient jaundice, alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin increased; anaphylaxis, allergic reaction; dizziness, headache, seizure, acute kidney injury, creatinine increased, vaginal infection, vomiting.
Pregnancy & Lactation	**Pregnancy Category B** Teratogenic effects were not observed in animal reproduction studies. Cefixime crosses the placenta and can be detected in the amniotic fluid. There are no well-controlled studies of cefixime in pregnant women; effects of cefixime on the fetus are unknown. An increase in most types of birth defects was not found following first trimester exposure to cephalosporins. It is not known whether cefixime is excreted in human milk.

9.2.3 Formulation and Stability

Cefixime is available in scored 400 mg film coated tablets, 400 mg capsules, 100 mg chewable tablets, and 200 mg chewable tablets. The chewable tablets are tutti-frutti flavor and contain aspartame and fd&c red #40 aluminum lake. Cefixime is also available in two strengths as a powder for oral suspension, which when reconstituted, provides either a 100 mg/5mL or 200 mg/5 mL suspension. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum. After reconstitution, suspension may be stored for 14 days at room temperature or under refrigeration.

Cefixime tablets and powder for oral suspension are stored at 20 - 25°C (68 - 77°F). Do not freeze. The suspension bottle should be kept tightly closed.

9.2.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Cefixime may be administered with or without food. Administration with food may decrease abdominal distress. Shake the suspension prior to withdrawing dose or administration.

9.2.5 Supplier

Commercially available from various manufacturers. See package insert for further information

9.3 IRINOTECAN

[CPT-11,Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348 (03/07/17)

9.3.1 Source and Pharmacology

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

9.3.2 Toxicity

Incidence	Toxicities
Common (> 20% of patients)	• Anemia • Thrombocytopenia • Neutrophil count decreased • White blood cell count decreased • Nausea • Vomiting • Constipation • Anorexia • Fever • Asthenia • Cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and diarrhea) • Alopecia • Bilirubin increased • Mucositis • Dyspnea • Cough • Weight loss • Pain
Occasional (4-20% of patients)	• Abdominal fullness • Flatulence • Vasodilation • Hypotension • Dehydration • Edema • AST increased • Alkaline phosphatase increased • Ascites • Jaundice • Febrile neutropenia • Infection • Headache • Dizziness • Chills • Insomnia • Rash • Dyspepsia • Somnolence • Thromboembolic events • Pneumonia
Rare (≤ 3% of patients)	• Anaphylaxis • Bradycardia • Disorientation/confusion • Colitis • Renal failure (secondary to severe dehydration)

	• Ileus • Pancreatitis • Pneumonitis (L)
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.

(L) Toxicity may also occur later

9.3.3 Formulation & Stability

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

9.3.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

For oral use, the appropriate volume of irinotecan solution (20 mg/ml) is drawn up undiluted into a plastic oral syringe. Each dose is to be mixed with juice (crangrape, cranapple, cranberry, or other "cran" juice or juice cocktail) **immediately** before administration. The oral syringes containing undiluted irinotecan are stable for 21 days when stored in a refrigerator. Irinotecan has a very unpleasant flavor, therefore, the juice will be used to mask the drug taste (See Appendix VI). See protocol for pre-medication and supportive care measures.

9.3.5 Supplier

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

9.4 TEMOZOLOMIDE - ORAL

(Temodar®, Temodal®) NSC #362856 (06/26/18)

9.4.1 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 N^7-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.

9.4.2 Toxicity

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
Pregnancy & Lactation	**Pregnancy Category D** 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.

9.4.3 Formulation and Stability

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

9.4.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

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

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

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

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10 mg/mL suspension triturate the contents of ten 100 mg capsules (1000 mg), 500 mg povidone K-30 and 25 mg anhydrous citric acid dissolved in 1.5 mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100 mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension should be stored in the refrigerator at 2°-8°C (36-46°F) for no more than 2 weeks after preparation. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension.[35]

Alternatively, the capsules can be opened and mixed with apple sauce or juice, which should be used immediately after mixing or must be used in 2 hours after mixing (See Appendix V).

9.4.5 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 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 35 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 ABI-009 (See 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 required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) Patient did not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

A minimum of 4 patients will be enrolled in this study if the first two patients develop DLTs at DL1 and DL-1. The projected maximum number of evaluable patients is 24. This includes 6 evaluable patients at each of DL 1-3 and 6 additional evaluable patients in a PK expansion cohort. Therefore, the projected maximum number of patients enrolled into this study allowing for 20% inevaluability is 29, and this number is expected to be accrued over 15-29 months. The study design includes several contingencies that may increase the maximum sample size if all contingencies are needed to estimate the MTD. A maximum of 51 patients may be possible in the unlikely scenario that all dose levels require expansion to 12 patients plus 6 additional patients for pharmacokinetic analysis and a 20% inevaluable rate. The maximum sample size of 51 patients could accrue over 26-51 months.

11.1.1 Amendment #4

The projected maximum number of additional (i.e., in addition to the 18 already enrolled) evaluable patients required to complete the study with this amendment is 12. This includes 6 evaluable patients at DL -2 and 6 additional evaluable patients in a PK expansion cohort. Therefore, the projected maximum number of additional patients enrolled into the study allowing for 30% inevaluability is 18, and this number is expected to be accrued over 9-18 months. The overall study will have an expected maximum of 36 patients.

The study design includes several contingencies that may increase the maximum sample size if all contingencies are needed to estimate the MTD. A maximum of 26 additional patients may be possible in the unlikely scenario that DL-2 requires expansion to 12 patients plus 6 additional patients for pharmacokinetic analysis and a 30% inevaluable rate. The maximum sample size of 26 additional patients could accrue over an additional 13-26 months. The overall study will have an absolute maximum enrollment of 44 patients.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

Any patient who receives at least one dose of the study drug(s) or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycles 1 and 2, patients must receive at least 85% of the prescribed dose of protocol therapy per protocol guidelines in Cycle 1 and 85% of the prescribed dose of protocol therapy in Cycle 2, and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience a DLT (See Section 5.5) during Cycles 1 and 2 of therapy.

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

  - 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

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

- 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

The rolling six phase 1 trial design will be used for the conduct of this study[36]. Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	**# Pts with DLT**	**# Pts without DLT**	**# Pts with Data Pending**	***Decision***
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend

6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

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).

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

11.3.1 Amendment #4

Patients will be enrolled at DL -2 using the rolling 6 study design. If DL -2 is determined to be safe (at most 1 out of 6 evaluable patients with DLT), then up to 6 more patients will be enrolled at DL -2 in a PK expansion cohort. If DL -2 is determined to not be tolerable (2 or more dose limited patients out of 6 evaluable patients), the study will be closed to accrual.

11.4 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.

The gender and minority distribution of the study population is projected to be[1]:

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	0	0	**2**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	4	0	0	**6**
White	9	14	4	1	**28**
More Than One Race	0	0	0	0	**0**
Total	**12**	**19**	**4**	**1**	**36**

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11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of ABI-009 as a single agent and in combination with temozolomide and irinotecan 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 ABI-009, 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, and will be reported descriptively.

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

[1]These distributions are based on historical Phase 1 enrollments.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the current CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

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 on the next consecutive cycle 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).[37] 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 must show definitive evidence of progression to be considered evaluable.

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 Response Assessment

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-	No	SD	documented at least once ≥ 28 days from baseline

	PD/not evaluated			
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.

** 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: 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

12.2.6 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 12.8 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 12.8 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

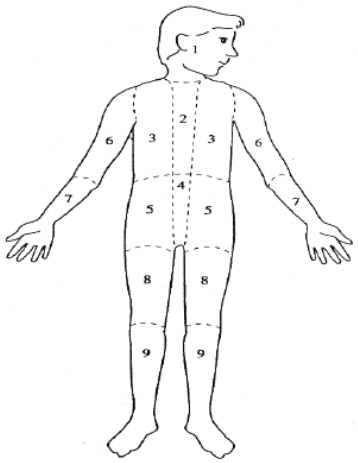
scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

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 Response Assessment

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

12.4.5 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 from the sequence of the overall response assessments as described in Table 3 in Section 12.8.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.5.2 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 Section 12.8.

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 12.8 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. 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

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 Case Report Forms 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 5.0. The descriptions and grading scales found in the CTCAE version 5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ ctc.htm**.**).

Step 2: Grade the adverse event using the NCI CTCAE version 5.0.

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 **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 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 below under the section entitled "Additional Instructions or Exceptions."

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 version 5.0 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
GASTROINTESTINAL DISORDERS	Constipation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
INFECTIONS AND INFESTATIONS	Mucosal inflammation
INFECTIONS AND INFESTATIONS	Thrush
INFECTIONS AND INFESTATIONS	Infection
INVESTIGATIONS	Weight loss
INVESTIGATIONS	Aspartate aminotransferase increased
METABOLISM AND NUTRITION DISORDERS	Hypokalemia
METABOLISM AND NUTRITION DISORDERS	Hypophosphatemia

METABOLISM AND NUTRITION DISORDERS	Hypertriglyceridemia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash/desquamation

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 (email the ADVL1514 COG Study Assigned Research Coordinator 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 https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited 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 https://ctepcore.nci.nih.gov/ctepaers. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Email supporting documentation to the ADVL1514 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 case report 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 or equal to 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 CRF 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

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients following their chemotherapy for cancer must be reported to the NCI Cancer Therapy Evaluation Program (CTEP) via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

Secondary Malignancy:

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A 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:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) 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, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1514 COG Study Assigned Research Coordinator along with any additional medical information (Appendix III). 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 Grade 3 "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. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

13.7.2 Fetal Death

- Pregnancy loss is defined in CTCAE version 5.0 as "Death in utero."

- Any pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognized any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE version 5.0 as "Newborn deaths occurring during the first 28 days after birth" 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 "Death neonatal" under the "general disorders and administration" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study.

- 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.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

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 case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 Access to Rave for Data Submission/Data Reporting

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the COG or PEP-CTN roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/
or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com, or by email to the COG Study Assigned Data Manager.

14.3 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If this study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If this study has been assigned to CDUS-abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CTEP-AERS.
This is not a responsibility of institutions participating in this trial.

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 PEP-CTN 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 PEP-CTN 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 COG PEP-CTN 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: CORRELATIVE STUDIES GUIDE

Correlative Study	Appendix	Sample Volume		Tube Type
		Volume per sample	Total Cycle 1 and Cycle 2	
Pharmacokinetic Study (PK)	XI-A and XI-B	2 ml	48 ml	Preservative-free heparin (green top)
Tumor Tissue (Required) *See Section 8.4 for details*	XII	-	-	-
Total Blood Volume			**48 ml**	

APPENDIX III: 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:	Frequency:	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 initial reporting email both the Pregnancy CTEP-AERS Report and this additional Pregnancy Information Form to the ADVL1514 COG Study Assigned Research Coordinator. For follow-up reporting, email only this Pregnancy Information Form to the ADVL1514 COG Study Assigned Research Coordinator (See Section 13.7).

APPENDIX IV: TEMOZOLOMIDE DOSING NOMOGRAM FOR TEMOZOLOMIDE 125 MG/M^2/DOSE

Temozolomide dose assignment: 125 mg/m^2

BSA (m^2)	Administered daily dose (mg)
0.2-0.49*	4.17 mg/kg*
0.50-0.53	65
0.54-0.59	70
0.60-0.65	80
0.66-0.69	85
0.70-0.75	90
0.76-0.81	100
0.82-0.85	105
0.86-0.91	110
0.92-0.97	120
0.98-1.01	125
1.02-1.07	130
1.08-1.15	140
1.16-1.23	150
1.24-1.31	160
1.32-1.39	170
1.40-1.47	180
1.48-1.55	190
1.56-1.67	200
1.68-1.83	220
1.84-1.95	240
1.96-2.00	250
> 2.0	250

*Dosing for patients with BSA <0.5 m^2 is by mg/kg, rounded to the nearest 5 mg

APPENDIX V: INSTRUCTIONS FOR TEMOZOLOMIDE PREPARATION, ADMINISTRATION AND SAFE HANDLING FOR PATIENTS WHO ARE UNABLE TO SWALLOW CAPSULES

Patient Name: _____ Cycle#: _____ Date Range: _____

Temozolomide is an oral medicine for the treatment of cancer. This information sheet will help you prepare, administer, store, and dispose of the medicine. Please read the information before preparing and giving the medicine. If you have any questions, please contact:_____

WHAT DO I NEED?

Your Temozolomide dose is: _____mg
You should use the following number of capsules for each dose:

Number of temozolomide capsules per dose					
5 mg	**20 mg**	**100 mg**	**140 mg**	**180 mg**	**250 mg**

Give each dose by mouth one time each morning for 5 days in a row
You should take the temozolomide on the following days:_____

Supplies:
Temozolomide capsules (see the table above)
Disposable pad or paper towels
Disposable gloves and mask and a pair of goggles (eye protection)
Disposable cup and disposable spoon
A container to collect waste (zip top plastic bag or medical waste bag or container)
A small amount of applesauce or apple juice
- Two teaspoons (10 mL) should be enough. A single-serving container of applesauce may be used, but the patient must be able to eat the entire contents of the container to ensure the full dose is taken.
- Food should be cool or close to room temperature when administered; do not use hot or boiling food

HOW DO I STORE THE MEDICINE AND WASTE?

Store the medication in the original bottle away from food and out of the reach of children or pets. Store the waste container out of the reach of children or pets. Return the container to the clinic during your next visit.

WHAT SAFETY MEASURES SHOULD I TAKE?

If the medicine gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. If you spilled the medicine on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention if the skin becomes red, irritated, or if you are concerned. Call your doctor or nurse immediately at:_____
and/or contact the **Poison Center at 1-800-222-1222.**

HOW DO I PREPARE THE MEDICINE?

CAUTION: If you are pregnant, could become pregnant, or are breast-feeding, DO NOT prepare or administer this medicine.

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Wash your hands with soap and water; dry them well.
4. Put on disposable gloves, disposable mask, and a pair of goggles or eye protection.
5. Place a disposable pad or paper towel on the clean working space and place all supplies on the pad or paper towel.
6. Fill a cup with a small amount of apple juice or applesauce (or use pre-filled applesauce cup).
7. Open each capsule required for the daily dose over the cup with the apple juice or applesauce.
   - Hold one capsule over the center of the cup.
   - To open, pinch both ends of one capsule with gentle pressure. Slowly rotate one end in small, back and forth movements while holding the other end steady until the capsule sections begin to separate.
   - Gently separate the ends so the powder falls into the center of the food. Look inside each end of the capsule. Tap and shake each end of the capsule until all medicine powder is out of the capsule.
   - Repeat the steps above for each capsule needed.
8. The medicine will not dissolve completely if mixing in apple juice. Keep extra apple juice on hand to add to any remaining powder left at the bottom of the cup. If you need more apple juice or applesauce, remove your gloves before touching the main container. Wear new gloves before adding the additional apple juice or applesauce to the medicine to prevent contaminating the main container with any powder that may be on your gloves.
9. Give the medicine mixture to the patient immediately.

HOW DO I TAKE/GIVE THE MEDICINE?

- Take/give an anti-nausea medicine 30-60 minutes before the temozolomide only if instructed to do so by your doctor.
- Take/give temozolomide at around the same time each day with or without food.
- Take/give the temozolomide dose within 8 hours prior to receiving the study medicine, ABI-009. Temozolomide should be given 1 hour before irinotecan.
- When you are finished, place all used supplies in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- If the dose is vomited within 30 minutes, the dose should be repeated. If the dose is vomited more than 30 minutes after the dose, do not repeat the dose. If the patient is unable to take a dose, or a dose is accidentally missed, place the remaining medicine from this dose in the waste container, seal, and contact your doctor or nurse for instructions.

APPENDIX VI: PARENT GUIDELINES FOR ADMINISTRATION OF ORAL IRINOTECAN

- The hospital pharmacist will provide you with 5 doses of irinotecan, each in an oral syringe. Because irinotecan has an unpleasant taste, it is usually mixed with a small amount of juice **IMMEDIATELY BEFORE** giving the medicine to your child.

- The best juice to use is CranGrape Juice, although cranapple or cranberry juice or juice cocktail is fine as well.

- **DO NOT** mix the irinotecan in orange juice, apple juice, milk or soda.

- Use a disposable cup to mix the irinotecan with juice. The amount of juice used is up to you. The more juice used, the more the flavor of the irinotecan will be masked. However, it is critical that your child drink **ALL** of the juice mixed with irinotecan. Most parents start by mixing the irinotecan in about one teaspoon (5 ml) of juice. Discard the cup when empty after the irinotecan + juice has been taken.

- Irinotecan should be mixed with juice only on the day the dose is given. The other doses should be stored in a **REFRIGERATOR**. Irinotecan will last for 21 days at a time, provided it has not been mixed with juice.

- Irinotecan is taken 1 hour after temozolomide.

- Use of nausea medicines (Zofran, Kytril, or Anzemet) may be helpful, and these medicines are best given about 30-60 minutes before the irinotecan. Please discuss this with your doctor.

If your child is unable to take the medicine, or vomits within 30 minutes of taking the medicine, please call your doctor for further instructions.

APPENDIX VII: INSTRUCTIONS FOR IRINOTECAN PREPARATION, ADMINISTRATION AND SAFE HANDLING

Patient Name: _____ Cycle#: _____ Date Range: _____

Irinotecan is a chemo drug that requires safe handling. This information sheet will help you safely prepare, administer, and dispose of the drug. Please read the information before preparing and taking the drug. If you have any questions, please contact:

_____

WHAT DO I NEED?

Your dose is: Irinotecan _____ mg

- Take each dose by mouth once time each day for 5 days in a row.
- You should take the irinotecan on the following days:_____
- Take the dose within 8 hours prior to the study drug ABI-009

Supplies:

- Irinotecan syringe(s) from your pharmacy
- Disposable pad or paper towels
- Disposable gloves and mask
- Oral syringe, medicine cup, or measuring spoon
- Disposable cup for mixing drug with juice
- Disposable spoon or straw to stir the mixture
- A container to collect waste (zip-top plastic bag or medical waste bag or container)
- One of the juices below:
  - Cran-Grape or Cran-Apple juice
  - Cranberry juice
  - Cranberry juice cocktail

  ***DO NOT* use orange juice, apple juice, grapefruit juice, milk, or soda.**

HOW DO I STORE THE DRUG SYRINGES?

Store the medication in syringes in the refrigerator away from food and out of the reach of children or pets.

WHAT SAFETY MEASURES SHOULD I TAKE?

If the drug gets into eyes, hold eyelids open while flushing with water for at least 15 minutes. Call your doctor or nurse immediately at: _____ and/or contact the Poison Center at 1-800-222-1222.

If you spilled the drug on your skin, remove contaminated clothing. Wash area with soap and large amount of water. Seek medical attention (see contact information above) if the skin becomes red or irritated or if you are concerned.

HOW DO I PREPARE THE DRUG?

***Caution**: If you are pregnant, could become pregnant, or are breast-feeding, we suggest that you DO NOT prepare or administer this drug without FIRST checking with your health care provider.*

1. Choose a quiet working space away from food, windows, fans or heat ducts.
2. Clean the working space with damp paper towels.
3. Place a disposable pad or paper towel on the clean working space and place all needed items and drug on the pad or paper towel.
4. Wash your hands with soap and water; dry them well.
5. Put on disposable gloves and mask.
6. Fill a disposable cup with 5 mL (1 teaspoon) of juice. *Note: more juice can be used to improve the taste but you **must** make sure the entire dose is taken.*
7. Add the irinotecan to the cup by slowly squeezing the syringe in the cup. Be careful to do this slowly so the drug doesn't splash or spill.
8. Stir the mixture with the plastic spoon or straw.
9. Take/Give the mixture to the patient immediately.

HOW DO I TAKE/GIVE THE DRUG?

- Take/Give an anti-nausea medicine 30-60 minutes before irinotecan if instructed to do so by your doctor.
- Take/Give irinotecan 1 hour after temozolomide.
- Take/Give irinotecan at around the same time each day.
- Take/Give irinotecan on an empty stomach, at least one (1) hour after food. Do not eat for at least one (1) hour.
- When you are finished, place the dirty gloves, spoon, cup, and other tools used to mix the drug in a plastic zip top bag or the waste container that was provided to you by your doctor, nurse, or pharmacist.
- If the dose is vomited within 30 minutes, the patient is unable to take the dose, or the dose is accidentally missed, contact your doctor or nurse for instructions.

WHAT SHOULD I DO WITH LEFTOVER DRUG AND USED SUPPLIES?

If the patient could not take the dose or part of the dose, first place the remaining drug from this dose in the waste container and seal. Then call your doctor or nurse to let them know that some of the dose was missed. Store the waste container out of the reach of children or pets. Return the waste container to the clinic at the next visit.

APPENDIX VIII: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for loperamide to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight.

Early diarrhea
Early onset diarrhea associated with irinotecan is usually preceded by sweating and abdominal cramping. Patients who have the onset of these symptoms followed by diarrhea within several hours after taking irinotecan should contact the treating physician immediately. The treating physician may consider treatment with atropine. If symptoms do not improve with administration of atropine, treatment for late diarrhea (as outlined below) should be started.

Late diarrhea (more than 24 hours after the administration of the first dose of irinotecan)
Each family will be instructed to have antidiarrheal medication available and begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any increase in the number of bowel movements over what is normal for him/her, begin taking loperamide. **If he/she does not start taking the loperamide right away, the diarrhea may become severe and last several days or require hospitalization.**

Please follow these directions carefully, using dosing guidelines below:

- Take _____ at the first sign of diarrhea.
- Continue taking _____ every __ hours until your normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed _____ in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS FOR LATE DIARRHEA (maximum dose of Loperamide for adults is 16 mg/day)	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful of the 1 mg/5 mL oral solution]) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [(1 teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution) or one-half tablet every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution) or one-half tablet every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

APPENDIX IX: MEDICATION DIARY

COG Patient ID: ___________ ACC # : _____ Institution :________________________________
Please do not write patient names on this form.

Course #:________
For each day, fill in the **date and time** temozolomide, irinotecan, and cefixime (or equivalent antibiotic to prevent diarrhea) were given. Irinotecan should be given one hour after administration of temozolomide. Make note of other drugs and supplements taken. Cefixime or an available equivalent antibiotic will be used as diarrheal prophylaxis. Initiation of antibiotic treatment at least two days prior to the start of irinotecan is recommended. This antibiotic therapy should continue throughout protocol therapy. Return the completed diary to your institution after each treatment course.
PLEASE CAREFULLY READ THE STEPS FOR DRUG ADMINISTRATION (SEE RECOMMENDATIONS FOR ADMINISTRATION OF TEMOZOLOMIDE AND PARENT GUIDELINES FOR ADMINISTRATION OF ORAL IRINOTECAN) BEFORE GIVING DRUGS.

Day:						
						Date: _____ **Cefixime** Time:______ _ Dose:______ _
Date:____ **Cefixime** Time:____ __ Dose:_____	Date:_____ Temozolomide, Irinotecan, ABI-009 given in Clinic. DO NOT TAKE AT HOME **Cefixime** Time:________ Dose:________	Date: _____ **Temozolomide** Time:________ Dose:________ **Irinotecan** Time:_______ Dose:_______ **Cefixime** Time:________ Dose:________	Date: _______ **Temozolomide** Time:________ Dose:________ **Irinotecan** Time:_______ Dose:_______ **Cefixime** Time:________ Dose:________	Date: _______ **Temozolomide** Time:________ Dose:________ **Irinotecan** Time:_______ Dose:_______ **Cefixime** Time:________ Dose:________	Date: ________ **Temozolomide** Time:________ Dose:________ **Irinotecan** Time:_______ Dose:_______ **Cefixime** Time:________ Dose:________	Date: _____ **Cefixime** Time:______ __ Dose:______ _
Date:____ **Cefixime** Time:____ _ Dose:_____	Date: _______ ABI-009 given in Clinic **Cefixime** Time:________ Dose:_______	Date: ____________	Date: ____________	Date: ____________	Date: _____________	Date: __________
Date:____	Date: _____________	Date: ____________	Date: ____________	Date: ____________	Date: _____________	Date:_____ **Cefixime** Time:______ _ Dose:______ _
Date:____ **Cefixime** Time:____ _ Dose:_____						

NOTES:

APPENDIX X: UNACCEPTABLE ENZYME-INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Recommended Non-enzyme inducing anticonvulsants
Clonazepam
Diazepam
Ethosuximide
Ezogabine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Perampanel
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Carbamazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine

APPENDIX XI-A: PHARMACOKINETIC STUDY FORM FOR ABI-009

COG Pt ID # _____ Cycle 1, Day 1 Date: _____ Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

ABI-009 Dose Level: _____mg/m^2 ABI-009 Total Daily Dose: _____mg

ABI-009 Sampling Schedule during Cycle 1 (Single Agent) and Cycle 2 (Combination Therapy):

Blood samples (2 ml) will be collected in EDTA tubes (lavender top) at the following time points: Day 1 (pre-infusion, end of infusion, 1 hr., 2 hrs., 4 hrs., and 8 hrs. after beginning the infusion), Day 2 (24 hrs. after beginning the Day 1 infusion), Day 4 (72 hrs. [± 24 hrs.] after beginning the Day 1 infusion), Day 8 (pre-infusion) of Cycle 1 and 2.

Record the exact time the sample is drawn along with the exact time ABI-009 is given on Days 1 and 8.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Cycle 1, Day 1**	Prior to Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
ABI-009 Infusion on Day 1 Date:___/___/___ **Start Time:** |__|__| : |__|__| **Stop Time:** |__|__| : |__|__|				
2	**Cycle 1, Day 1**	30 min. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
3	**Cycle 1, Day 1**	1 hr. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
4	**Cycle 1, Day 1**	2 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
5	**Cycle 1, Day 1**	4 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
6	**Cycle 1, Day 1**	8 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
7	**Cycle 1, Day 2**	24 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
8	**Cycle 1, Day 4**	72 hrs. (± 24 hrs.) after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
9	**Cycle 1, Day 8**	Prior to Day 8 ABI-009 infusion	___/___/___	|__|__| : |__|__|
ABI-009 Infusion on Day 8 Date:___/___/___ **Start Time:** |__|__| : |__|__| **Stop Time:** |__|__| : |__|__|				
10	**Cycle 2, Day 1**	Prior to Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
ABI-009 Infusion on Day 1 Date:___/___/___ **Start Time:** |__|__| : |__|__| **Stop Time:** |__|__| : |__|__|				
11	**Cycle 2, Day 1**	30 min. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
12	**Cycle 2, Day 1**	1 hr. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
13	**Cycle 2, Day 1**	2 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|

14	**Cycle 2, Day 1**	4 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
15	**Cycle 2, Day 1**	8 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
16	**Cycle 2, Day 2**	24 hrs. after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
17	**Cycle 2, Day 4**	72 hrs. (± 24 hrs.) after beginning Day 1 ABI-009 infusion	___/___/___	|__|__| : |__|__|
18	**Cycle 2, Day 8**	Prior to Day 8 ABI-009 infusion	___/___/___	|__|__| : |__|__|
ABI-009 Infusion on Day 8 Date:___/___/___ Start Time: |__|__| : |__|__| Stop Time: |__|__| : |__|__|				

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel responsible for sample collection)

APPENDIX XI-B: PHARMACOKINETIC STUDY FORM FOR IRINOTECAN

COG Pt ID # _____ Cycle 2, Day 1 Date: _____ Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Irinotecan Dose Level: _____mg/m^2 Irinotecan Daily Dose: _____mg

Irinotecan/SN-38 Sampling Schedule during Cycle 2 (Combination Therapy):

Blood samples (2 ml) will be collected in heparinized tubes (green top) at the following time points: Day 1 (pre-dose, 10 min, 1 hrs., 3 hrs., and 6 hrs. after irinotecan dose), Day 2 (pre-dose [24 hrs. after Day 1 dose]) of Cycle 2.

Record the exact time the sample is drawn along with the exact time Irinotecan is given on Days 1 and 2.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Cycle 2, Day 1**	Prior to Day 1 irinotecan dose	___/___/___	|__|__| : |__|__|
Irinotecan Dose on Day 1 Date:___/___/___ **Time:** |__|__| : |__|__|				
2	**Cycle 2, Day 1**	10 min. after Day 1 irinotecan dose	___/___/___	|__|__| : |__|__|
3	**Cycle 2, Day 1**	1 hr. after Day 1 irinotecan dose	___/___/___	|__|__| : |__|__|
4	**Cycle 2, Day 1**	3 hrs. after Day 1 irinotecan dose	___/___/___	|__|__| : |__|__|
5	**Cycle 2, Day 1**	6 hrs. after Day 1 irinotecan dose	___/___/___	|__|__| : |__|__|
6	**Cycle 2, Day 2**	Prior to Day 2 irinotecan dose	___/___/___	|__|__| : |__|__|
Irinotecan Dose on Day 2 Date:___/___/___ **Time:** |__|__| : |__|__|				

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel responsible for sample collection)

APPENDIX XII: TISSUE STUDY FORM (REQUIRED TISSUE)

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Body Surface Area: _____m^2 ABI-009 Dose Level: _____mg/m^2 ABI-009 Total Daily Dose: _____mg

Tumor Sample Labeling:

Samples should be labeled with the following information:

Protocol number: **ADVL1514**
Institution: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
Site of Acquired Tissue: _____

Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse

Shipment of Tumor Tissue:

Paraffin-embedded tumor specimens or tissue slides must be packaged appropriately and shipped at room temperature to the Specialized Histopathology Core at Brigham and Women's Hospital (at the address below). If a tumor block is not available, scrolls from the tumor block and/or 8-10 (minimum: 6) unstained slides may be shipped instead. Please indicate above the date of the sample, site of tissue acquisition and whether it was obtained at diagnosis or relapse. Shipments should be sent **Monday through Thursday only** for priority overnight delivery using the COG FedEx account (do not ship on Friday). One copy of this form should be uploaded into RAVE.

A second copy should be sent with the tissue sample to the lab address below.

Attn: Specialized Histopathology Core
Brigham and Women's Hospital
20 Shattuck Street
Thorn Building, Rm 603C
Boston, MA 02115
Attention: Teri Bowman, Laboratory Manager

Notes: _____

_____

_____

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 responsible for samples)

APPENDIX XIII: POTENTIAL DRUG INTERACTIONS

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

Cefixime

Drugs that may interact with cefixime
• Aminoglycoside antibiotics (such as gentamicin, tobramycin) • Oral contraceptives ("birth control") • Probenecid • Warfarin
Food and supplements that may interact with cefixime**
• Thuja

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

Irinotecan

Drugs that may interact with irinotecan*

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Clozapine, nefazodone
• Antifungals
  ○ Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Anti-rejection medications
  ○ Cyclosporine
• Antiretrovirals and antivirals
  ○ Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir
• Anti-seizure medications
  ○ Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, carvedilol, dronedenarone, diltiazem, propafenone, quinidine, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  ○ Aprepitant, bosentan, cobicistat, conivaptan, ivacaftor, mifepristone, modafinil, natalizumab

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

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

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

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

Temozolomide

Drugs that may interact with temozolomide*
• Clozapine, leflunomide, natalizumab, tofacitinib, valproate products
Food and supplements that may interact with temozolomide**
• Echinacea

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

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*
The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

APPENDIX XIV: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5] alfentanil[4,5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

ivacaftor				
ketoconazole				
lansoprazole				
lapatinib				
losartan				
lovastatin[5]				
lurasidone[5]				
macrolide antibiotics				
maraviroc[5]				
medroxyprogesterone				
methadone				
midazolam[5]				
midostaurin[5]				
modafinil				
nefazodone				
nilotinib				
olaparib				
ondansetron				
osimertinib				
paclitaxel				
palbociclib				
pazopanib				
quetiapine[5]				
quinidine[4]				
regorafenib				
romidepsin				
saquinavir[5]				
sildenafil[5]				
simvastatin[5]				
sirolimus[4,5]				
sonidegib				
sunitinib				
tacrolimus[4,5]				
tamoxifen				
telaprevir				
temsirolimus				
teniposide				
tetracycline				
tipranavir[5]				
tolvaptan[5]				
triazolam[5]				
trimethoprim				
vardenafil[5]				
vemurafenib				
venetoclax[5]				
vinca alkaloids				
zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section _____ regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX XV: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN- 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for ALT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L- ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX XVI: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

CTSU Registration Procedures

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

IRB Approval:
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Requirements for ADVL1514 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

APPENDIX XVII: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**	ADVL1514
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	ABI-009

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
ABI-009 interacts with certain specific enzyme(s) in your liver or other tissues like the gut, AND certain transport proteins that help move drugs in and out of cell.

	Explanation
CYP isoenzymes	The enzyme(s) in question is CYP3A4. ABI-009 is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.
Protein transporters	The protein(s) in question is P-glycoprotein. ABI-009 is moved in and out of cells/organs by this transport protein.

These are the things that you need to know:
The study drug ABI-009, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4 enzyme and P-glycoprotein.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
  - St. John's Wort, graperfruit or grapefruit juice
- Make sure your doctor knows to avoid certain prescription medications.
  - Antofungal agents (e.g., voriconazole, itraconazole, posaconazole), macrolide antibiotics (clarithromycin, telithromycin), anticonvulsants (e.g., carbamazepine, phenobarbital, phenytoin), and antibiotics (e.g., rifabutin, rifampin) and other drugs (e.g., HIV-protease inhibitors, amiodarone, dronedarone, carvedilol).
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTI | NIH NATIONAL CANCER INSTITUTE | NIH NATIONAL CANCER INSTI | NIH NATIONAL CANCER INSTI

EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: ADVL1514

Study Drug(S): ABI-009

Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

amiodarone
atazanavir
boceprevir
carbamazepine
carvedilol
clarithromycin
cobicistat
darunavir
delavirdine
dronedarone
enzalutamide
fosphenytoin
grapefruit/grapefruit juice
idelalisib
indinavir
itraconazole
ketoconazole
lapatinib
lopinavir/ritonavir
nefazodone
nelfinavir
phenobarbital
phenytoin
posaconazole
primidone
propafenone
ranolazine
rifampin
ritonavir
saquinavir
St. John's wort
telaprevir
telithromycin
tipranavir
verapamil
voriconazole

DRUG INTERACTIONS

Carry this card with you at all times

ABI-009 interacts with a specific enzyme in your liver or other tissues like the gut, transport proteins that help move drugs in and out of cells, the heart's electrical activity, and must be used very carefully with other medicines.

Your healthcare providers should be aware of any medicines that are strong inducers/inhibitors of CYP3A4 and P-glycoprotein transport protein.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version 06/2020

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

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Fold at dotted lines: