CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health

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June 2, 2020

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Dear Ms. Kruhm,

Enclosed please find Amendment #10 to **ADVL1312**, *A Phase 1/2 Study of AZD1775 (MK-1775) in Combination with Oral Irinotecan in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Tumors.*

The protocol has been amended in response to the Request for Rapid Amendment from Dr. Charles Kunos, dated May 21, 2020.

SUMMARY OF CHANGES

The following specific revisions have been made to the protocol and informed consent document. Additions are in **boldfaced font** and deletions in ~~strikethrough font~~.

SUMMARY OF CHANGES PROTOCOL DOCUMENT:

#	Section	Page	Comments
1.	General	All	The version date and amendment number have been updated throughout the protocol
2.	9.1.6	36-39	CAEPR has been updated to version 2.7, dated April 27, 2020

SUMMARY OF CHANGES INFORMED CONSENT DOCUMENTS:

#	Section	Comments
1.	General	The version date has been updated throughout
2.	Risks...	Risks list for AZD1775 has been updated

Activated: March 17, 2014
Closed:

Version Date: 06/02/20
Amendment #: 10

CHILDREN'S ONCOLOGY GROUP

ADVL1312

A PHASE 1/2 STUDY OF AZD1775 (MK-1775) IN COMBINATION WITH ORAL IRINOTECAN IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH RELAPSED OR REFRACTORY SOLID TUMORS

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

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AGENT NSC# AND IND#'s

NCI-Supplied Agent:
MK-1775 (AZD1775)
(NSC # 751084)

Commercial Agent:
Irinotecan (CPT-11, Camptosar™), NSC #616348
Cefixime (Suprax®)

IND Sponsor: [DCTD, NCI]

SEE SECTION 8.3.6, 8.4.6, and APPENDIX X AND XI FOR SPECIMEN SHIPPING ADDRESSES

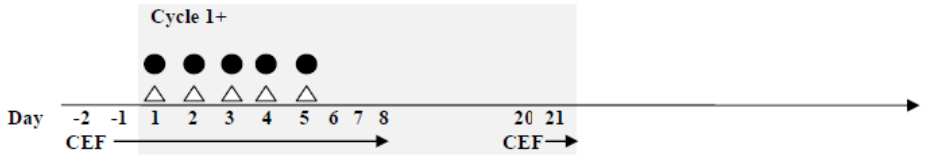
This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers 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

Wee1 is a tyrosine kinase that is activated in response to DNA damage and plays a role in chemo-resistance and tolerance of oncogene induced cellular stress. The Wee1 inhibitor, AZD1775 (MK-1775), was developed to overcome this checkpoint and render cells more sensitive to chemotherapy, and may be more effective in tumors with high levels of the MYC or MYCN oncogene. In the phase 1 portion of this study (Part A), patients with recurrent or refractory solid tumors including CNS tumors will receive the Wee1 inhibitor AZD1775 (MK-1775) in combination with irinotecan. Both agents will be administered orally on days 1-5 of a 21-day cycle with a step-wise inter-patient dose escalation of AZD1775 (MK-1775). Patients will be accrued to dose levels using a 3+3 design. Toxicity will be graded according to the CTCAE v 5.0 and response will be assessed by RECIST criteria. There will be analysis of AZD1775 (MK-1775) pharmacokinetics and the mechanism-based biomarker of AZD1775 (MK-1775) induced replication checkpoint over-ride. Analysis of Wee1 signaling and MYC and MYCN levels will be performed from archival tumor tissue in patients with available tissue and from bone marrow in consenting patients with bone marrow involvement. Once the recommended phase 2 dose of AZD1775 (MK-1775) in combination with irinotecan is determined, there will be a phase 2 expansion for patients with refractory or recurrent neuroblastoma (Part B) for patients with refractory or recurrent medulloblastoma/CNS PNET (Part C) and for patients with relapsed or refractory rhabdomyosarcoma (Part D).

EXPERIMENTAL DESIGN SCHEMA



△ AZD1775 (MK-1775)
● Irinotecan
CEF: Cefixime or an available equivalent antibiotic will be administered at least 2 days prior to the first dose of irinotecan, during, and 3 days after irinotecan in each cycle.

See Table 8.1 for required disease evaluations. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Therapy may

otherwise continue for up to 18 cycles.

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 of AZD1775 (MK-1775) administered on days 1 through 5 every 21 days, in combination with oral irinotecan, to children with recurrent or refractory solid tumors.

1.1.2 To define and describe the toxicities of AZD1775 (MK-1775) in combination with oral irinotecan administered on this schedule.

1.1.3 To characterize the pharmacokinetics of AZD1775 (MK-1775) in children with refractory cancer.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of AZD1775 (MK-1775) and irinotecan within the confines of a Phase 1 study.

1.2.2 To obtain initial Phase 2 efficacy data on the anti-tumor activity of AZD1775 (MK-1775) in combination with irinotecan administered to children with relapsed or refractory neuroblastoma, in children with relapsed or refractory medulloblastoma/CNS PNET (central nervous system primitive neuroectodermal tumor) and in children with relapsed or refractory rhabdomyosarcoma.

1.2.3 To investigate checkpoint over-ride by AZD1775 (MK-1775) via the mechanism-based pharmacodynamic (PD) biomarker of decreased CDK1 phosphorylation in correlative and exploratory studies.

1.2.4 To evaluate potential predictive biomarkers of AZD1775 (MK-1775) sensitivity, including MYC, MYCN, p-Wee1, EZH2 and γ-H2AX in tumor tissues in correlative and exploratory studies.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development and Dosing

Although patients with localized solid tumors generally do well, patients with refractory and relapsed disease have a poor prognosis. New therapeutic regimens that combine chemotherapy with targeted chemosensitizing agents merit study in this patient population.

2.1.1 Rationale for Wee1 inhibition strategies

Wee1 is a tyrosine kinase that phosphorylates and inhibits CDK1 (the HUGO term for CDC2) at a conserved tyrosine 15 residue, affecting proper coordination of DNA replication as well as entry into mitosis.[1] In the presence of DNA damage or replication stress (by chemotherapy, radiation or oncogenes) CDK1 activity is restrained by the checkpoint kinases CHK1 and Wee1, allowing for repair of DNA prior to mitosis and tolerance of replication stress and maintenance of tumor cell viability.[2] Inhibition of CHK1 or Wee1 under these circumstances leads to

replication fork collapse or mitotic catastrophe, generation of double-strand DNA breaks and ultimately cellular death. Therefore, checkpoint inhibitors have been evaluated in clinical trials as chemotherapy and radiation sensitizers.[3] The Wee1 inhibitor MK-1775 has been evaluated in combination with gemcitabine, carboplatin and cisplatin, 5-FU, topotecan and cisplatin and carboplatin and paclitaxel.[4]

2.1.2 Rationale for Wee1 inhibition strategies in pediatric solid tumors

In an effort to identify novel therapeutics for neuroblastoma, an unbiased RNA interference screen of the entire protein kinome was performed and the Cell Cycle Checkpoint Kinase 1 (CHK1) was the most potent in a panel of ten neuroblastoma cell lines.[5] Upon examination of downstream signaling, this effect was phenocopied by inhibition of the CDK1 kinase, Wee1.[6] Like CHK1, Wee1 was highly expressed in neuroblastoma, particularly tumors with MYCN amplification and constitutively phosphorylated in neuroblastoma cell lines and diagnostic primary tumors of children with advanced disease. This single agent sensitivity resulted in synergistic growth inhibition in combination with cytotoxic chemotherapy agents, including camptothecins. [6] There is also potent synergistic growth inhibition with dual CHK1 and Wee1 targeting.[6,7] Neuroblastoma is likely sensitive to single agent Wee1 inhibition due to intrinsic replication stress and high CDK1 activity due to high levels of MYC and MYCN.[2] *MYCN* is an oncogenic driver in high-risk neuroblastoma via focal genomic amplification, and tumors without *MYCN* amplification have high levels of c-MYC. Yet, both oncogenes have remained undruggable. As has been recently shown with *MYC*-induced lymphomas, targeting the ATR/CHK1 and Wee1 pathways in MYC-driven tumors may be a synthetic lethal means of targeting MYC and MYCN.[8,9] As such, medulloblastoma is an embryonal tumor that also involves MYC / MYCN in tumor initiation and maintenance and marks the most clinically aggressive subset of medulloblastomas.[10-12] Like neuroblastoma, medulloblastoma cell lines are also sensitive to single agent Wee1 inhibition (unpublished results). In addition, Wee1 has been shown to be overexpressed in diffuse intrinsic pontine glioma (DIPG) tumors and MK-1775 was a radiation sensitizer in a mouse model of DIPG.[13]

2.1.3 Rationale for Chemotherapy Backbone

In adult clinical trials, MK-1775 has been developed in combination with gemcitabine, cisplatin, carboplatin, 5-FU, topotecan plus cisplatin and carboplatin plus paclitaxel. The rationale for combining MK-1775 with irinotecan in a pediatric phase 1/2 clinical trial is multi-factorial. Irinotecan induces replication arrest and MK-1775's mechanism of action involves replication arrest over-ride providing mechanistic support for this combination. There is pre-clinical data showing synergistic growth inhibition of MK-1775 in combination with irinotecan in preclinical models of neuroblastoma.[6] The multiple five-day dosing regimen of irinotecan allows for serial dosing of MK-1775, allowing for a more prolonged exposure than single day dosing and irinotecan induced downregulation of CHK1. Finally, irinotecan containing regimens have been shown to have activity in combination in neuroblastoma (providing a backbone to test targeted agents) [14] and there is single agent activity of irinotecan in medulloblastoma (16% overall response rate).[15]

To date, MK-1775 has not been combined with irinotecan in a clinical trial, but

MK-1775 was combined with topotecan and cisplatin in an adult phase 1 trial for cervical cancer. [4]

2.1.4 Rationale for Proposed MK-1775 and Irinotecan Dosing

MK-1775 has been administered to adults as a single agent and in combination with several chemotherapeutics. The schedule of administration of MK-1775 was determined by the chemotherapy regimen and included single dosing and multiple day dosing regimens.

The proposed starting dose, schedule and dose escalation of MK-1775 on a 5 day schedule were based on the following considerations: [4]

- Wee1 restrains CDK1 activity and is involved in the DNA damage response, and irinotecan causes DNA strand breaks.[2] Inhibitors of Wee1 including MK-1775 may potentiate the DNA damage in tumor cells. However, MK-1775 may also potentiate toxicity. Therefore, the starting dose of irinotecan on this study (70 mg/m^2 PO) corresponds to the recommended phase 2 dose for heavily pretreated patients (40 mg/m^2 IV) and the starting dose used in combination regimens.[16,17] In the absence of dose limiting toxicity, the dose of irinotecan will be escalated from 70 mg/m^2 to 90 mg/m^2. [17]

- Irinotecan is administered on a daily 5-day schedule every 21 days; therefore, the proposed administration of MK-1775 will be daily x 5 every 21 days.[15] MK-1775 has a short half-life (average of 9 hours). In dogs, the No Observed Adverse Effect Level (NOEL) of MK-1775 was 100 mg/m^2 (5 mg/kg) daily for 7 days. Given the novel combination, schedule and dosing in children, a conservative approach was taken with dosing. The proposed starting dose of MK-1775 daily for 5 days on this trial is 50 mg/m^2, 50% of the NOEL in dogs receiving MK-1775 daily x 7 days. The highest MK-1775 dose proposed on this study (110 mg/m^2 daily x 5 days) is at the NOEL. The proposed starting dose on this trial (50 mg/m^2) was also determined by the tolerated adult phase 1 clinical trial that evaluated patients receiving 3 days of IV topotecan, 1 day of IV cisplatin and 5 days of MK-1775 (50 mg for 9 doses) every 21 days. The highest proposed dose in this trial's escalation (110 mg/m^2) is based on the adult phase 1 multiple day dosing trials in which 5 doses of MK-1775 were administered over 2.5 days in combination with carboplatin and cisplatin. The MTD of MK-1775 was 225 mg and 200 mg, respectively, which when converted to 5-day single dose administration would be approximately 116 mg/m^2/day.

- Preclinical data indicates that MK-1775 concentrations ≥ 0.28μM produce a target effect (EC50 for p-CDK1) after gemcitabine.[4] Clinical studies showed accumulation of drug with BID dosing, but this was minimal with daily dosing. A single oral dose of 100 mg MK-1775 (57 mg/m^2) in adults in combination with chemotherapy has an average C_{max} of approximately 0.3 μM; therefore, all proposed MK-1775 doses on this study may produce a biologically relevant concentration. In the absence of dose limiting toxicity, MK-1775 dose escalation is proposed to increase the systemic exposure and prolong time above this threshold concentration.

2.1.5 Rationale for Cefixime

There are two distinct patterns of irinotecan-associated diarrhea: early and late onset. Early onset diarrhea occurs within 4 hours of treatment, is associated with cholinergic symptoms and is readily reversible with atropine. Late onset diarrhea develops during the second week of therapy and is one of the main dose limiting toxicities of irinotecan in pediatric studies.[18] With the addition of antibiotics, such as cefixime, that selectively eradicate intestinal bacteria that would otherwise re-activate the metabolized irinotecan, investigators have been able to improve tolerability of irinotecan. Using cefixime combined with as needed use of loperamide, Furman et al [19] were able to increase the MTD of protracted oral irinotecan by 50%, and a similar increase was noted with protracted IV irinotecan dosing.[20]

2.2 Preclinical Studies

2.2.1 Antitumor Activity of Irinotecan in pre-clinical models

Irinotecan is a camptothecin prodrug whose active metabolite (SN-38) induces cytotoxicity in the presence of topoisomerase I. Topoisomerase I permits relaxation of supercoiled DNA by inducing single strand breaks, which reduces torsional strain during DNA replication and transcription. When an active topoisomerase I enzyme is present, camptothecins stabilize topoisomerase-induced DNA strand breaks which ultimately leads to apoptosis. Anti-tumor activity of irinotecan has been demonstrated in mouse models of neuroblastoma[21], rhabdomyosarcoma[22] and CNS malignancies.[22,23]

2.2.2 Antitumor Activity of MK-1775 in pre-clinical models

Kinase screening assays identified MK-1775 as a selective and potent (IC50= 5.18 nM) inhibitor of Wee1.[24] In vitro synergistic antiproliferative effects were observed in tumor cells treated with MK-1775 in combination with gemcitabine, cisplatin, carboplatin and 5-FU. In tumor bearing mouse xenografts, MK-1775 was administered according the chemotherapy schedule. There was enhanced anti-tumor efficacy, increased survival and tolerability noted in multiple xenograft models when MK-1775 was combined with gemcitabine, cisplatin, carboplatin, 5-FU, radiation or capecitabine.[4,24-28]

While MK-1775 has the potential to enhance chemotherapy sensitivity, with continuous dosing there is single agent activity in some tumor models. In vitro testing of eight sarcoma lines with MK-1775 had an average IC50 of 342 nM (± 154 nM).[29] There was anti-tumor efficacy of twice daily dosing of MK-1775 in mouse xenografts bearing tumors derived from non-small cell lung cancer and colorectal carcinoma.[4] MK-1775 enhanced the radiation response in DIPG mouse xenografts.[13] Finally, MK-1775 also had single agent antiproliferative activity in 10 of 11 human derived neuroblastoma cell lines with an average IC_{50} of 300 nM (± 193 nM) and cell lines derived from the MYCN genetically engineered neuroblastoma mouse model (IC50s ~ 200 nM).[6] The average IC50 in 4 medulloblastoma cell lines treated with MK-1775 alone was 454 nM (unpublished

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results). MK-1775 in combination with SN-38 (the active metabolite of irinotecan) resulted in significant synergistic inhibition in eight of ten of the human neuroblastoma cell lines tested. [6]

2.2.3 MK-1775 Toxicology[4]

In the 7 day oral toxicity studies, MK-1775 was administered by 25, 75, or 300 mg/kg in rats, and at 5 or 15 mg/kg in dogs, once daily for 7 days. Expected toxicity of the hematopoietic organs and GI tract were observed in both rats and dogs. In rats, however, this was associated with mortality at 75 mg/kg (450 mg/m^2) and 300 mg/kg (1800 mg/m^2). During the 2 week recovery period, MK-1775 related changes recovered or showed a trend towards reversibility in rats dosed at 25 mg/kg (150 mg/m^2) and dogs at 15 mg/kg (300 mg/m^2). In the anesthetized cardiovascular dog study, MK-1775 marginally prolonged QTc by an average of 5% and 7%, at the 3 and 10 mg/kg doses, respectively. Only minimal effects on blood pressure (-5%) and heart rate (-5%) were observed at the 10 mg/kg dose. There were no effects on other cardiographic measures, *i.e.*, QRS duration or PR interval, at either dose. In mice, MK-1775 had no effect on CNS function (at a dose of 10 mg/kg), including gross behavior, spontaneous activity, neural reflexes, or thermoregulation during the 24-hour post dose period.

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2.2.4 Preclinical Pharmacokinetic Studies [4]

The PK studies were conducted in male Sprague-Dawley rats and Beagle dogs following IV and PO administration of MK-1775. MK-1775 was rapidly distributed and eliminated with the mean half-life ($t_{½}$) 1.6 hours in rats and 1.1 hours in dogs. MK-1775 has moderate plasma protein binding with the unbound fraction in rat, human and dog begin 23.2%, 40% and 39.5%, respectively. The major metabolic pathway of MK-1775 in human liver preparations was oxidative metabolism. In human hepatocytes, the major metabolites formed were an *N*-desmethyl metabolite and an *N*-oxide derivative. All metabolites observed in human liver preparations were also formed *in vivo* in the rat and dog. Oxidative metabolism of MK-1775 was mediated predominantly by cytochrome P450 3A4 (CYP3A4) and flavin-containing monooxygenase 3 (FMO3). MK-1775 was a weak reversible inhibitor of CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (IC50 of 51, 56, 12, and 14 µM, respectively). In addition, MK-1775 was a time-dependent inhibitor of CYP3A4. MK-1775 is a substrate of P-glycoprotein (Pgp).

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2.3 Adult Studies

2.3.1 Phase 1 Studies [4]

MK-1775 clinical data are derived from the phase 1 dose-escalation study (PN001) in adult patients with advanced solid tumors, sponsored by Merck.[30] The study consists of a MK-1775 monotherapy arm and several combination therapy arms (MK-1775 with gemcitabine, cisplatin, or carboplatin). The study objectives include investigating safety, tolerability, PK, and PD of MK-1775 administered as monotherapy and as combination therapy. MK-1775 administered as a single agent at a single dose (≤ 1300 mg PO) was well tolerated, and no MTD has been established. A single patient experienced Grade 3 dehydration and urinary tract infection. To date, a total of 176 patients have received MK-1775, 9 patients received MK-1775 as one dose monotherapy. Eight out of the original 9 patients

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went on to get a combination with cisplatin, carboplatin or gemcitabine and an additional 35 patients were enrolled in the single-dose combination. In all, 44 patients took part in the single-dose monotherapy/combination portion of the study. The MTD for single dose MK-1775 given in combination but 24 hours after cisplatin (75 mg/m^2) or gemcitabine (1000 mg/m^2) has been established at 200 mg, and with carboplatin (AUC5) at 325 mg. AE data is available for 43 patients. Among all patients receiving single dose MK-1775 in combination with chemotherapy, the most common classifications for drug-related AEs ⩾ Grade 3 were blood and lymphocytic system disorders (7/43), gastrointestinal disorders (3/43) and investigations (3/43). The MTDs for BID dosing x 5 doses of MK-1775 with similar chemotherapy regimens were 200 mg with cisplatin and 225 with carboplatin. The DLTs for multiple dose cisplatin (75 mg/m^2) were Grade 3 colitis and Grade 4 neutropenia in 3 of 4 patients at 250 mg MK-1775 BID for 2.5 days. The DLTs for multiple dose carboplatin (AUC 5) were Grade 3 diarrhea and nausea and Grade 4 neutropenia, febrile neutropenia and pancytopenia in 6 of 12 patients at 325 mg MK-1775 BID for 2.5 days. MK-1775 in combination with gemcitabine is currently being evaluated on a QD × 2 schedule since the PD threshold was not met at the initially defined MTD on a BID schedule.

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The most frequent adverse events seen in the combination trials are myelosuppression, diarrhea, vomiting, nausea, constipation and abdominal pain. Investigational findings, including alterations in blood chemistry, have also been affected.

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In all, three patients had confirmed partial responses in the multiple dose combination study; this included two patients (squamous cell carcinoma and melanoma) receiving multiple doses of MK-1775 at 100 mg BID in combination with cisplatin, and one patient (squamous cell carcinoma) receiving single-dose MK-1775 at a dose of 200 mg in combination with cisplatin. In an investigator-sponsored study, two additional refractory ovarian cancer patients receiving 225 mg MK-1775 BID in combination with carboplatin have had confirmed partial responses.

Merck has also sponsored trials with the combination of MK-1775 with 5-FU with and without cisplatin in Japanese patients, combination with topotecan plus cisplatin in cervical cancer and carboplatin plus paclitaxel in ovarian cancer. The first two studies have been discontinued as a result of prioritization efforts; no safety concerns were identified. The carboplatin plus paclitaxel study is ongoing.

2.3.2 Phase 2 Studies

A phase II study of AZD1775 dosed orally twice daily over 2.5 days with carboplatin every 21-days, demonstrated that AZD1775 enhances carboplatin efficacy in patients with TP53 mutated ovarian cancers that were previously refractory or resistant to a platinum-based regiment.[31]

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies [4]

The AUC0-inf and C_{max} increased approximately proportionate to dose. For the majority of patients, C_{max} was reached ~3 hours after dosing (range 1.0-8.0 hours for monotherapy and 1.0-8.0 hours combination therapy). The mean terminal half-life ($t_{1/2}$) was ~9 hours (mean range 8.2-12.1 hours for monotherapy and 7.91-11.9

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hours for combination therapy). Target engagement was assessed by immunohistochemical scoring for variation from baseline in $pCDK1_{Tyr15}$ in a skin biopsy. A 50% reduction from baseline in $pCDK1_{Tyr15}$ was targeted, based on preclinical studies demonstrating significant antitumor effects of MK-1775/chemotherapy combinations at this level of target engagement in xenograft tumor samples. In the PN001 trial, 55% of patients at doses of greater than 100 mg showed target engagement.

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2.4 Pediatric Studies

2.4.1 Prior Experience in Children

Part A, the phase 1 dose escalation of ADVL1312, was completed in 2016.[32] Thirty-one eligible patients, median age 14 years (range 5-20) were enrolled on Part A of ADVL1312; 29 (93%) received prior chemotherapy (median 3 regimens) and 25 (81%) received prior radiation therapy. Sixteen patients had a primary CNS malignancy: malignant glioma (9), ependymoma (3), neuroepithelial tumor (1), medulloblastoma (2) and CNS Ewings sarcoma (1). Fifteen patients had extracranial solid tumors: soft tissue sarcoma (6), neuroblastoma (2), carcinoma (4), osteosarcoma (2) and Wilms' Tumor (1). The most common toxicities were hematologic and gastrointestinal (nausea, vomiting, diarrhea). Two patients experienced dose limiting toxicity, one with grade 3 diarrhea and dehydration and the second with grade 3 dehydration at DL5 (AZD1775 110 mg/m2 and irinotecan 90 mg/m2). Therefore, the MTD and recommended phase 2 dose from Part A of ADVL1312 is AZD1775 (85 mg/m2/day) in combination with irinotecan (90 mg/ m2/day) daily for five days every 21 days (Dose Level 4).

2.5 Overview of Proposed Pediatric Study

There will be four parts to the study. Part A is the phase 1 dose escalation of AZD1775 (MK-1775) in combination with oral irinotecan for individuals with refractory or recurrent solid tumors. Part A will be conducted in children with refractory or recurrent solid tumors, including CNS tumors. AZD1775 (MK-1775) will be administered in combination with oral irinotecan in a 21 day cycle. Part B will be a phase 2 expansion at the recommended phase 2 dose of AZD1775 (MK-1775) in combination with irinotecan for patients with recurrent or refractory neuroblastoma. Part C will be a phase 2 expansion at the recommended phase 2 dose of AZD1775 (MK-1775) in combination with oral irinotecan for patients with recurrent or refractory medulloblastoma/CNS PNET. Pharmacokinetics will be obtained in all patients in Part A of the study (see Section 8.3). Part D will be a phase 2 expansion at the recommended phase 2 dose of AZD1775 (MK-1775) in combination with oral irinotecan for patients with recurrent or refractory rhabdomyosarcoma. Correlative and exploratory pharmacodynamic, tumor tissue and bone marrow studies will be obtained as described in Sections 8.4, 8.5, and 8.6.

2.6 Rationale for inclusion of Part D (Amendment #4)

Since the initial protocol for ADVL1312 was developed, independent groups have shown that AZD1775 has promising in vitro and in vivo activity in pediatric rhabdomyosarcoma, supporting the addition of an expansion cohort in this disease. Kahen *et al* demonstrated that AZD1775 exhibited broad activity with high cell killing in four separate rhabdomyosarcoma cell lines (two embryonal and two alveolar).[33] Relevant to this amendment, AZD1775 was synergistic with irinotecan, which is a chemotherapeutic agent typically used clinically in rhabdomyosarcoma. Furthermore, in vivo studies with

orthotopic rhabdomyosarcoma xenografts performed at St. Jude's Children's Research Hospital (SJCRH) confirmed AZD1775 to have activity in rhabdomyosarcoma. AZD1775 in combination with irinotecan had a 42% response rate (CR + PR), an effect that was even greater with the addition of vincristine (70% response rate).[34] Part D will be a phase 2 expansion at the recommended phase 2 dose of AZD1775 (MK-1775) in combination with oral irinotecan for patients with recurrent or refractory rhabdomyosarcoma.

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/ >). This is the same account (user id and password) used for credentialing in the CTSU members' web site. 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. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. 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. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. Please see Appendix XVI for detailed CTEP and CTSU Registration Procedures including: registration in Registration and Credential Repository (RCR), requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1 Current Study Status

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

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

3.2 IRB Approval

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 email 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 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 following the steps in Section 3.1 above and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

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

3.5 Informed Consent/Assent

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

guidelines.

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

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

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

3.9 **Study Enrollment**
Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. 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 chemotherapy. The start of chemotherapy is defined as the initiation of treatment with AZD1775 (MK-1775) and irinotecan. The start of protocol therapy is defined as the initiation of cefixime or an available equivalent antibiotic (i.e. cefpodoxime). Laboratory tests need **not** be repeated if chemotherapy 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 chemotherapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not

receive protocol-prescribed chemotherapy and will be considered off protocol therapy. Imaging studies must be obtained within 14 days prior to start of chemotherapy (repeat the tumor imaging if necessary). For patients whose disease is evaluated with a bone marrow examination, the bone marrow aspirates and biopsies are required within 14 days prior to the start of chemotherapy.

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

4.1.2 Diagnosis: 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.

4.1.2.1 **Part A**: Patients with relapsed or refractory solid tumors, including patients with primary or metastatic CNS tumors.

4.1.2.2 **Part B**: Patients with relapsed or refractory neuroblastoma.

4.1.2.3 **Part C**: Patients with relapsed or refractory medulloblastoma or CNS embryonal tumors formally classified as PNET (pineoblastoma, CNS neuroblastoma, CNS ganglioneuroblastoma, embryonal tumor with multi-layered rosettes, medulloepithelioma, CNS embryonal tumor with rhabdoid features (INI1 intact) and CNS embryonal tumor, not otherwise specified)

4.1.2.4 **Part D**: Patients with relapsed or refractory rhabdomyosarcoma.

4.1.3 Body Surface Area:
Part A: Patients must have a body surface area ≥ 0.35 m^2 at the time of study enrollment if enrolling on Dose Levels 1-5. Patients must have a body surface area ≥ 0.46 m^2 at the time of study enrollment if enrolling on Dose Level 0.

Parts B, C, and D: Phase 2 Expansion: Patients must have a body surface area of > 0.49 m^2 at the time of study enrollment at the recommended phase 2 dose of AZD-1775.

4.1.4 Disease Status:
4.1.4.1 **Part A:** Patients must have either measurable or evaluable disease (see

Sections 12.2 and 12.3 for definitions).

4.1.4.2 **Part B:** Patients must have either measurable disease (see Section 12.2 for definitions) or must be evaluable for MIBG response without evidence of RECIST measurable lesions (see Section 12.4 for definitions). Patients with neuroblastoma in bone marrow only are not eligible.

4.1.4.3 **Part C:** Patients must have measurable disease by CT or MRI (see section 12.6 for definitions).

4.1.4.4 **Part D:** Patients must have measurable disease for Part D (see Section 12.2 for definitions)

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

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

4.1.7 Prior Therapy

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

a. Myelosuppressive chemotherapy: At least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. Neulasta) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
c. Biologic (anti-neoplastic agent): At least 7 days after the last dose of a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
d. Immunotherapy: At least 42 days after the completion of any type of immunotherapy, e.g. tumor vaccines.
e. 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.
f. XRT: At least 14 days after local palliative XRT (small port); At least 150 days must have elapsed if prior TBI, craniospinal XRT or if ≥ 50% radiation of pelvis; At least 42 days must have elapsed if other substantial bone marrow radiation, including therapeutic doses of MIBG.

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

4.1.7.2 Patients previously treated with irinotecan are eligible for this study.

4.1.8 Organ Function Requirements

4.1.8.1 Adequate Bone Marrow Function Defined as:

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

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.8.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 2 of every cohort of 3 patients must be evaluable for hematologic toxicity for Part A, the dose escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

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) ≤ 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 Cardiac Function Defined As:
- QTc ≤ 480 msec

Note: Patients should avoid concomitant medication known or suspected to prolong QTc interval or cause Torsades De Pointes. If possible, alternative agents should be considered.
Patients who are receiving drugs that prolong the QTc are eligible if the drug is necessary and no alternatives are available. See Appendix XV for drugs that may prolong the QTc.

4.1.9 Adequate Neurologic Function Defined as:
- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants and well controlled. (See Appendix II for a list of recommended non-enzyme inducing anticonvulsants).
- Nervous system disorders (CTCAE v5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

4.1.10 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.

4.1.11 Tissue blocks or slides must be sent per Section 8.6 if available, with exclusions as per Section 4.1.2. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

4.1.12 Patients must be able to swallow capsules.

4.2 Exclusion Criteria

4.2.1 Pregnancy, Breast-Feeding, and Contraception
a. Pregnant or breast-feeding women may not be entered on this study as there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal.
b. Males or females of reproductive potential may not participate unless they have agreed to use an effective double barrier contraceptive method for the entire duration of protocol therapy and for 3 months (males) and 1 month (females) after study drug discontinuation.

4.2.2 Concomitant Medications

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

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

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.2.4 CYP3A4 Agents: Patients who are currently receiving drugs that are strong or moderate inhibitors and/or inducers of CYP3A4 or sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range are not eligible. See Appendix III for a list of agents. **The use of aprepitant as an antiemetic is prohibited due to early drug interaction data demonstrating increased exposure to AZD1775 (MK-1775).**

Caution should be exercised with concomitant administration of AZD1775 (MK-1775) and agents that are sensitive substrates of CYP2C8, 2C9 and 2C19, or substrates of this enzyme with narrow therapeutic ranges, as well as agents that are inhibitors or substrates of P-gp.

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4.2.2.5 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.

4.2.2.6 Anticonvulsants: Patients must not have received enzyme inducing anticonvulsants for at least 14 days prior to enrollment (see Appendix II for a list of enzyme inducing and non-enzyme inducing anticonvulsants).

4.2.3 Cardiac Disease: Patients with cardiac diseases ongoing or in the past 6 months (e.g. congestive heart failure, acute myocardial infarction, significant uncontrolled arrhythmias) are not eligible for this trial.

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

4.2.7 Patients with a history of allergic reaction to irinotecan, cephalosporins or a severe penicillin allergy are not eligible.

4.2.8 Patients unable to swallow capsules whole are not eligible. Nasogastric or G tube administration is not allowed.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Cycle 1+				
	Day - 2	Cefixime		
Week 1	Day 1	↓	IRIN	AZD1775 (MK-1775)
	2		IRIN	AZD1775 (MK-1775)
	3		IRIN	AZD1775 (MK-1775)
	4		IRIN	AZD1775 (MK-1775)
	5		IRIN	AZD1775 (MK-1775)
	6			
	7			
	8			

	20 21	↓	**End of cycle**

Irinotecan (PO) will be administered 1 hour prior to AZD1775 (MK-1775) (PO) on days 1-5, with rest on days 6-21. Cefixime or an available equivalent antibiotic (i.e. cefpodoxime) will be used as diarrheal prophylaxis and administered at least 2 days prior to the first dose of irinotecan, during, and 3 days after the last dose of irinotecan of each cycle. Instructions for administration of oral irinotecan are included in Section 9.3 and Appendix V.

AZD1775 (MK-1775) should be taken on an empty stomach one hour prior or two hours after a meal. Capsules should be swallowed whole and not opened or manipulated. If a dose is vomited it should not be repeated; resume administration with the next regularly scheduled dose.

The doses of irinotecan and AZD1775 (MK-1775) will be as per Section 5.3. Cefixime will be dosed at 8 mg/kg PO once daily (max: 400 mg/day). If cefixime is not available, cefpodoxime should be dosed at 5 mg/kg/dose PO twice daily (10 mg/kg/day in two divided doses; max: 200 mg/dose).

The treatment regimen may be repeated for a total of 18 cycles, up to a total duration of approximately 12 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, and according to the dosing nomogram (see Appendix IV).

5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 21 days if the patient has at least stable disease, has again met laboratory parameters as defined in the eligibility criteria, Section 4.1.8, and the patient does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

5.3 Dose Escalation Schema

5.3.1 Part A : Inter-Patient Escalation

The starting dose will be 70 mg/m^2/dose of irinotecan and 50 mg/m^2/dose of AZD1775 (MK-1775). Dose levels for subsequent groups of patients are as follows.

Dose Level	**Irinotecan** mg/m^2/dose orally	**AZD1775 (MK-1775)** mg/m^2/dose orally
0	70	40
1*	**70**	**50**
2	70	65
3	90	65
4	90	85
5	90	110

*Starting Dose Level

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 70 mg/m^2/dose of irinotecan and 40 mg/m^2/dose of AZD1775 (MK-1775) (dose level 0).

5.3.2 Parts B, C, and D: Phase 2 Expansion

Patients with neuroblastoma (Part B), medulloblastoma/CNS PNET (Part C), and relapsed or refractory rhabdomyosarcoma (Part D) will be treated with irinotecan and AZD1775 (MK-1775) at the recommended phase 2 dose (RP2D) determined from the phase 1 component (Part A) of this trial.

The MTD/RP2D of Part A was determined to be Dose Level 4 (85 mg/m^2/dose AZD1775 and 90 mg/m^2/dose irinotecan on a 21-day cycle).

5.3.3 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. 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 the combination of irinotecan and AZD1775 (MK-1775). The DLT observation period for the purposes of dose-escalation (Part A) will be the first cycle of therapy.

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

5.5.1 Non-hematological dose-limiting toxicity

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

- Grade 3 nausea and vomiting < 3 days duration despite maximal supportive care
- 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. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix XII for toxicity grading table.
- Grade 3 fever
- Grade 3 infection
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation.

- Grade 3 diarrhea ≤ 3 days duration despite maximal supportive care
- Grade 3 mucositis or stomatitis ≤ 3 days duration

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

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

5.5.2 Hematological dose limiting toxicity

5.5.2.1 Hematological dose limiting toxicity is defined as:

In patients evaluable for hematological toxicity (see Section 4.1.8.1),

- Grade 4 neutropenia for > 7 days
- Platelet count < 20,000/mm^3 on 2 separate days, at least 48 hours apart, or requiring a platelet transfusion on 2 separate days, within a 7 day period
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

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

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who have dose-limiting thrombocytopenia should receive subsequent cycles at the same dose of AZD1775 (MK-1775) and a dose reduction of irinotecan to 65 mg/m^2 if original dose assignment was 90 mg/m^2, or to 50 mg/m^2 if original dose assignment was 70 mg/m^2. If dose-limiting thrombocytopenia recurs after the irinotecan is reduced, the AZD1775 (MK-1775) should be dose reduced to the next lower dose assignment indicated in the dosing nomogram (See Appx. IV). (Note: Patients enrolled at Dose Level 0 who experience dose-limiting thrombocytopenia after dose reduction of irinotecan should be removed from protocol therapy). If dose limiting thrombocytopenia recurs the patient should be removed from protocol therapy.

6.1.2 Patients who have dose-limiting neutropenia (Grade 4 neutropenia of > 7 days duration or delay in the start of the next cycle for > 14 days due to neutropenia) with no other dose-limiting toxicity should receive the same doses in the next cycle with myeloid growth factor support 24-48 hours after completion of irinotecan and AZD1775 (MK-1775). [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 treated with 65 mg/m^2 irinotecan (or to 50 mg/m^2 if original dose assignment was 70 mg/m^2) and the same dose of AZD1775 (MK-1775) for subsequent cycles. If the patient develops dose-limiting neutropenia at the dose reduced irinotecan, the patient should be treated at the next lowest dose of AZD1775 (MK-1775) indicated

in the dosing nomogram (See Appx. IV) or removed from protocol therapy if enrolled at Dose Level 0. If dose limiting neutropenia recurs the patient should be removed from protocol therapy.

6.1.3 Patients who experience dose-limiting thrombocytopenia after one dose reduction of irinotecan and one dose reduction of AZD1775 (MK-1775) or dose-limiting neutropenia after addition of myeloid growth factor and one dose reduction of AZD1775 (MK-1775) must be removed from protocol therapy.

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

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.5.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent doses at the next lower dose level. Note: Patients enrolled at Dose Level 0 who experience dose-limiting non-hematological toxicity should be removed from protocol therapy.

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

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

6.2.4 Dose modifications for diarrhea

See Appendix VI for specific guidelines for supportive care measures for patients who develop therapy-associated diarrhea.

- If dose-limiting Grade 3 (> 3 days) or Grade 4 therapy-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications and appropriate use of prophylactic antibiotics, the dose of irinotecan should be reduced to 65 mg/m^2 if original dose assignment was 90 mg/m^2, or to 50 mg/m^2 if original dose assignment was 70 mg/m^2 for subsequent cycles.
- If dose-limiting Grade 3 (> 3 days) or Grade 4 diarrhea recurs despite maximal use of anti-diarrheals, prophylactic antibiotics, after a single irinotecan dose reduction, the patient should come off protocol therapy.

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(s). 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, fluids, electrolytes and general supportive care are to be used as necessary (see Section 6.0). See Sections 7.5 and 9.1.5 for drugs that should not be used concomitantly due to potential interactions with irinotecan and/or AZD1775 (MK-1775). **Use of prophylactic antimicrobials to prevent irinotecan-associated diarrhea (cefixime or available equivalent, i.e. cefpodoxime) is required.** See the COG Supportive Care Guidelines 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 6.1 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 **Concomitant Medications**

Anticonvulsants should be used as clinically indicated and tapered as soon as possible. The use of enzyme inducing anticonvulsants is not permitted. See Appendix II for a list of unacceptable enzyme inducing and recommended non-enzyme inducing anticonvulsants. Irinotecan is metabolized by CYP3A4.

Moderate and potent inhibitors or inducers of CYP3A4 and sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range should not be used concomitantly with AZD1775 (MK-1775) (See Appendix III). Corticosteroids may induce CYP3A4 and are therefore not routinely recommended on study unless deemed absolutely necessary or when used in stable or decreasing doses from the time of study enrollment. **The use of aprepitant as an antiemetic is prohibited due to early drug interaction data demonstrating increased exposure to AZD1775 (MK-1775).**

Caution should be exercised with concomitant administration of AZD1775 (MK-1775) and agents that are sensitive substrates of CYP2C8, 2C9 and 2C19, or substrates of this enzyme with narrow therapeutic ranges, as well as agents that are inhibitors or substrates of P-gp.

Drugs that prolong the QTc may be used only if the drug is necessary and no alternatives are available. See Appendix XV for drugs that may prolong the QTc.

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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 chemotherapy. The start of chemotherapy is defined as the initiation of treatment with AZD1775 (MK-1775) and irinotecan. The start of protocol therapy is defined as the initiation of cefixime or an available equivalent antibiotic (i.e. cefpodoxime). Laboratory tests need **not** be repeated if chemotherapy 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 chemotherapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol-prescribed chemotherapy and will be considered off protocol therapy. Imaging

studies must be obtained within 14 days prior to start of chemotherapy (repeat the tumor imaging if necessary). For patients whose disease is evaluated with a bone marrow examination, the bone marrow aspirates and biopsies are required within 14 days prior to the start of chemotherapy.

STUDIES TO BE OBTAINED for PART A (Phase 1 Dose-Escalation):	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^	End of Study Treatment
History	X	Weekly	X	X
Physical Exam with vital signs	X	Weekly	X	X
Height, weight, BSA	X	X	X	
Performance Status	X		X	
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[1]	Weekly[2]	
Urinalysis	X			
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X	
Creatinine, ALT, bilirubin	X	Weekly	X	
Albumin	X		X	
Pregnancy Test	X[3]			
Tumor Disease Evaluation[4]	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles[5]	X
Bone Marrow Evaluation[6]	X	End of Cycle 1	With Tumor Disease Evaluation	
Pharmacokinetics[7]		X		
Pharmacodynamics[8]		X		
Bone Marrow for Correlative Biology Studies[9]	X	End of Cycle 1[9]	With Tumor Disease Evaluation[9]	
Tumor Tissue Submission[10]	X			
Patient Diary[11]		X	X	
EKG[12]	X			

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

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

2 If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3. If patient remains on study for > 4 cycles and ≥ Grade 3 cytopenias are not observed, CBCs may be checked prior to subsequent cycles and as clinically indicated.

3 Women of childbearing potential require a negative pregnancy test prior to starting protocol therapy; sexually active patients may not participate unless they have agreed to use an effective double barrier contraceptive method. Abstinence is an acceptable method of birth control.

4 Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy performed prior to enrollment if the patient was enrolled with or has a history of MIBG avid tumor. Otherwise, the NBL patient must have both CT/MRI and bone scan prior to enrollment. For patients with neuroblastoma and measurable disease by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or bone scan. For patients with neuroblastoma with evaluable disease by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) to image patients; CT/MRI are not required but may be performed as clinically indicated.

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

6 Patients with neuroblastoma must have bilateral bone marrow aspirates and biopsies. These do not need to be repeated if negative at study enrollment and patient is responding to therapy.

7 See Section 8.3 for timing and details regarding pharmacokinetic (PK) studies.

8 See Section 8.4 for timing and details regarding pharmacodynamic studies.

9 For patients with known or suspected marrow disease for whom consent for correlative studies has been obtained, collect bone marrow (5-10 mL) in preservative-free heparin when marrow evaluations are being performed for clinical indications. See Section 8.5 for details.

10 See Section 8.6 for details regarding tumor tissue submission. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

11 Patient diary (see Appendix XIII) should be reviewed and uploaded into RAVE at the end of each cycle.

[12] 12-lead EKG to be obtained at baseline and as clinically indicated.

STUDIES TO BE OBTAINED for PART B, PART C, and PART D (Phase 2 Expansion):	Pre-Study	During Cycle 1	Prior to Subsequent cycles^	End of Study Treatment
History	X		X	X
Physical Exam with vital signs	X		X	X
Height, weight, BSA	X		X	
Performance Status	X		X	
CBC, differential, platelets[1]	X	Weekly	Weekly	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X		X	
Creatinine, ALT, bilirubin	X		X	
Albumin	X			
Pregnancy Test	X[2]			
Tumor Disease Evaluation[3]	X	End of Cycle 1	Every other cycle x 2 then q 3 cycles[4]	X
Bone Marrow Evaluation[5]	X	End of Cycle 1	With Tumor Disease Evaluation	
Bone Marrow for Correlative Biology Studies[6]	X	End of Cycle 1	With Tumor Disease Evaluation	
Tumor Tissue Submission[7]	X			
Patient Diary[8]		X	X	
EKG[9]	X			

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

[1] If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3. If patient remains on study for > 4 cycles and ≥ Grade 3 cytopenias are not observed, CBCs may be checked prior to subsequent cycles and as clinically indicated.

[2] Women of childbearing potential require a negative pregnancy test prior to starting protocol therapy; sexually active patients may not participate unless they have agreed to use an effective double barrier contraceptive method. Abstinence is an acceptable method of birth control.

[3] Patients with neuroblastoma must have both CT/MRI and MIBG scintigraphy performed prior to enrollment if the patient was enrolled with or has a history of MIBG avid tumor. Otherwise, the NBL patient must have both CT/MRI and bone scan prior to enrollment. For patients with neuroblastoma and measurable disease by CT or MRI, lesions should be measured and followed using the same modality (CT or MRI) in addition to MIBG or bone scan. For patients with neuroblastoma with evaluable disease by MIBG scintigraphy or bone scan, use the same modality (MIBG scintigraphy or bone scan) to image patients; CT/MRI are not required but may be performed as clinically indicated.

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

[5] Patients with neuroblastoma must have bilateral bone marrow aspirates and biopsies. These do not need to be repeated if negative at study enrollment and patient is responding to therapy.

[6] For patients with known or suspected marrow disease for whom consent for correlative studies has been obtained, collect 5-10 mL bone marrow in preservative-free heparin when marrow evaluations are being performed for clinical indications. See Section 8.5 for details.

[7] See Section 8.6 for details regarding tumor tissue submission. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

[8] Patient diary (see Appendix XIII) should be reviewed and uploaded into RAVE at the end of each cycle.

[9] 12-lead EKG to be obtained at baseline and as clinically indicated.

8.2 **Radiology Studies**

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

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

COG institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1312) and date and shipped to Syed Aamer at the address below:

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

8.3 Pharmacokinetics (Required for Part A only)

8.3.1 Description of Studies and Assay
Plasma will be collected and AZD1775 (MK-1775) concentrations will be analyzed using an appropriate bioanalytic method.

8.3.2 Sampling Schedule
Blood samples will be obtained during Cycle 1 at the time points listed in Appendix VIII.

8.3.3 Sample Collection and Handling Instructions
Blood samples (2-3 mL) will be collected in lavender-top K_2EDTA tubes, gently inverted 6 to 8 times, and immediately placed in an ice bath. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.3.4 Sample Processing
Blood must be processed within 30 minutes from the time it is drawn. Centrifuge the blood samples for 10 minutes at 1500xg in a refrigerated centrifuge at 4°C. Remove at least 1 mL plasma by transfer pipette and transfer the plasma into a 3.6 ml nunc tube. Cap the tube tightly. Freeze immediately at -70 °C and store frozen until shipment.

8.3.5 Sample Labeling
Each tube must be labeled with the patient's I.D., patient's accession number, the study I.D. (ADVL1312), and the date and time the sample was drawn. Complete the Pharmacokinetic Study Form (see Appendix VIII), recording the date and time of collection for each sample. A copy of this form must accompany the sample(s) at time of shipment.

8.3.6 Sample Shipping Instructions

Samples may be batched for shipment, in freezer boxes containing at least 10 kg of DRY ICE. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours.

Shipments should be sent **Monday or Tuesday only** for priority overnight delivery to the following address:

Mark Hoffmann
Principal Investigator, Bioanalytical Services Covance Laboratories, Inc.
3301 Kinsman Blvd.
Madison, Wisconsin 53704
USA
Phone: 608-230-1762
Fax: 608-242-2735
Email: mark.hoffmann@covance.com

A notification email should be sent to Mark Hoffmann with courier name, airway bill number, expected delivery date/time and shipment contact.

8.4 **Pharmacodynamics (for Part A only)**

Preclinical studies showed that inhibition of p-CDK1 correlated with AZD1775 (MK-1775) exposures that resulted in tumor regression and immunohistochemical evidence of Wee1 inhibition in both tumor tissues and skin punch biopsies. While this trial is designed to define a maximally tolerated dose, the two correlative and exploratory studies below will aid in determining at which dose(s) p-CDK1 and γ-H2AX target engagement are occurring. Both studies will be done from the same collection (with the p-CDK1 being the priority if sample is limited).

8.4.1 Description of Studies

8.4.1.1 *p-CDK1 inhibition*: Whole blood will be collected for analysis of CDK1 phosphorylation in peripheral blood mononuclear cells (PBMCs).

8.4.1.2 γ-H2AX *induction*: Whole blood will be collected for analysis of γ-H2AX *induction* in peripheral blood mononuclear cells (PBMCs).

8.4.2 Sampling Schedule

Samples will be collected in consenting patients at the following 4 time points:

Day 1: prior to the irinotecan dose, prior to the AZD1775 (MK-1775) dose and 4 hours after the dose of AZD1775 (MK-1775) is given.

Day 2: prior to the irinotecan dose.

8.4.3 Sample Collection and Handling Instructions

Blood samples (1 ml per time point) will be collected in heparinized (green-top) tubes transferred to a smart tube followed by a 30 minute incubation period in a 37°C water bath. For each time point a separate smart tube will be used. After the 37°C incubation period, the smart tubes will be activated and then incubated at room temperature for 8 minutes. Samples will be stored at -80°C until shipment. Record the exact time that the sample is drawn along with the exact time that the drug is administered. Transport of frozen vials, if necessary, should take place on

dry ice. Record the exact time that the sample is drawn along with the exact time that the drug is administered. Please see details of preparation in Appendix IX-B.

8.4.4 Sample Labeling

Each tube must be labeled with the patient's I.D., patient's accession number, the study I.D. (ADVL1312), and the date and time the sample was drawn. Data should be recorded on the Pharmacodynamic Study Form (Appendix IX-A), which must accompany the sample(s).

8.4.5 Sample Shipping Instructions

Samples may be batched for shipment, in freezer boxes containing at least 10 kg of DRY ICE.

Shipments should be sent **Monday or Tuesday only** for priority overnight delivery to the following address:

Attn: Dr. Kristina Cole
The Children's Hospital of Philadelphia
The Colket Translational Research Building
Room 3300
3501 Civic Center Boulevard
Philadelphia, PA 19104

Please notify Dr. Cole of a pending shipment along with the Federal Express tracking number by e-mail at colek@email.chop.edu.

8.5 **Bone marrow Studies (for Parts A, B, or C, or D)**

Preclinical studies have shown that tumors with activated Wee1 (as measured by p-Wee1) or high levels of MYC / MYCN are more sensitive to Wee1 inhibition and are potential predictive biomarkers.

8.5.1 Description of Studies

Bone marrow samples will be analyzed for expression of potential predictive biomarkers of Wee1 inhibition responsiveness in correlative and exploratory studies.

8.5.2 Sampling Schedule

Samples will be collected at baseline and with disease re-evaluations in consenting patients with known or suspected marrow disease.

8.5.3 Sample Collection and Handling Instructions

Bone marrow samples (5-10 mL) will be collected and placed in tubes containing preservative-free heparin.

8.5.4 Sample Processing

Marrow samples in preservative-free heparin do not require additional on-site processing, but must be shipped to the Dr. Kristina Cole on the same day that they are obtained (see Appendix X).

8.5.5 Sample Labeling

Each tube must be labeled with the patient's I.D., patient's accession number, the study I.D. (ADVL1312), and the date and time the sample was drawn. Data should

be recorded on the Bone Marrow Study Form (see Appendix X), which must accompany the sample(s).

8.5.6 Sample Shipping Instructions

See Appendix X for detailed shipping and contact information for Dr. Cole's laboratory. Samples should be shipped on the same day that they are obtained. Specimens should be packed using appropriate biohazard materials and shipped at room temperature using an overnight courier.

8.6 **Tissue Studies (for Parts A, B, C, or D)**

Preclinical studies have shown that tumors with activated Wee1 (as measured by p-Wee1), high levels of EZH2 or high levels of MYC / MYCN are more sensitive to Wee1 inhibition and are potential predictive biomarkers. Archival tumor tissue should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.6.1 Description of Studies

Tissue will be collected from original diagnosis, relapse or any subsequent resection or biopsy for correlative and exploratory studies.

8.6.2 Sample Collection, Handling, and Shipment

Tissue blocks or slides will be shipped to Dr. Kristina Cole at the Children's Hospital of Philadelphia as described in Appendix XI. Detailed instructions regarding collection, handling, and shipping of tissue samples are located in Appendix XI.

9.0 AGENT INFORMATION

9.1 **AZD1775 (MK-1775)**

NSC#751084;

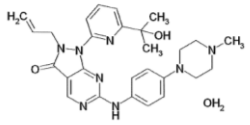
9.1.1 Structure and molecular weight

Chemical name: 2-allyl-1-[6-(1-hydroxy-1-methylethyl)pyridin-2-yl]-6-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one

Molecular formula: $C_{27}H_{32}N_8O_2 \cdot 0.5H_2O$

Molecular weight: 500.6

Chemical Structure of MK-1775:



9.1.2 Supplied by: Division of Cancer Treatment and Diagnosis (DCTD), NCI

9.1.3 Formulation

The agent is supplied as dry filled capsules in 25 mg (yellow color) and 100 mg

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(orange color) strengths in size 2 gelatin capsules. The dry-filled capsules consist of a roler-compacted granule of drug substance, lactose monohydrate, microcrystalline, cellulos, croscarmellose sodium, and magnesium stearate. Each high-density polyethylene (HDPE) bottle contains 20 capsules.

The pharmaceutical collaborator does not have stability data to support repackaging AZD1775 (MK-1775) capsules in any container other than what is provided.

9.1.4 Storage and Stability

AZD1775 (MK-1775) is to be stored at 2 to 30° C (36 to 86° F. Do not freeze. Shelf life studies of AZD1775 (MK-1775) are on-going. If a storage temperature excursion is identified, promptly return AZD1775 (MK-1775) to 2 - 30° C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

There is no stability data to support repackaging AZD1775 (MK-1775) capsules in any container other than the original bottle. Do not repackage in the pharmacy; dispense in the original container.

9.1.5 Administration

Patients will take AZD1775 (MK-1775) orally based on assigned dose, one hour after oral irinotecan.

AZD1775 (MK-1775) should be taken on an empty stomach one hour prior or two hours after a meal. Capsules should be swallowed whole and not opened or manipulated. If a dose is vomited it should not be repeated; resume administration with the next regularly scheduled dose.

AZD1775 (MK-1775) is primarily metabolized by CYP3A4 and is a weak, time-dependent inhibitor of CYP3A4; do not use in patients taking moderate and potent 3A4 inhibitors and inducers. The use of enzyme inducing anticonvulsants is not permitted (Appendix II).
Avoid concomitant CYP3A4 moderate or strong inhibitors/inducers, and sensitive substrates with a narrow therapeutic index. AZD1775 (MK-1775) is also a weak inhibitor of CYP2C19. Caution should be exercised with concomitant administration of sensitive substrates or substrates with a narrow therapeutic index.

In vitro transporter studies have shown that AZD1775 (MK-1775) was an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a substrate for P-gp and BCRP. The PK parameters of AZD1775 (MK-1775) could be altered if AZD1775 (MK-1775) is coadministered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when coadministered with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when coadministered with AZD1775 (MK-1775) and the use of atorvastatin is therefore prohibited.

The use of aprepitant as an antiemetic is prohibited due to early drug interaction

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data demonstrating increased exposure to AZD1775 (MK-1775). AZD1775 (MK-1775) is a p-glycoprotein substrate, but has not been evaluated as an inhibitor of p-glycoprotein; caution should be used with p-glycoprotein substrates and inhibitors.

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

9.1.6 AZD1775 (MK-1775) Toxicities

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 323 patients.* Below is the CAEPR for AZD1775 (adavosertib).

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

Version 2.7, April 27, 2020[1]

Adverse Events with Possible Relationship to AZD1775 (adavosertib) (CTCAE 5.0 Term) [n= 323]			**Specific Protocol Exceptions to Expedited Reporting**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Atrial fibrillation	
		Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal hemorrhage[2]	
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***

Adverse Events with Possible Relationship to AZD1775 (adavosertib) (CTCAE 5.0 Term) [n= 323]			Specific Protocol Exceptions to Expedited Reporting
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Fever		*Fever (Gr 2)*
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatitis)	
INFECTIONS AND INFESTATIONS			
	Infection[3]		*Infection[3] (Gr 3)*
INVESTIGATIONS			
	Alanine aminotransferase increased		*Alanine aminotransferase increased (Gr 3)*
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
	Neutrophil count decreased		*Neutrophil count decreased (Gr 4)*
	Platelet count decreased		*Platelet count decreased (Gr 4)*
	Weight loss		
	White blood cell decreased		*White blood cell decreased (Gr 4)*
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
	Dehydration		
	Hypokalemia		*Hypokalemia (Gr 2)*
	Hypomagnesemia		*Hypomagnesemia (Gr 2)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		*Back pain (Gr 2)*
	Muscle cramp		
	Myalgia		*Myalgia (Gr 2)*
NERVOUS SYSTEM DISORDERS			
	Dizziness		*Dizziness (Gr 2)*
	Headache		*Headache (Gr 2)*
		Intracranial hemorrhage	
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		*Cough (Gr 2)*
	Dyspnea		*Dyspnea (Gr 2)*
		Hypoxia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		*Rash[4] (Gr 2)*
VASCULAR DISORDERS			
		Phlebitis	

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

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage,

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Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[4]Rash may include rash, erythema, eczema, and rash maculo-papular.

[5]Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.

[6]Acute kidney injury includes renal impairment and acute renal insufficiency.

Adverse events reported on AZD1775 (adavosertib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD1775 (adavosertib) caused the adverse event:

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BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Blood and lymphatic system disorders - Other (right leg deep vein thrombosis); Leukocytosis
Cardiac disorders - Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired; Tinnitus
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (eye swelling); Eye pain; Keratitis; Photophobia; Scleral disorder; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Belching; Bloating; Cheilitis; Colitis; Colonic obstruction; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Flatulence; Gastric ulcer; Gastritis; Hemorrhoids; Oral pain; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation; Malaise; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased
METABOLISM AND NUTRITION DISORDERS - Alkalosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoid tumor); Tumor pain
NERVOUS SYSTEM DISORDERS - Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Paresthesia; Peripheral neuropathy[5]; Presyncope; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression

RENAL AND URINARY DISORDERS - Acute kidney injury[6]; Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Reproductive system and breast disorders - Other (female genital tract fistula)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Apnea; Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: AZD1775 (adavosertib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.7 Agent Ordering and Agent Accountability

AZD1775 (MK-1775) will be supplied by the NCI. NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

9.1.8 Clinical Drug Request

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB anytime. Refer to the PMB's website for specific policies and guidelines related to agent management. Questions about IB access may be directed to the PMB IB coordinator via email.

9.1.9 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.10 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

9.1.11 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

9.2 Cefixime (11/17/17)

(Suprax®)

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.
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 Administration

Given orally at 8 mg/kg/day (maximum dose 400 mg) divided every 12-24 hours. May be administered with or without food; administer with food to decrease GI distress. However, if administered with food ensure that sufficient time has elapsed prior to administering AZD1775 (MK-1775) (refer to section 9.1.5 for details)

Shake the suspension prior to withdrawing dose or administration.

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

9.2.5 Supplied by: Commercially available from various manufacturers. See package insert for more detailed information.

9.3 **IRINOTECAN** **(03/07/17)**

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

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 and (Appendix V). For oral use, the appropriate volume of irinotecan solution (20 mg/ml) should be 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 protocol for pre-medication and supportive care measures.

For this protocol, irinotecan is administered orally, 1 hour prior to AZD1775 (MK-1775).

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

9.3.5 Supplied by:

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

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section 6.0).
c) Refusal of further protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 18 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 AZD1775 (MK-1775) (and/or irinotecan, if applicable). See Sections 4.0 and 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 attributed to protocol therapy that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any further required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) Patient did not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Strata:
Part A: Patients with relapsed or refractory solid tumors (Phase 1)
Part B: Patients with relapsed or refractory neuroblastoma (Phase 2)
Part C: Patients with relapsed or refractory medulloblastoma/CNS PNET (Phase 2)
Part D: Patients with relapsed or refractory rhabdomyosarcoma (Phase 2)

A minimum of 3 evaluable patients with relapsed or refractory solid tumors including CNS tumors (Part A) will be entered at each dose level for determination of MTD. Once the MTD or recommended phase 2 dose has been defined, up to 6 additional patients with relapsed/refractory solid tumors may be enrolled to acquire PK data in a representative number of young patients (*i.e.* 6 patients in each group of < 12 years old and ≥ 12 years old). Review of the enrollment rate into previous COG new agent studies indicates that 1-2 patients per month are available, which will permit completion of this part of the study within 22-44 months. Assuming an inevaluability rate of 20%, a maximum of 44 patients is anticipated in Part A. In the unlikely scenario that all dose levels require expansion to 12 evaluable patients (Section 11.2.2), a maximum of 80 patients is anticipated.

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

Disease Group/Part	Patients/Year
Neuroblastoma	36
Medulloblastoma/CNS PNET	15
Rhabdomyosarcoma	8

A minimum of 29 patients and a maximum of 74 patients are expected to enroll in Parts B, C, and D, assuming an inevaluability rate of 20%. We anticipate that the entire study will require 37-82 months for enrollment and evaluation of all parts.

The MTD/RP2D of Part A was determined to be Dose Level 4 (85 mg/m^2/dose AZD1775 and 90 mg/m^2/dose irinotecan on a 21-day cycle). Part A has been completed 37 patients were enrolled, no patients were ineligible.

11.2 Definitions

11.2.1 Evaluable For Adverse Effects

Any patient who experiences DLT at any time during protocol therapy is considered evaluable for Adverse Effects. Note: Patients who experience dose-limiting diarrhea must have received at least 85% of the protocol-specified supportive care (e.g. cefixime or equivalent) in Cycle 1 to be considered evaluable for this Adverse Effect.

Patients without DLT who receive all of the prescribed dose in Cycle 1 protocol guidelines and had the appropriate toxicity monitoring studies performed are also considered evaluable for Adverse Effects. Patients who are not evaluable for Adverse Effects at a given dose level will be replaced.

11.2.2 Maximum Tolerated Dose

The MTD or recommended phase 2 dose will be the maximum doses of AZD1775 (MK-1775) and irinotecan at which fewer than one-third of patients experience DLT (See Section 5.5) when receiving AZD1775 (MK-1775) in combination with irinotecan in Part A. In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

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

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

11.2.3 Evaluability for Response

Any patient who is enrolled and receives at least one dose of AZD1775 (MK-1775) in combination with irinotecan will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy; or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 11.4. Two objective status determinations are required to confirm best response (Section 12.7). All other patients will be considered non-responders. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See Section 8.2 regarding shipping instructions. Preliminary assessment of activity using institutionally provided tumor measurements will be entered into CDUS quarterly. The central review by COG will be provided as the final reviewed assessment of response when such becomes available.

11.3 **Dose Escalation and Determination of MTD (Part A)**

The 3+3 design will be used for dose-escalation in Part A for determination of MTD in each Part of the study

11.3.1 Three patients are studied at the first dose level.

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

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

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

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

11.3.1 If two or more of a cohort of up to six patients experience DLT at a given dose

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

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

The MTD/RP2D of Part A was determined to be Dose Level 4 (85 mg/m^2/dose AZD1775 and 90 mg/m^2/dose irinotecan on a 21-day cycle).

11.4 Phase 2 Evaluation in Neuroblastoma (Part B), Medulloblastoma/CNS PNET (Part C) and Rhabdomyosarcoma (Part D)

The best response of disease to AZD1775 (MK-1775) in combination with irinotecan will be examined separately in each of Parts B, C, and D.

11.4.1 Study Design for patients with Neuroblastoma (Part B)

The following Simon's optimal two stage design[35] will be used in Part B.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 patients	0	Terminate the trial: agent ineffective
	1 or more	Inconclusive result, continue trial (proceed to stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the trial: agent ineffective
	3 or more	Terminate the trial: agent effective

AZD1775 (MK-1775) in combination with irinotecan will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

11.4.2 Study Design for patients with Medulloblastoma/CNS PNET (Part C)
The following Simon's optimal two stage design[35] will be used in Part C.

	Cumulative Number of Responses	Decision
Stage 1: Enter 9 patients	1 or less	Terminate the trial: agent ineffective
	2 or more	Inconclusive result, continue trial (proceed to stage 2)
Stage 2: Enter 10 additional patients	5 or less	Terminate the trial: agent ineffective
	6 or more	Terminate the trial: agent effective

AZD1775 (MK-1775) in combination with irinotecan will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 15% and of sufficient activity if the true response rate is 40%. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 15%, the rule described above will identify it of sufficient activity for further study with probability 0.05 (type I error), and the trial will have an expected sample size of 13 with 60% probability of early termination. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 40%, the rule described above will identify it of sufficient activity for further study with probability 0.81 (power against the alternative hypothesis P = 0.40).

11.4.3 Study Design for patients with Rhabdomyosarcoma (Part D)
The following Simon's optimal two stage design[35] will be used in Part D.

	Cumulative Number of Responses	Decision
Stage 1: Enter 10 patients	0	Terminate the stratum: agent ineffective
	1 or more	Inconclusive result, continue stratum (proceed to stage 2)
Stage 2: Enter 10 additional patients	2 or less	Terminate the stratum: agent ineffective
	3 or more	Terminate the stratum: agent effective

AZD1775 (MK-1775) in combination with irinotecan will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If AZD1775 (MK-1775) in combination with irinotecan has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Response in all patients will be determined according to the evaluation criteria outlined in Section 12.0 as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) and reported as final results. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

Data collected from any patients enrolled at the MTD or recommended phase 2 dose or enrolled onto Parts B, C, or D will be utilized in the Phase 2 study.

11.4.4 Method of Analysis

Response criteria are described in Section 12.0. Response rates will be calculated as the percent of patients whose best response is a CR or PR and confidence intervals will be constructed according to the method of Chang.[36] A responder is defined as a patient who achieves a best confirmed response (as defined in Section 12.7) of PR or CR on the study.

11.5 **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.

11.6 **Pharmacokinetic and Correlative Studies and Response Analysis**

A descriptive analysis of pharmacokinetic (PK) parameters of AZD1775 (MK-1775) 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 AZD1775 (MK-1775), 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.

Decreased p-CDK1 indicating Wee1 inhibition by AZD1775 (MK-1775) and predictive biomarkers of AZD1775 (MK-1775) sensitivity will also be investigated. All these analyses will be descriptive and exploratory and hypotheses generating in nature.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized 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 web site 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 at least 21 days following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[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 combination therapy, and have had their disease re-evaluated will be considered evaluable for response.

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

12.2.2 Disease Parameters

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

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

12.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and

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

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

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

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

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

12.2.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-

up is a sign of PD based on a new lesion.

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

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

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR):	Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

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

12.3.2 Complete Response
Disappearance of all evaluable disease.

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

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

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

12.3.6 Overall Best Response Assessment

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

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable or evaluable disease.

12.4.1 MIBG Positive Lesions

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

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

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

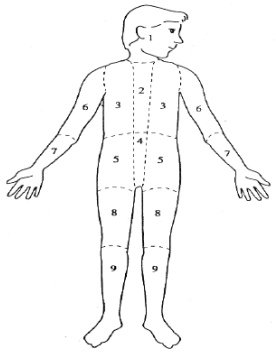
12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

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

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

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



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

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

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 5 in Section 12.7.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

Note: Neuroblastoma patients who do not have MIBG positive lesions or bone marrow involvement should be assessed for response as solid tumor patients with measurable or evaluable disease.

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 14 days prior to start of protocol therapy 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 12.7.

12.6 Response Criteria for Patients with CNS Tumors

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

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

12.6.3 Selection of Target and Non-Target Lesions
For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

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

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

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

12.6.5 Response Criteria for Non-Target Lesions:

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

12.6.6 Response criteria for tumor markers (if available):

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

12.6.7 Overall Response Assessment

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

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

PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

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

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥21 days Confirmation**
CR	Non-CR/Non-PD	No	PR	≥21 days Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥21 days from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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

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

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

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

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

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

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

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

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

12.7.2 **Duration of Response**

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

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

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

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

Step 1: Identify the type of adverse event using the NCI CTCAE version 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 web site 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 (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR below under the section titled "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 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 that 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 AND LYMPHATIC SYSTEM 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	Dyspepsia
METABOLISM AND NUTRITION DISORDERS	Dehydration
NERVOUS SYSTEM DISORDERS	Dysgeusia
PSYCHIATRIC DISORDERS	Insomnia

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.6 of the protocol. Additional protocol-specific exceptions to expedited reporting of serious adverse events are the toxicities in bold font listed under the drug information section of the protocol (Section 9.1).

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 call CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

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

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at https://ctepcore.nci.nih.gov/ctepaers/pages/task.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at https://ctepcore.nci.nih.gov/ctepaers/pages/task. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Send supporting documentation to the NCI by fax (fax # 301-230-0159) and by email to the ADVL1312 Study-Assigned Research Coordinator. **ALWAYS include the ticket number on all faxed documents**.

13.4 Definition of Onset and Resolution of Adverse Events

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

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

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

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

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

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

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2)

should be reported at the end of each cycle using the forms provided in the data form packet (See Section 14.1).

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

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

13.6 **Reporting Secondary AML/MDS**

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of 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 treatment for cancer on NCI-sponsored trials.

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 faxed along with any additional medical information to (301) 230-0159 and also emailed to the ADVL1312 Study-Assigned Research Coordinator. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy

occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy) under the Pregnancy, puerperium and perinatal conditions System Organ Class (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 Pregnancy Loss (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**.

- Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

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 data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 CDUS

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

14.3 CRADA/CTA/CSA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting

or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the 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: 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 III: 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]	atazanavir	aprepitant	barbiturates	bosentan
alfentanil[4,5]	boceprevir	conivaptan	carbamazepine	dabrafenib
amiodarone[4]	clarithromycin	crizotinib	enzalutamide	efavirenz
aprepitant/fosaprepitant	cobicistat	diltiazem	fosphenytoin	etravirine
atorvastatin	darunavir	dronedarone	phenobarbital	modafinil
axitinib	delavirdine	erythromycin	phenytoin	nafcillin
bortezomib	grapefruit[3]	fluconazole	primidone	rifapentin
bosutinib[5]	grapefruit juice[3]	fosamprenavir	rifampin	
budesonide[5]	idelalisib	grapefruit[3]	St. John's wort	
buspirone[5]	indinavir	grapefruit juice[3]		
cabozantinib	itraconazole	imatinib		
calcium channel blockers	ketoconazole	isavuconazole		
cisapride	lopinavir/ritonavir	mifepristone		
citalopram/escitalopram	nefazodone	nilotinib		
cobimetinib[5]	nelfinavir	verapamil		
conivaptan[5]	posaconazole			
copanlisib	ritonavir			
crizotinib	saquinavir			
cyclosporine[4]	telaprevir			
dabrafenib	telithromycin			
dapsone	voriconazole			
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				

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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 7.5 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)

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APPENDIX IV: AZD1775 (MK-1775) DOSING NOMOGRAM

AZD1775 (MK-1775) Dose Assignment Parts B, C, D
(Recommended Phase 2 Dose 85 mg/m^2)

BSA (m^2)	Total Daily Dose (mg/day)
0.49-0.73	50
0.74-1.03	75
1.04-1.32	100
1.33-1.62	125
1.63-1.91	150
1.92-2.2	175
2.21-2.5	200
≥ 2.51	225

AZD1775 (MK-1775) Dose Modification Parts B, C, D
(Dose Reduction for toxicity ≈ 65 mg/m^2)

BSA (m^2)	Total Daily Dose (mg/day)
0.49-0.73	25
0.74-1.03	50
1.04-1.32	75
1.33-1.62	100
1.63-1.91	100
1.92-2.2	125
2.21-2.5	150
≥ 2.51	175

APPENDIX V: 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 1 hour before the other study drug AZD1775 (MK-1775)

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 at around the same time each day one (1) hour before the study drug AZD1775.
- Take/Give irinotecan on an empty stomach, at least one (1) hour after food.
- Wait one (1) hour after irinotecan before taking AZD1775. Wait at least one (1) hour after AZD1775 before giving/eating any food.
- 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 20 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 VI: PATIENT INSTRUCTIONS FOR TREATING DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

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. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given loperamide based on body weight.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking loperamide (Imodium). **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 2 hours until the diarrhea slows or the 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):

LOPERAMIDE DOSING RECOMMENDATIONS FOR LATE DIARRHEA (maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (one-half teaspoonful of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg per day (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (1 teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (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 (one teaspoonful of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg per day (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (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 (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg per day (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (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 (2 teaspoonfuls of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg per day (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (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 (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 (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 VII: CORRELATIVE STUDIES GUIDE

PART A **Correlative Study**	**Appendix**	**Blood Volume**				**Tube Type**
		Volume per sample	**Total Volume > 30 kg**	**Total Volume 20-30 kg**	**Total Volume <20 kg**	
Pharmacokinetics	VIII	2-3 ml	28-42 ml	28-42 ml	12-18 ml	Lavender-top K_2EDTA
Pharmacodynamics	IX	5-8 ml*	32 ml	20 ml	----	Heparinized (green-top)
Bone Marrow Studies	X	5-10 ml	10-20 ml	10-20 ml	10-20 ml	Preservative-free heparin (green top)
Tumor Tissue (Required) *See Section 8.6 for details*	XI	-	-	-	-	-
Total Blood Volume			**60-74 ml**	**48-62 ml**	**12-18 ml**	
Total Bone Marrow Volume			**10-20ml**	**10-20ml**	**10-20ml**	

*Sample volume is 5 ml for patients 20-30 kg and 8 ml for patients > 30 kg.

PART B, C, or D **Correlative Study**	**Appendix**	**Sample Volume**		**Tube Type**
		Volume per sample	**Total Cycle 1**	
Bone Marrow Studies	X	5-10ml	10-20 ml	Preservative-free heparin (green top)
Tumor Tissue (Required) *See Section 8.6 for details*	XI	-	-	-
Total Bone Marrow Volume			**10-20ml**	

APPENDIX VIII: PHARMACOKINETIC STUDY FORM (PART A ONLY)

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

AZD1775 (MK-1775) Dose Level: _____mg/m^2 AZD1775 (MK-1775) Total Daily Dose: _____mg

Blood samples (2-3 mL) will be collected in K2 EDTA (lavender-top) tubes in patients ≥ 20 kg at the following time points (+/- 10 minutes): Day 1 (pre-dose, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr and 24 hours after dose), Day 4 (pre-dose), Day 5 (pre-dose, 1 hr, 2 hr, 4 hr, 6 hr, and 8 hr after dose) of Cycle 1.

For patients < 20 kg, samples will be collected at the following time points (+/- 10 minutes): Day 1 (pre-dose, 1 hr and 8 hr after dose) and Day 5 (pre-dose, 1 hr and 8 hr after dose).

Record the exact time the sample is drawn along with the exact time AZD1775 (MK-1775) is given on Day 1.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1*	**Day 1**	Prior to irinotecan dose	___/___/___	|__|__| : |__|__|
AZD1775 Dose on Day 1 Date: ___/___/___			**Time:** |__|__| : |__|__|	
2*	**Day 1**	1 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
3	**Day 1**	2 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
4	**Day 1**	4 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
5	**Day 1**	6 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
6*	**Day 1**	8 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
7	**Day 2**	24 (±2) hrs after Day 1 AZD1775 dose (prior to irinotecan on Day 2)	___/___/___	|__|__| : |__|__|
AZD1775 Dose on Day 2 Date: ___/___/___			**Time:** |__|__| : |__|__|	
8	**Day 4**	Prior to irinotecan dose	___/___/___	|__|__| : |__|__|
AZD1775 Dose on Day 4 Date: ___/___/___			**Time:** |__|__| : |__|__|	
9*	**Day 5**	Prior to irinotecan dose	___/___/___	|__|__| : |__|__|
AZD1775 Dose on Day 5 Date: ___/___/___			**Time:** |__|__| : |__|__|	
10*	**Day 5**	1 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
11	**Day 5**	2 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
12	**Day 5**	4 hr after AZD-1775 dose	___/___/___	|__|__| : |__|__|
13	**Day 5**	6 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|
14*	**Day 5**	8 hr after AZD1775 dose	___/___/___	|__|__| : |__|__|

* Patients < 20 kg should have only these samples collected.

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 who collected samples)

APPENDIX IX-A: PHARMACODYNAMIC STUDY FORM (PART A ONLY)

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 Dose Level: _____mg/m^2 AZD1775 Total Daily Dose: _____mg

Blood samples (8 ml for patients > 30 kg and 5 ml for patients 20-30 kg) will be collected:

Cycle 1 Day 1 prior to the irinotecan infusion, prior to the AZD1775 (MK-1775) dose, 4 hours after the dose of AZD1775 is given, and prior to the irinotecan dose on Day 2.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Collected (24-hr clock)
1	Cycle 1, Day 1	prior to the irinotecan dose		|__|__| : |__|__|
Irinotecan Dose on Day 1 Date:___/___/___ Time: |__|__| : |__|__|				
2	Cycle 1, Day 1	prior to the AZD1775 dose		|__|__| : |__|__|
AZD1775 Dose on Day 1 Date:___/___/___ Time: |__|__| : |__|__|				
3	Cycle 1, Day 1	4 hours after the AZD1775 dose		|__|__| : |__|__|
4	Cycle 1, Day 2	24 (±2) hrs after Day 1 AZD1775 dose (prior to the irinotecan dose on Day 2)		|__|__| : |__|__|

One copy of this Pharmacodynamic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.4.6. See Section 8.4 for detailed guidelines for packaging and shipping PD samples.

Record any notes for Sample Storage Conditions below.

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 who collected samples)

APPENDIX IX-B: PD SAMPLE COLLECTION GUIDELINES

Required Items:

- Whole blood collection at required PD time points as outlined in Appendix IX-A
- Smart Tubes at room temperature (one per incubation condition): will be provided by study team
- Water bath pre-warmed to 37°C
- -80°C freezer or dried ice
- Complete RPMI (optional)

Protocol:

1. Use an approved tube containing sodium heparin (ie. green top Vacutainer) to collect PD sample. Ensure good mixing with the anticoagulant by inverting the securely capped tube at least 6 times. Begin incubation of the blood with the Smart Tube system as soon as possible, ideally within two hours of the blood draw. Keep the blood at room temperature until it is assayed with the Smart Tube system.

2. Add 1 milliliter (ml) of the whole blood sample to each Smart Tube. Immediately cap the Smart Tube and vortex or invert six times to ensure good mixing with the agents added.

3. Place the Smart Tubes in the 37°C water bath for 30 minutes.

4. At the end of the 30 minutes incubation time remove the Smart Tubes from the water bath and activate the Smart Tubes manually. To activate a Smart Tube manually, make sure the cap is screwed on securely and then bend the Smart Tube in the middle until you feel the ampoule inside break, then invert the Smart Tube 10 times to ensure good mixing (gently shaking the Smart Tube up and down 10 times is an acceptable alternative to inverting it 10 times).

5. Incubate the activated Smart Tubes at room temperature for 8 minutes.

6. Immediately transfer the Smart Tubes to a -80°C freezer or place in direct contact with dry ice. The Smart Tubes should be stored at -80°C until the sample is analyzed. Samples frozen in Smart Tubes should not be stored at temperatures warmer than -80°C. Smart Tubes have not been validated for storage in liquid nitrogen. Samples will be stored at -80°C and shipped when all PD time points have been collected. Tubes need to be shipped on dry ice. All samples should be shipped to address as outlined in section 8.4.3. Samples should NOT be shipped on a Friday or before a holiday.

APPENDIX X: BONE MARROW STUDY FORM (PART A, B, C OR D)

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

Bone marrow samples (5-10 ml) will be collected in preservative-free heparin (green-top) tubes at baseline and with disease re-evaluations in consenting patients with known or suspected marrow disease.

Type of sample:	☒bone marrow
Check the box to indicate when sample was drawn:	☐baseline ☐other
Date Sample Collected:	
Time Sample Collected:	
Sample Volume	_____ mL
Number of tubes	

Sample(s) should be shipped at room temperature to the address below the same day the samples are obtained, if possible. Samples should be shipped via overnight priority delivery for arrival on a Monday through Friday only. Weekend deliveries are not accepted at the laboratory. Bone marrow samples that cannot be delivered on a weekday should be stored refrigerated at 4°C until they are shipped that following Monday. Data should be recorded on this study form, and a copy of the form should be sent with the sample(s) at each shipment. A copy of the form should also be uploaded into RAVE.

Samples should be shipped to:

Attn: Dr. Kristina Cole
The Children's Hospital of Philadelphia
The Colket Translational Research Building
Room 3300
3501 Civic Center Boulevard
Philadelphia, PA 19104

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 who collected samples)

APPENDIX XI: TISSUE STUDY FORM (PART A, B, C, OR D)

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

Tumor Sample Labeling:
Samples should be labeled with the following information:

Protocol number: **ADVL1312**
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 must be packaged appropriately and shipped at room temperature to Dr. Kristina Cole (at the address below). If a tumor block is not available, please send as many scrolls from the tumor block and/or a minimum of 10 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 lab address below.

Attn: Dr. Kristina Cole
The Children's Hospital of Philadelphia
The Colket Translational Research Building
Room 3300
3501 Civic Center Boulevard
Philadelphia, PA 19104

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 who collected samples)

APPENDIX XII: 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 XIII: MEDICATION DIARY FOR AZD1775 (MK-1775)

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

Complete each day with the time and dose given for cefixime (CEF) or equivalent, irinotecan, and AZD1775 (MK-1775). If a dose is not due or is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below. (NOTE: irinotecan should be taken 1 hour prior to AZD1775 (MK-1775); note the time taken in the comments column).*** Cefixime or an available equivalent antibiotic (i.e. cefpodoxime) will be used as diarrheal prophylaxis and administered at least 2 days prior to the first dose of irinotecan, during, and 3 days after the last dose of irinotecan. AZD1775 (MK-1775) capsules should not be opened or crushed but should be swallowed whole. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform your study doctor or nurse if that occurs. AZD1775 (MK-1775) should be taken on an empty stomach 1 hour before or 2 hours after food. If you vomit after taking the medication, the dose will not be repeated. Add the dates to the calendar below and return the completed diary to your institution after each treatment cycle. Your institution will upload this document into RAVE after each treatment cycle.

EXAMPLE			*Number of AZD1775 (MK-1775) capsules*		*Comments*
	Date	*Time*	*25 mg*	*100 mg*	
Day 1	*1/15/14*	*8:30 AM*	2	1	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #:_____ AZD1775 (MK-1775) Dose:_____ Start Date: |__/__|__/__|__/__| **End Date:** |__/__|__/__|__/__|

PRE	Date	Time			Comments
Day -2		**CEF: _____**			
Day -1		**CEF: _____**			
	Date	**Time**	**25 mg**	**100 mg**	**Comments**
Day 1		**CEF: _____ Irinotecan: _____**			
		AZD1775: _____			
Day 2		**CEF: _____ Irinotecan: _____**			
		AZD1775: _____			
Day 3		**CEF: _____ Irinotecan: _____**			
		AZD1775: _____			
Day 4		**CEF: _____ Irinotecan: _____**			
		AZD1775: _____			
Day 5		**CEF: _____ Irinotecan: _____**			
		AZD1775: _____			
Day 6		**CEF: _____**			
Day 7		**CEF: _____**			

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

	Date	Time			Comments
Day 8		**CEF:** _____			
Day 9					
Day 10					
Day 11					
Day 12					
Day 13					
Day 14					
	Date	**Time**			**Comments**
Day 15					
Day 16					
Day 17					
Day 18					
Day 19					
Day 20		**CEF:** _____			
Day 21		**CEF:** _____			

APPENDIX XIV: 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.

AZD1775 (MK-1775)

Drugs that may interact with AZD1775 (relevant drugs listed by generic name)
• **Some antibiotics (chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, norfloxacin, rifabutin, rifampin, telithromycin)** • **Some antidepressants (fluoxetine, fluvoxamine, nefazodone)** • **Some antiepileptics (carbamazepine, oxcarbazepine, phenobarbital, phenytoin)** • **Some antifungals (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)** • **Some antiretrovirals and antivirals (boceprevir, delaviridine, efavirenz, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir)** • **Several other specific agents, including the following:** o **Aprepitant** o **Amiodarone** o **Barbiturates** o **Cimetidine** o **Diltiazem** o **Imatinib** o **Mifepristone** o **Modafinil** o **Pioglitazone** o **Verapamil**
Food and supplements* that may interact with AZD1775
• **Echinacea** • **St. John's Wort** • **Some fruits and juices: grapefruit, grapefruit juice, Star fruit**

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

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.*

Drugs that may interact with irinotecan

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

Food and supplements* that may interact with irinotecan
• **Echinacea** • **St. John's Wort** • **Some fruits and juices: grapefruit, grapefruit juice, Star fruit**

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

APPENDIX XV: MEDICATIONS ASSOCIATED WITH PROLONGED QT_C

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference: Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date December 2nd, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Medications that prolong QTc	
Amiodarone	Flecainide
Anagrelide	Fluconazole
Arsenic trioxide	Haloperidol
Azithromycin	Ibutilide
Chloroquine	Methadone
Chlorpromazine	Moxifloxacin
Ciprofloxacin	Ondansetron
Citalopram	Pentamidine
Clarithromycin	Pimozide
Disopyramide	Procainamide
Dofetilide	Propofol
Domperidone	Quinidine
Droperidol	Sevoflurane
Dronedarone	Sotalol
Erythromycin	Thioridazine
Escitalopram	Vandetanib

Medications that MAY prolong QTc	
Aripiprazole	Lapatinib
Bortezomib	Lenvatinib
Bosutinib	Leuprolide
Ceritinib	Mirtazapine
Clomipramine	Nicardipine
Crizotinib	Nilotinib
Dabrafenib	Olanzapine
Dasatinib	Osimertinib
Degarelix	Pazopanib
Desipramine	Promethazine
Dolasetron	Risperidone
Eribulin mesylate	Sorafenib
Famotidine	Sunitinib
Foscarnet	Tacrolimus
Gemifloxacin	Vemurafenib
Granisetron	Venlafaxine
Isradipine	Vorinostat

APPENDIX XVI: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial 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.

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

Requirements For APEC1621I 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)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For 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.

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.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Data Submission / Data Reporting

Data collection for this study will be done exclusively 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) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

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.