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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January 31, 2019

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Dear Ms. Kruhm,

Enclosed please find Amendment #8 to **ADVL1217**, *A Phase 1 Study of AZD1775 (MK-1775) Concurrent with Local Radiation Therapy for the Treatment of Newly Diagnosed Children with Diffuse Intrinsic Pontine Gliomas.*

The protocol has been amended in response to the Request for Amendment from Dr. Malcolm Smith, dated December 20, 2018, in which COGC transitions to PEP-CTN.

Please contact us if you have any further questions.

Sincerely,

Alina Stout, Protocol Coordinator for
Sabine Mueller, M.D., Ph.D., **ADVL1217** Study Chair, and
Brenda Weigel, M.D., PI, PEP-CTN

SUMMARY OF CHANGES

The following specific revisions have been made to the protocol and informed consent documents:

I. Protocol Changes:

#	Section	Comments
1.	Title Page	The version date has been updated. The amendment number has been updated. The "Lead Organization" has been updated. The list of "Participating Organizations" has been removed. The following sentence has been revised: "**For PEP-CTN Operations and Data/Statistics Contacts See: http://members.childrensoncologygroup.org** ~~For Group Operations and Statistics & Data Center Contacts See: http://members.childrensoncologygroup.org~~"
2.	TOC	The Table of Contents has been updated.
3.	Study Committee	The following sentence has been revised: "For ~~Group Operations (GOC) and~~**PEP-CTN Operations and Data/Statistics** ~~Statistics & Data Center (SDC) c~~Contacts see: …"
4.	Certificate of Confidentiality	The following sentence has been revised: "~~The Children's Oncology Group has received~~**his trial is covered by** a Certificate of Confidentiality…"
5.	13.3	The CTEP-AERS sponsor email address has been updated from "~~COGCADEERS@childrensoncologygroup.org~~" to "**PEPCTNAERS@childrensoncologygroup.org**".
6.	14.4	References to "Developmental Therapeutics" have been replaced with references to "PEP-CTN".

II. Informed Consent Document Changes:

#	Section	Comments
7.	General	The version date has been updated.
8.	1st page	References to the "Phase 1 Consortium" have been replaced with references to PEP-CTN.
9.	"Will my medical	The following sentence has been revised:

	information…?"	"T~~he Children's Oncology Group has received~~**his trial is covered by** a Certificate of Confidentiality…"

Activated: August 19, 2013
Closed:

Version Date: 01/31/19
Amendment #: 8

CHILDREN'S ONCOLOGY GROUP

ADVL1217

A PHASE 1 STUDY OF AZD1775 (MK-1775) CONCURRENT WITH LOCAL RADIATION THERAPY FOR THE TREATMENT OF NEWLY DIAGNOSED CHILDREN WITH DIFFUSE INTRINSIC PONTINE GLIOMAS

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

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AGENT NSC#

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

SEE SECTION 8.4.6 AND 8.5.5 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

AZD1775 (formerly MK-1775) is an oral selective Wee1 kinase inhibitor. Wee1 kinase is a critical driver of G_2-M cell cycle progression. Activated Wee1 phosphorylates CDC2, inhibiting its function. In normal cells, increasing levels of inactivated, phosphorylated CDC2 prevents damaged cells from entering into mitosis before DNA is repaired. Like normal cells, most cancer cells rely on this pathway to delay cell cycle progression and allow repair of DNA damage caused by rapid cell division or DNA-damaging agents. Without a proficient G_2 checkpoint, cancer cells progress through the cell cycle with damaged DNA and ultimately succumb to fatal mitosis. Wee1 is highly expressed in pediatric high-grade gliomas, including diffuse intrinsic pontine gliomas (DIPG) and *in vitro* and *in vivo* studies have shown that the combination of Wee1 inhibitor AZD1775 (MK-1775) radiosensitizes pediatric glioma cells.

This is a dose escalation study of AZD1775 (MK-1775) in combination with radiation for newly diagnosed children with DIPG. We will evaluate the MTD and toxicity profile of AZD1775 (MK-1775) in combination with a standard radiation therapy regimen used in the treatment of this disease. Pharmacokinetic and pharmacodynamics studies will be conducted to further define the exposure to and activity of AZD1775 (MK-1775) in combination with radiation in pediatric patients.

EXPERIMENTAL DESIGN SCHEMA

AZD1775 (MK-1775) will be administered orally after a predetermined number of radiation therapy fractions given on a Monday through Friday schedule for a total of 30 fractions over 6 weeks. The number or fractions followed by AZD1775 (MK-1775) will depend upon assigned dose level.

Treatment	Monday through Friday	Saturday and Sunday
Radiation therapy	X	
AZD1775 (MK-1775)	X^	
Rest Period		X

^Frequency of AZD1775 (MK-1775) will vary depending on dose level. See Section 5.1 and Appendix V for specific dosing.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) or recommended phase 2 dose and schedule of the Wee1 inhibitor AZD1775 (MK-1775) administered concurrently with radiation therapy in children with newly diagnosed diffuse intrinsic pontine glioma (DIPG).

1.1.2 To define and describe the toxicities of AZD1775 (MK-1775) given concurrently with radiation therapy in children with newly diagnosed DIPG.

1.1.3 To characterize the pharmacokinetics of AZD1775 (MK-1775) in children with newly diagnosed DIPG when given concurrently with radiation therapy.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of AZD1775 (MK-1775) within the confines of a phase 1 study, including response rate, progression free survival, and overall survival of treated patients.

1.2.2 To assess the biologic activity of AZD1775 (MK-1775) by measuring expression of p-CDC2 and p-HH3 in peripheral blood mononuclear cells (PBMCs) before and after administration of AZD1775 (MK-1775) in children with newly diagnosed DIPG.

1.2.3 To assess the biologic activity of AZD1775 (MK-1775) by measuring expression of γ-H2AX in PBMCs, a marker of DNA double-strand breaks (dsDNA), before and after administration of AZD1775 (MK-1775) in children with newly diagnosed DIPG.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Pre-clinical studies provide the rationale for targeting Wee1 in combination with radiation for the treatment of children with DIPG. Wee1 is significantly over-expressed in pediatric high-grade gliomas as well as DIPGs and the Wee1 inhibitor AZD1775 radiosensitizes a variety of cancer cells including pediatric high-grade gliomas. Therefore, we propose a phase 1 study of AZD1775 administered concurrently with focal radiation therapy. We know from prior experience that focal radiation therapy for children with DIPG is generally well tolerated and that radiation therapy by itself has no significant hematological toxicity. Other expected side effects from treatment with AZD1775, based on adult phase 1 studies, include gastrointestinal related toxicity as well as constitutional symptoms such as fatigue.

<u>Diffuse Intrinsic Pontine Gliomas in Children:</u>

The diagnosis of DIPG continues to carry a dismal prognosis with virtually no long-term survivors.[1] Despite several lines of research, outcomes for these children have not significantly changed over many decades and most children die after a median survival of 9 months even when treated on recently conducted clinical trials. DIPGs continue to be diagnosed mainly by radiographic appearance. In children who undergo biopsies the most common histological diagnoses are high-grade gliomas.[1] Radiation therapy is the only proven effective therapy in prolonging life for children with DIPGs. Therefore, demonstrating synergy of targeted agents with radiation is a key step towards producing novel drugs with potential to impact survival.

Radiation causes DNA damage that activates a cascade of signaling events leading to cell cycle arrest that allows DNA repair, and should DNA damage fail to be repaired, cell death ensues. Disruption of normal cell-cycle check-points due to p53 mutation is common in cancer cells including pediatric HGGs as well as in DIPGs.[2,3] Whereas normal cells with wild-type (wt) p53 have both the G_1 and G_2 checkpoints at their disposal to protect against DNA damage, cancer cells with p53 mutations have a greater dependency on the G_2 checkpoint to initiate repair mechanisms in order to prevent entry into fatal mitosis.[4] Therefore, targeting the remaining G_2 checkpoint in tumors may increase tumor specific toxicity of DNA-damaging therapies such as radiation.

Cell cycle control

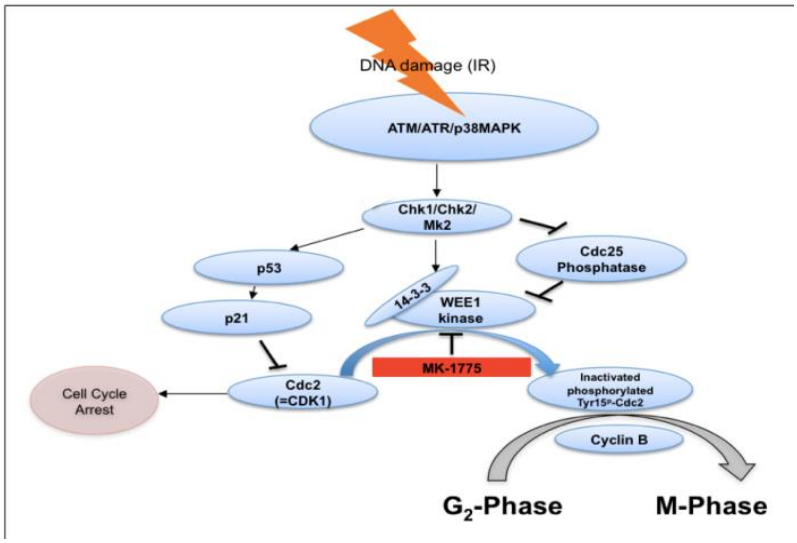

Figure 1: Schematic Overview of selective kinases, phosphatases and inhibitors involved in the G_2 arrest. DNA damage activates cell cycle checkpoints to arrest cells in G_1 or G_2. G_2 checkpoint prevents inappropriate mitosis of unrepaired DNA. Entry into mitosis requires the association of cyclin B with Cdc2 (also called CDK1). p21 is a universal CDK inhibitor with ability to bind to G_1 and G_2 cyclin CDK complexes supporting a role of p53 in G_1 and G_2 arrest. In p53 proficient cells, p21 leads to G2 arrest independent of WEE1 that cannot be abrogated by AZD1775.

Key signaling cascades involved in cell cycle arrest and DNA repair are the ataxia-

telangiectasia (ATM)-Chk2, Rad3-related protein (ATR)/Chk1, and p38MAPK/MAPKAP KINASE 2 (MK2) stress kinase pathways.[5] The ATR/Chk1 pathway is activated by bulky DNA lesions whereas the ATM/Chk2 pathway responds to DNA double strand breaks. The p38MAPK/MK2 pathway is activated by several cellular stressors including radiation and chemotherapy. The p38MAPK/MK2 pathway seems to play an important role in p53 deficient cells to maintain adequate checkpoint signaling.[5,6] All three of these DNA repair cascades, ATM, ATR and p38MAPK/MK2, converge on Cdc25, a positive regulator of cell cycle progression. Cdc25 is inhibited by phosphorylation by either Chk1 or Chk2. Wee1, a critical regulator of this cascade, plays a key role in cell cycle progression, as discussed below.

Role of Wee1 in Cell Cycle Control

Wee1 kinase is a critical driver of G_2-M cell cycle progression. In response to DNA damage, several mediators, including ATM and ATR, activate Chk1 through specific phosphorylation events. Chk1 activates Wee1 through phosphorylation of the Y15 residue and inactivates the inhibitory effects of Wee1 on Cdc25 phosphatases. Cdc25 phosphatases remove inhibitory phosphate groups from cyclin dependent kinases (Cdk), and Wee1 kinase promoting cell cycle progression. Once activated, Wee1 is stabilized by the 14-3-3 complex.[7-9] Activated Wee1 phosphorylates CDC2, inhibiting its function (see Figure 1). In normal cells, increasing levels of inactivated, phosphorylated CDC2 prevent damaged cells from entering into mitosis before DNA is repaired. Like normal cells, most cancer cells rely on this pathway to delay cell cycle progression and allow repair of DNA damage caused by rapid cell division (through growth factor activation) or DNA-damaging agents. Without a proficient G_2 checkpoint cancer cells progress through the cell cycle with damaged DNA and ultimately succumb to fatal mitosis.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

AZD1775 is a specific, ATP competitive and highly selective inhibitor of the Wee1 kinase (IC_{50} = 5.18 nM). AZD;-1775 was first described in 2009 by Hirai *et al.* as a selective and potent Wee1 inhibitor. The initial studies showed that AZD1775 (MK-1775) inhibits the phosphorylation of CDC2 on Tyr15 at nanomolar concentrations compared to the inhibitory activities against a panel of 223 tested kinases. Furthermore, these studies showed that AZD1775 (MK-1775) abrogates chemotherapy (cisplatin, gemcitabine, carboplatin) induced G_2 arrest in p53 deficient cell lines.[10] Since the initial publication, several preclinical studies have successfully tested AZD1775 (MK-1775) in combination with conventional chemotherapy or radiation in a variety of cancer models as outlined below.

Effects of Wee1 kinase inhibition in combination with conventional chemotherapy

Wee1 inhibition acts synergistically with conventional chemotherapy.[11-13] *In vitro* studies reveal that the Wee1 inhibitor AZD1775 (MK-1775) increases cytotoxic effects of conventional DNA damaging chemotherapy agents such as gemcitabine, carboplatin, cisplatin and 5-

fluorouracil in a variety of cancer types including colorectal, non-small-cell-lung, and pancreatic cancers *in vitro* and *in vivo*.[10,11,13] The central mechanism by which Wee1 inhibition increases cytotoxicity is abrogation of the chemotherapy induced G_2/M arrest, which in turn propels cells into premature mitosis. Interestingly, a recent study evaluating Wee 1 inhibition in combination with cytarabine for the treatment of acute myeloid anemia (AML)[14] used a genome wide short-hairpin RNA screen to demonstrate that Wee1 is a critical mediator of AML cell survival after cytarabine exposure. In these preclinical studies inhibition of CDC2 phosphorylation (Y15) and induction of histone H3 phosphorylation (p-HH3) were observed upon treatment with AZD1775 (MK-1775).[14]

Effects of Wee1 kinase inhibition in combination with radiation

Inhibition of Wee1 in combination with radiation reduces tumor growth in orthotopic models of adult glioblastoma (GBM) and propels cells into premature mitosis.[15] Treatment with AZD1775 (MK-1775) in combination with radiation also delays tumor growth in human lung cancer Calu-6 xenografts.[16] Although all groups describe similar radiosensitizing functions of Wee1 inhibition, conflicting results have been reported regarding the p53-dependence of such radiosensitization. Specifically, Drs. Mueller and Haas-Kogan at UCSF and others[15] have found that the radiosensitization effects of Wee1 inhibition are independent of p53 status whereas others have reported that Wee1 inhibition is only effective in p53 deficient cells.[10,16,17] This controversy notwithstanding, Mir *et al.* demonstrated that the radiosensitizing effects of Wee1 inhibition are dependent on Wee1 expression levels and not on p53 status.[15] Thus, two rationales exist for selective cytotoxicity of AZD1775 (MK-1775) against cancer cells compared to normal cells: p53 mutations and elevated Wee1 expression levels, both particularly relevant to pediatric gliomas (as described below).

The role of Wee1 in human brain tumors

Limited data are available describing the role of Wee1 in brain tumors. Wee1 kinase is overexpressed in adult GBMs and higher levels of overexpression correlate with worse clinical outcome. Using orthotopic models of adult GBMs, Mir *et al.* demonstrated that combining radiation therapy with Wee1 inhibition, using either small interference RNA or a small molecule inhibitor (PD0166285) improved survival in U251 and E98-FM orthotopic *in vivo* models of adult GBM.[15] We have extended these preclinical studies to establish a role for Wee1 inhibition in the treatment of pediatric HGGs. The preclinical evidence for using AZD1775 (MK-1775) in combination with radiation for pediatric gliomas has been generated by Drs. Mueller and Haas-Kogan at UCSF as detailed below and presented at the Annual Meeting of the Society of Neuro-Oncology 2011.[18] Further support of combining AZD1775 (MK-1775) in combination with radiation therapy for children with DIPG is presented in Caretti et al. [19]

Based on published results in adult HGGs, Drs. Mueller and Haas-Kogan assessed expression profiles of Wee1 in a cohort of pediatric gliomas. In

collaboration with Drs. Gupta and Smirnov (Department of Neurosurgery, UCSF) this group performed expression analyses with the Agilent 4x44k human array platform on all grade pediatric gliomas as well as on normal brain samples as controls. As shown in Figure 2, Wee1 is over-expressed in pediatric gliomas of all grades, with grade 4 tumors displaying highest expression levels. Of particular interest, this analysis included a pediatric DIPG primary cell line [modified with the human telomerase reverse transcriptase (htert)] that demonstrated the highest Wee1 expression levels. Statistical analyses showed that Wee1 was significantly over-expressed in HGGs (grades 3+4) compared to low-grade gliomas (grades 1+2) (p=0.007). Wee1 expression has also been evaluated in a published gene expression dataset (27 DIPGs, 6 low-grade gliomas and 2 normal brain specimens) by Dr. Blaney. As shown in Figure 3, Wee1 is significantly up-regulated in DIPGs compared to low-grade gliomas (LGG) and normal brain (two sided t-test p=0.005) reinforcing Wee1 as a promising target for the treatment of DIPGs. In another independent cohort of pediatric gliomas using a gene expression dataset published by Paugh *et al.*,[20] Wee1 was expressed 4-fold higher in HGGs (including AA and GBM) compared to anaplastic oligo-astrocytomas (p=0.01).

Gene Expression Analysis of Wee1 in a panel of pediatric gliomas

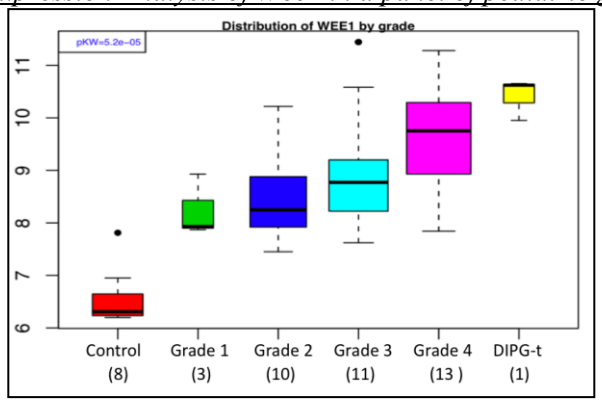

Figure 2: Expression analysis of Wee1 in pediatric gliomas based on grade; Y-scale is a $\log_2$ transformation of expression measure and each unit corresponds to a 2-fold change in expression. DIPG-t: DIPG derived primary cell line, h-tert modified.

Gene Expression Analysis of Wee1 in a panel of pediatric DIPGS

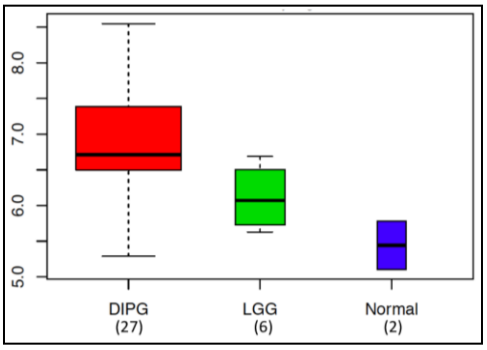

Figure 3: Expression analysis of Wee1 in DIPGs, low-grade gliomas (LGG) and normal brain. Y-scale is a $\log_2$ transformation of expression measure and each unit corresponds to a 2-fold change in expression

Immunohistochemical analyses of Wee1 on a panel of pediatric gliomas of all grades (n= 43) confirmed up-regulation of Wee1 protein. Figure 4 shows representative immunohistochemistry (IHC) stained samples. Similar to results found based on mRNA expression, Wee1 expression on the protein level is higher in high-grade versus low-grade pediatric gliomas.

Expression of Wee1 protein in a panel of pediatric high-grade gliomas based on immunohistochemistry analysis

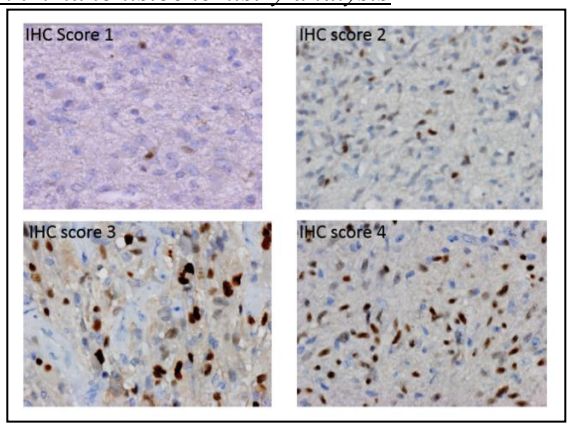

Figure 4: Immunohistochemical analysis of Wee1 expression in a panel of pediatric gliomas. IHC Score: 1 = <10%; 2= 10-15%; 3 = 25-75%; 4= >75% of total cells stained positive for Wee1 expression.

Preclinical experience of AZD1775 (MK-1775) in combination with radiation therapy in models of pediatric high-grade gliomas

In *in vitro* clonogenic survival assays, AZD1775 (MK-1775) exhibits dose-dependent anti-proliferative effects in multiple pediatric and adult high-grade glioma cell lines including a pediatric DIPG derived cell line (SF8628) and this effect is enhanced by radiation (Figure 5).

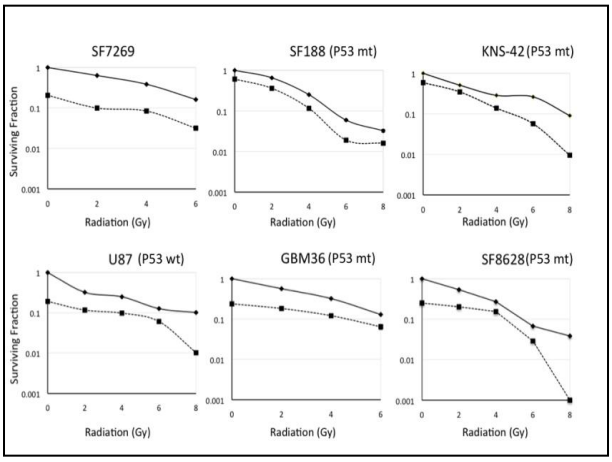

Figure 5: Clonogenic survival of several pediatric (SF7269, SF188, KNS-42, SF8628) and adult (U87, GBM36) high-grade glioma cell lines.

A newly established DIPG xenograft model allowed AZD1775 (MK-1775) to be evaluated together with radiation *in vivo*. Tumor cells derived from a biopsy of a child with DIPG were directly injected into mice, propagated and subsequently modified with the luciferase gene to monitor *in vivo* tumor burden as previously described.[21] When tumors were visualized by bioluminescence, mice were treated with AZD1775 (MK-1775) alone (60 mg/kg twice daily for a total of 10 days), radiation alone (0.5 Gy x 3 fractions), or a combination thereof. Each treatment group contained 10 mice. As shown in Figure 6, combination of AZD1775 (MK-1775) and radiation led to statistically significant prolonged survival compared to each treatment modality alone.

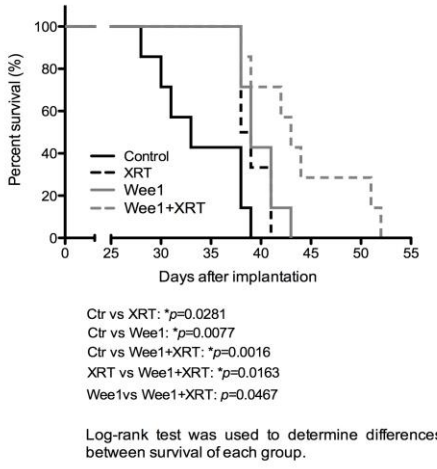

Figure 6: *In vivo* efficacy of AZD1775 (MK-1775) in combination with XRT in an orthotopic model of pediatric DIPG. Kaplan Meier estimator was used to generate survival curves and differences in survival were calculated using a log-rank test.

Based on the underlying mechanism of action the clinical development of AZD1775 (MK-1775) should focus on combination treatment strategies.

Accumulated evidence reveals AZD1775 (MK-1775) as a new therapeutic agent for the treatment of pediatric HGGs, specifically DIPGs, in combination with radiation therapy.

2.2.2 Animal Toxicology

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2.2.3 Preclinical Pharmacokinetic Studies

2.3 Adult Studies

Phase 1 Studies

AZD1775 (MK-1775) was evaluated in a first in human study as monotherapy as well as in combination with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumors (PN001). This study is ongoing as of February, 2013. In this study, the specified maximum dose of 1300 mg as single oral dose was well tolerated and no MTD has been established for monotherapy. The MTD for the single dose combination treatment with either gemcitabine (1000 mg/m^2) or cisplatin (75 mg/m^2) was 200 mg and for the combination of AZD1775 (MK-1775) with carboplatin (AUC5) was 325 mg. In this PN001 trial AZD1775 (MK-1775) was given 24 hours after gemcitabine or cisplatin. The MTDs for BID dosing x 5 doses of AZD1775 (MK-1775) with similar chemotherapy regimens were 200 mg with cisplatin and 225 mg with carboplatin. AZD1775 (MK-1775) in combination with gemcitabine is currently being evaluated on a QD x2 schedule.

The completed or terminated early studies include:

- PN001 (NCT00648648) (except for Part 3): a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumors

- PN004 (NCT01357161): a Phase II study evaluating AZD1775 combined with carboplatin and Paclitaxel in patients with platinum-sensitive p53-mutant ovarian cancer

- PN005 (NCT01047007):: a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5 FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumors.

- PN008 (NCT01076400): a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients

with cervical cancer

- PN011: a Phase I study of single-agent AZD1775, in patients with refractory solid tumors, sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program in collaboration with AstraZeneca and Merck. This study reported AZD1775 monotherapy activity in patients carrying BRCA mutations for the first time.

- D6011C00001 (NCT02087176; SCRI LUN 262): a lead-in Phase II multicentre, randomized, double-blind study comparing AZD1775 plus docetaxel with placebo plus docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC)

- D6011C00002 (NCT02087241; SCRI LUN 261): a Phase II study of AZD1775 plus pemetrexed and carboplatin followed by a randomized comparison of pemetrexed and carboplatin with or without AZD1775 in patients with previously untreated stage IV non-squamous NSCLC

Ongoing:

- D6010C00004 (NCT02272790; SCRI GYN 49): a multicentre Phase II study of AZD1775 plus either Paclitaxel, gemcitabine, carboplatin, or pegylated liposomal doxorubicin in patients with platinum-resistant epithlial ovarian, fallopian tube, or primary peritoneal cancer

- D6010C00005 (NCT02511795; SCRI REFMAL 384): a Phase I study evaluating AZD1775 in combination with olaparib in refractory solid tumors.

- D6011C00003 (NCT02341456): a Phase Ib dose-finding study evaluating AZD1775 as monotherapy and in combination with carboplatin and Paclitaxel in adult Asian patients with advanced solid tumors

- D6015C00001 (NCT02482311; SCRI REFMAL 383): a Phase I, dose escalation, safety and pharmacokinetic study of AZD1775 monotherapy (Schedule 1) in patients with advanced or metastatic solid tumors

- D6015C00002 (NCT02617277; SCRI REFMAL 412): a Phase I study assessing the safety, tolerability, and pharmacokinetics of AZD1775 in combination with MEDI4736 in patients with advanced solid tumors

- D6015C00003 (NCT02610075; SCRI REFMAL 398): a Phase Ib study to determine the maximum-tolerated dose (MTD) of

AZD1775 monotherapy (Schedule 2) in patients with locally advanced or metastatic solid tumors.

To date, AZD1775 (MK-1775) has not been tested in combination with radiation therapy in children. An ongoing study in adults patients with glioblastoma is testing the safety and early efficacy of the combination of AZD1775, temozolomide and radiation therapy followed by a maintenance phase of temzolomide and AZD1775 in newly diagnosed adult subjects with glioblastoma.

Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Work by Drs. Mueller and Haas-Kogan have demonstrated that tumors from mice treated with AZD1775 (MK-1775) and radiation have increased expression of γ-H2AX, a marker of double strand DNA breaks, as well as pHH3 compared to single modality treatment. As expected, glioma cells treated with AZD1775 (MK-1775) showed dose dependent reduction in p-CDC2 expression.

2.4 Pediatric Studies

Prior Experience in Children

The phase 1 study of AZD1775 in combination with irinotecan has found the combination is well tolerated in pediatric relapse or refractory solid tumor patients. The pediatric recommended phase 2 dose was defined as AZD1775 85 mg/m^2/dose PO + IRIN 90 mg/m^2/dose PO; Cefixime 8 mg/kg PO or Cefpodoxime 5 mg/kg PO BID. Phase 2 expansions in medulloblastoma and neuroblastoma are currently accruing. (ADVL1312 Fall 2016 study progress report)

2.5 Overview of Proposed Pediatric Study

As outlined above, there are compelling pre-clinical studies that provide the rationale for targeting Wee1 in combination with radiation for the treatment of children with DIPG. Therefore, we propose a phase 1 study of AZD1775 (MK-1775) administered concurrently with focal radiation therapy. We know from prior experience that focal radiation therapy for children with DIPG is generally well tolerated and that radiation therapy by itself has no significant hematological toxicity. In the current phase 1 study we plan to first increase the number of days children are treated with specific Wee1 inhibitor AZD1775 (MK-1775) concurrently with radiation and then dose escalate depending on how well AZD1775 (MK-1775) is tolerated (see the treatment plan in Section 5.1 for details). Due to the unknown pharmacokinetics of AZD1775 (MK-1775) after prolonged administration, the age requirement of the first patient enrolled will be ≥ 7 years. After considering toxicity and results of PK analysis for this patient, we will open the study to children less than 7 years of age.

Radiation therapy is given at the current standard dose of 5400 cGy in 30 fractions of 180 cGy Monday through Friday for a total of 30 fractions over 6 weeks. AZD1775 (MK-1775) will be administered according to the schedule in Section 5.1 after radiation therapy. Dose escalation will occur as outlined in Section 5.2.1. The starting dose of AZD1775 (MK-1775) for this trial was based on 40% of the

adult MTD in the multi-dose schedule of AZD1775 (MK-1775) in combination with chemotherapy in adult patients with solid tumors.

2.6 Amendment #4B Regarding Escalation of AZD1775 Dosing (2016)

As of April 2015, 26 patients have been treated on ADVL1217: 6 on Dose Level 1, 6 on dose level 2, 7 on dose level 3 and 7 on dose level 4. To date, the medication has been very well tolerated with minimal side effects. None of the patients treated at dose levels 1-3 experienced dose-limiting toxicity. One patient treated at dose level 4 (AZD1775 95 mg/m^2 daily Mon-Fri during Weeks 1-6) had a dose-limiting toxicity of grade 3 ALT increase.

Since the inception of the trial new information about PD as well as additional safety data from an ongoing adult glioblastoma (GBM) trial has become available. PD data from ongoing adult studies demonstrate that a minimum of 200-225 mg PO BID is required to see compelling modulation of p-CDC2 as the downstream effector molecule of Wee1 kinase. Also, PK analysis from one pediatric patient enrolled in ADVL1217 supports that pediatric patients will have a similar PK profile of AZD1775 compared to the adult population; however, that needs to be viewed with caution given that we only have data available from one patient.

Further, additional safety information is available from the ongoing adult glioblastoma trial. Patients enrolled in this trial receive AZD1775 during radiation therapy (on days of radiation therapy) concurrent with the adult standard of care temozolomide dose of 75 mg/m^2. In addition AZD1775 is given as adjuvant therapy on day 1-5 concurrently with temozolomide at 200 mg/m^2 (day 1-5) on a 28-day cycle. This trial determined the MTD of AZD1775 in combination with temzolomide and radiation therapy to be 200 mg/day (~ 115 mg/m^2) (during radiation therapy) and 425 mg/day (~ 245 mg/m^2) (Level 5) for the adjuvant arm.

Because toxicity in patients treated on ADVL1217 has been relatively modest to date, the dose of AZD1775 will now be escalated stepwise to the dose of 200 mg/m^2 /dose daily Mon-Fri during Weeks 1-6 (Dose Level 7).

Recent results from a phase 0 study of AZD1775 in adult subjects with recurrent adult GBM demonstrate that AZD1775 crosses the blood brain barrier and therefore strengthens the use of this agent in children with DIPG.[22] Tumors with such elevated replication stress are expected to be sensitive to AZD1775 based on the underlying mechanisms of action. We have investigated the expression of these checkpoint inhibitors in pediatric gliomas and have found that these are also upregulated in pediatric high-grade gliomas.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Current Study Status

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

page:

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

3.2 IRB Approval

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

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.
ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal
EMAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)
FAX: 215-569-0206
MAIL: CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

3.3 Patient Registration

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

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

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative

therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

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

3.7 Eligibility Checklist

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

3.8 Institutional Pathology Report

Because DIPGs are often not biopsied, enrollment of patients with typical-appearing DIPG (see Section 4.1.2) without an institutional pathology report is allowed. For patients with brainstem tumors not considered typical DIPG as defined in Section 4.1.2, they will only be eligible if their tumors are biopsied and meet the eligibility criteria as defined in Section 4.1.2. Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 Study Enrollment

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

3.10 Dose Assignment

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

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of chemotherapy. The start of chemotherapy is defined as the initiation of treatment with AZD1775 (MK-1775). The start of protocol therapy is defined as the initiation of radiation therapy. 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 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).

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 36 months and ≤ 21 years of age at the time of study enrollment. The first patient enrolled on study must be ⩾ 7 years of age. Pending results of PK analysis, the study will open to children of ages 3-21 years of age.

4.1.2 Diagnosis: Patients with newly diagnosed DIPGs, defined as tumors with a pontine epicenter and diffuse involvement of the pons, are eligible without histologic confirmation.

Patients with brainstem tumors that do not meet these criteria or are not considered to be typical intrinsic pontine gliomas will only be eligible if the tumors are biopsied and proven to be an anaplastic astrocytoma, glioblastoma, gliosarcoma, diffuse midline glioma with histone H3 K27M mutation, or anaplastic mixed glioma. Patients with pilocytic astrocytoma, fibrillary astrocytoma, gangliogliomas, or other mixed gliomas without anaplasia are not eligible.

Patients with disseminated disease are not eligible, and MRI of spine must be performed if disseminated disease is suspected by the treating physician.

Enrollment must be no later than 28 days after the date of radiographic diagnosis or surgery, whichever is the later date.

4.1.3 Body Surface Area: Patients must have a body surface area ≥ 0.35 m^2 at the time of study enrollment.

4.1.4 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). 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.

4.1.5 Prior Therapy

Patients must not have received any prior anti-cancer therapy such as chemotherapy, radiation therapy, immunotherapy or bone marrow transplant for the treatment of DIPG. Prior dexamethasone and/or surgery are allowed.

4.1.6 Organ Function Requirements

4.1.6.1 Adequate Bone Marrow Function Defined as:

- 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).

4.1.6.2 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**
3 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 utilizing child length and stature data published by the CDC.[23]

4.1.6.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 × upper limit of normal (ULN) for age.
- SGPT (ALT) ≤ 3 × ULN = 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- SGOT (AST) ≤ 3 × ULN = 150 U/L. For the purpose of this study, the ULN for SGOT is 50 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.6.4 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) resulting from prior therapy must be ≤ Grade 2 with the exception of tendon reflex (DTR). Any grade of DTR is eligible.

4.1.6.5 Adequate Cardiac Function Defined as:
- QTc≤ 480 msec

4.1.6.6 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.

4.2 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. Negative serum or urine pregnancy test within 3 days prior to enrollment.

b. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive methods as follows: fertile females of childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation. Male patients willing to abstain or use barrier contraception (i.e. condoms) for the duration of the study and for 3 months after treatment stops.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients receiving corticosteroids are eligible for this trial.

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 Anticonvulsants: Patients must not currently be receiving enzyme inducing anticonvulsants (see Appendix II for a list of enzyme inducing and non-enzyme inducing anticonvulsants).

4.2.2.5 Herbal Preparations are not allowed throughout the study. These herbal medications include but are not limited to: St. John's wort, kava, ephedra (ma hung), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and

ginseng. Patients should stop using these herbal medications 7 days prior to study enrollment.

4.2.2.6 Any known hypersensitivity or contraindication to the components of the study drug AZD1775.

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

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

4.2.5 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.

4.2.6 Major surgical procedures ≤ 28 days of beginning study treatment, or minor surgical procedures (including VP shunt placement or stereotactic biopsy of the tumor) ≤ 7 days. No waiting period required following port-a-cath or other central venous access placement.

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

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

AZD1775 Administration During Radiation Therapy (Cycle 1)

Treatment	Monday through Friday	Saturday and Sunday
Radiation Therapy	X	
AZD1775 (MK-1775)	X^	
Rest Period		X

^Frequency of AZD1775 (MK-1775) will vary depending on dose level assignment.

Radiation therapy (XRT) will be given at the current standard dose of 5400 cGy in 30 fractions of 180 cGy Monday through Friday for a total of 30 fractions over 6 weeks, with a rest period on Saturday and Sunday of each week. In the event a radiation fraction is not administered due to a holiday (per institutional schedule) or for another reason (e.g., adverse event, mask re-fitting, etc) it will be made up during week seven (or eight). See Section 15.0 for radiation therapy guidelines.

During radiation, AZD1775 (MK-1775) will be administered orally based on the table above, once each day after that day's radiation therapy fraction, for the duration of radiation treatment

Drug doses should be adjusted based on the BSA calculated from height and

weight measured within 7 days prior to the beginning of chemoradiotherapy course, and according to the dosing nomogram (see Appendix V-A). See Appendix V-B for scheduling guidelines based on the day of the week that XRT is initiated. The original dose assignment should be maintained throughout the entire period of radiation therapy.

. If a patient vomits after the dose of AZD1775 (MK-1775) the dose should NOT be repeated.

Note: It is recommended but not required that Day 1 of protocol therapy begin on a Monday. If a fraction of radiation is delayed because of holiday or other logistical reasons (*e.g.* equipment malfunction), patients should also hold AZD1775 (MK-1775) and only take AZD1775 (MK-1775) on days radiation is given.

Patients should have AZD1775 (MK-1775) prescribed at the beginning of chemotherapy, with detailed instructions about the days of the week that drug is to be administered.

5.2 Criteria for Starting Subsequent Cycles

5.2.1 Chemoradiotherapy

Radiation therapy should not be interrupted for AZD1775-related DLTs unless clinically indicated.

5.3 Dose Escalation Schema

Inter-Patient Escalation The starting dose of AZD1775 (MK-1775) (50 mg/m^2; dose level 1) is 40% of the known MTD in adult studies of chemotherapy combination regimens (adult MTD 200 mg which corresponds to 115 mg/m^2). If dose level 1 is well tolerated, we will escalate treatment first by increasing the number of days AZD1775 (MK-1775) is given and then by escalating the dose of AZD1775 (MK-1775) stepwise to 95 mg/m^2 as shown in the table below. If dose level 4 is well tolerated, further dose escalation will be considered after evaluation of the pharmacokinetics and toxicity profile. PK simulation predicts higher exposures in children ≤ 6 years of age compared to older children (7 years and above). Therefore the age requirement of the first patient enrolled on dose level 1 will be 7 years or older. PK analysis will be performed prior to opening the study to younger children.

	Day 1-5 Week 1					Day 8-12 Week 2					Day 15-19 Week 3					Day 22-26 Week 4					Day 29-33 Week 5					Day 36-40 Week 6				
Dose Level 1: AZD1775 (MK-1775) 50 mg/m^2 daily Mon-Fri, alternating weeks (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-	x	x	x	x	x						x	x	x	x	x						x	x	x	x	x					

1775) 50 mg/m²																														
Dose Level 2: AZD1775 (MK-1775) 50 mg/m² daily Mon-Fri dosing, alternating with weeks of QOD dosing (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 50 mg/m²	x	x	x	x	x	x	-	x	-	x	x	x	x	x	x	x	-	x	-	x	x	x	x	x	x	x	-	x	-	x
Dose Level 3: AZD1775 (MK-1775) 50 mg/m² daily Mon-Fri During Weeks 1-6 (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
MK-1775 50 mg/m²	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dose Level 4: AZD1775 (MK-1775) 95 mg/m² daily Mon-Fri During Weeks 1-6 (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 95 mg/m²	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dose Level 5: AZD1775 (MK-1775) 130 mg/m² daily Mon-Fri During Weeks 1-6 (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 130 mg/m²	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dose Level 6: AZD1775 (MK-1775) 160 mg/m² daily Mon-Fri During Weeks 1-6 (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 160 mg/m²	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dose Level 7: AZD1775 (MK-1775) 200 mg/m² daily Mon-Fri During Weeks 1-6 (See Appendix V-B if start date not on Monday)																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 200 mg/m²	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

"x" = treatment; "-" = no treatment

* Further dose escalation will be considered after evaluation of the pharmacokinetics and toxicity profile.

If the MTD has been exceeded at dose level 1, then the subsequent cohort of patients will be treated

at dose level -1 (see below):

Treatment De-Escalation (Dose Level -1)

	Day 1-5 Week 1					Day 8-12 Week 2					Day 15-19 Week 3					Day 22-26 Week 4					Day 29-33 Week 5					Day 36-40 Week 6				
Dose Level -1: AZD1775 (MK-1775) 50 mg/m^2 QOD alternating weeks **See Appendix V-B if start date is not on Monday**																														
XRT	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AZD1775 (MK-1775) 50 mg/m^2	x	-	x	-	x	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-

If dose level -1 is not is not well tolerated, further de-escalation will not occur. The study will be closed for accrual.

Intra-Patient Escalation

Intra-patient dose escalation is not allowed on this study.

5.4 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/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 AZD1775 (MK-1775). The DLT observation period for the purposes of dose-escalation will be the entire duration of radiation therapy.

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

Interruption of Radiation Therapy

Interruption of planned radiation for 5 consecutive fractions or 10 fractions total due to AZD1775 (MK-1775)-attributable toxicity (and not due to technical issues).

Non-Hematological Dose-Limiting Toxicity

5.5.1.1 Any Grade 3 or Grade 4 non-hematological toxicity attributable to AZD1775 (MK-1775) with the specific exclusion of:

- Grade 3 nausea and vomiting of less < 3 days duration (Grade 3 nausea or vomiting ≥ 3 days in the presence of antiemetics will be considered a DLT)
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline

within 7 days. See Appendix X for values that represent thresholds between CTCAE grades.
Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation

- Any Grade 2 non-hematological toxicity attributable to AZD1775 (MK-1775) that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires interruption of AZD1775 (MK-1775) for 7 days.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

Hematological dose limiting toxicity
- Grade 3 thrombocytopenia (platelet count < 50,000/mm^3)
- Grade 4 neutropenia

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 During Radiation Therapy

For AZD1775 (MK-1775)-related hematologic DLTs, AZD1775 (MK-1775) will be withheld until criteria in 6.1.1 and 6.1.2 are met, and AZD1775 (MK-1775) will be restarted at one dose level lower, if not already at Dose Level -1. If the same DLT is experienced at the lower dose level then AZD1775 (MK-1775) should be discontinued. If a different DLT is encountered, then the patient may restart AZD1775 (MK-1775) at the next lower dose level, if not already at Dose Level -1. Please contact the Study Chair and Operations Center if guidance is required with regard to the day/schedules for AZD1775 (MK-1775) administration in the event the dose is de-escalated.

In the event of hematological DLT, a CBC should be checked at least every other day until recovery of ANC ≥ 1,000/mm^3 and platelet ≥ 100,000/mm^3.

A patient who experiences any DLT despite being treated on Dose Level -1 will then complete radiation therapy without AZD1775 (MK-1775). **Radiation is conventional therapy for diffuse intrinsic pontine gliomas and should be continued despite AZD1775 (MK-1775)-related DLT, unless there is a strong clinical contraindication.**

6.1.1 Radiation should not be interrupted unless clinically indicated.

6.1.2 . Radiation should not be interrupted unless clinically indicated.

6.2 Dose Modifications for Non-Hematological Toxicity During Radiation Therapy

If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.5.2, AZD1775 (MK-1775) will be withheld until the toxicity resolves to meet eligibility or baseline parameters. Patients may then resume treatment at the next lower dose level. For patients enrolled at Dose Level 1, the dose should be reduced to Dose Level -1. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

A patient who experiences any DLT despite being treated on Dose Level -1 will then complete radiation therapy without AZD1775 (MK-1775). **Radiation is the standard of care and should be continued despite AZD1775 (MK-1775)-related DLT, unless there is a strong clinical contraindication.**

If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

If the same dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, the patient must be removed from protocol therapy.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug except radiation therapy per study protocol. 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

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

7.3.2 **Evaluation and management of diarrhea**

.

7.3.3 .

7.3.4 Promethazine, prochlorperazine, and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.

7.3.5 .

7.3.6 Patients should be strongly encouraged to maintain liberal oral fluid intake.

7.3.7 Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

7.4 Growth Factors

. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

7.5.1 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). Prophylactic anticonvulsants are strongly discouraged.

7.5.2 CYP3A4

7.5.3 CYP2C19

7.5.4 Transporters

7.5.5 **Herbal Preparations:**

Herbal Preparations are not allowed throughout the study. These herbal medications include but are not limited to: St. John's wort, kava, ephedra (ma hung), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study treatment.

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). The start of protocol therapy is defined as the initiation of radiation therapy. 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 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).

STUDIES TO BE OBTAINED	Pre-Study	During Radiation Therapy
History	X	Weekly
Physical exam with vital signs	X	Weekly
Neurologic exam	X	End of radiation therapy
Height, weight, BSA	X	
Performance status	X	

CBC, differential, platelets	X	Twice weekly (every 3 to 4 days)[2]
Urinalysis	X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly
Creatinine, ALT, bilirubin	X	Weekly
Albumin	X	Weekly
Tumor disease evaluation	X	End of radiation therapy[6]
Pregnancy test[3]	X[3]	
Patient diary[4]		Weekly
Pharmacokinetics[5]	See Section 8.4	
Pharmacodynamics	See Section 8.5	
EKG[7]	X	

1 See Table 8.2 for required observations during the follow-up period.
2 In the event of hematological DLT, a CBC should be checked at least every other day until recovery of ANC ≥ 1,000/mm^3 and platelet ≥ 100,000/mm^3 (See Section 6.1).
3 Women of childbearing potential require a negative pregnancy test negative 3 days prior to enrollment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.
4 Patient diary (see Appendix IV) should be reviewed and uploaded into RAVE weekly and after completion of protocol therapy.
5 If patients undergo CSF collection anytime while being treated with AZD1775 (MK-1775), patients can opt to send samples for PK evaluation.
6 Tumor disease evaluation should be obtained within 3-4 weeks after completion of radiation therapy (within 3-4 weeks after completion of radiation therapy and then according to Table 8.2)
7 12-lead EKG to be obtained at baseline and as clinically indicated

8.2 Required Observations Following Completion of Radiation Therapy

The following studies are required until the patient is off study as defined in Section 10.2.

STUDIES TO BE OBTAINED	30 Days After Last dose of AZD1775 (AZD1775 (MK-1775))	Every 3 Months
History	X	X
Physical exam with vital signs	X	X
Neurologic exam	X	X
CBC, differential, platelets	X	X
Tumor disease evaluation[1]	X[1]	X

1 Tumor disease evaluation should be obtained within 3-4 weeks after completion of radiation therapy and then every 3 months ± 14 days.

8.3 Radiology Studies

Central Radiology Review for Response: Patients who respond (CR, PR) to therapy or have long term stable disease (SD > 6 months from study entry) on study will be centrally reviewed. Further, central review of disease progression will also occur. COG

Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

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

COG institutions that are not connected via the ImageInBox can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1217) 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

8.4 Pharmacology (Required)

8.4.1 Description of Studies and Assay

To date there is no experience with AZD1775 (MK-1775) in the pediatric population. To better characterize the pharmacokinetic (PK) properties of AZD1775 (MK-1775) in children, we will perform PK analyses on children treated on this study.

AZD1775 (MK-1775) will be measured in plasma using LC/MS/MS assay methodology and analyzed by Merck

8.4.2 Sampling Schedule-**See Appx. V-B and Appx. VII for details**

8.4.2.1 Blood samples will be obtained at the time points outlined in Appendix VII.

8.4.3 Sample Collection and Handling Instructions

8.4.3.1 Blood samples (2-3 mL) will be collected in 4 ml K_2 EDTA (lavender-top) tubes, gently inverted 6 to 8 times, and immediately processed (See Section 8.4.4). Record the exact time that the sample is drawn along with the exact time that the drug is administered on the Pharmacokinetic Study Form (see Appendix VII).

If the blood samples cannot be centrifuged immediately, the tubes will be placed on ice. The total time from drawing blood to transferring the plasma to the freezer cannot exceed 30 minutes.

8.4.4 Sample Processing

See Appendix XI for processing details. Freeze immediately at -20 °C and store frozen until shipment. Complete the Pharmacokinetic Study Form (see Appendix VII), recording the date and time of collection for each sample. A copy of this form must accompany the sample(s) at time of shipment.

8.4.5 Sample Labeling

Each tube must be labeled with the COG patient ID and accession number, the study I.D. (ADVL1217), and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (see Appendix VII), which must accompany the sample(s).

8.4.6 Sample Shipping Instructions

Samples should be batched and shipped on dry ice prepaid via overnight Federal Express, Monday through Wednesday to:

Covance Central Laboratory Services
Attn: Phyllis Sellars - Special Handling
8211 SciCor Drive
Indianapolis, Indiana 46214
Phone: 317-271-1200
Fax: 1-800-335-1462
Emails: SMSpecialHandlingIndy@Covance.com, Phyllis.Sellars@Covance.com and Cheryl.Hinton@Covance.com

The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours. A notification email should be sent to the emails above with courier name, airway bill number, expected delivery date/time and shipment contact. The PK Pre-Alert Form, available on the protocol homepage, should be completed and faxed to the number listed on the form.

8.5 Pharmacodynamics (Required)

8.5.1 Description of Studies

We will assess the expression of p-CDC2, p-HH3 and γ-H2AX in peripheral blood mononuclear cells (PBMC) collected within 7 days prior to treatment start as well as at the time points listed in Appendix VIII. Levels of γ-H2AX, p-CDC2 and p-HH3 expression will be assessed using flow cytometry.

γ-H2AX, p-CDC2 and p-HH3 measurement by flow cytometry:

Samples will be collected at each site using the Smart Tube kit (see Appendix IX for details). Once received at the laboratory of Dr. Mueller, samples will be thawed at 37°C for 30 seconds, and then washed with PBS. All subsequent steps will take place on ice. Samples will be blocked for one hour in Block-9 staining buffer (1g/l BSA, 8% mouse serum, 0.1g/l RNaseA, phosphate inhibitors, 0.25 g/l herring sperm DNA, 0.1% Triton X-100, 5mM EDTA, 0.05% NaN3, filtered through 0.22µm filter), and then incubated in 1:100 FITC-conjugated γ-H2AX/p-CDC2

and p-HH3 antibody. Additionally, the sample will be stained with 0.25ug/sample 7-Amino-Actinomycin D (7-AAD) (559925, BD Pharmigen) for the visualization of DNA content. Sample analysis will be performed by FACS Calibur flow cytometer (BD Biosciences), where data for about 20,000 total events will be collected. γ-H2AX levels will be visualized in FL1-H, and the DNA content in the FL3-H channel respectively.

Summary of assays to assess PD of AZD1775 (MK-1775) in PBMCs:

Molecular Feature	Assay (Reagent)
p-CDC2	R&D AF888
p-HH3	Cell Signaling #9701
γ-H2AX	Millipore 16-202A

PD analyses will be carried out in the laboratory of Dr. Sabine Mueller upon validation of the p-CDC2 and p-HH3 assays.

Baseline expression of γ-H2AX, p-CDC2 and p-HH3 prior to AZD1775 (MK-1775) treatment will be established. We expect that expression of p-CDC2 will decrease and expression of γ-H2AX and p-HH3 increase after treatment with AZD1775 (MK-1775) and radiation. Since there might be physiologic variations in expression of these markers, we will obtain 2 baseline samples and calculate the intra-patient standard deviation of baseline levels. We will consider a change of 2 standard deviations as significant.

8.5.2 Sampling Schedule

Two baseline samples will be collected before the first dose of AZD1775 (MK-1775). Every effort should be made to obtain the baseline (pre-treatment) samples on two different days, if feasible.

Blood samples will also be collected at the time points outlined in Appendix VIII.

8.5.3 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. Please see details of preparation in Appendix IX.

8.5.4 Sample Labeling

Each tube must be labeled with the COG patient ID and accession number, the study I.D. (ADVL1217), and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form (see Appendix VIII), which must accompany the sample(s).

8.5.5 Sample Shipping Instructions

Samples should be batched and shipped on dry ice to the address below:

Mueller Laboratory
Attn: Xiaodong Yang/Yuying Zhai
Helen Diller Family Cancer Research Building
1450 Third Street, Room 402
San Francisco, CA 94158

Prior to shipping, contact Xiaodong Yang at 415-476-0543 or emailxiaodong.yang@ucsf.edu, yuying.zhai@ucsf.edu and sabine.mueller@ucsf.edu with the tracking number. Samples should **NOT** be shipped on a Friday or before a holiday.

9.0 AGENT INFORMATION

9.1 AZD1775 (MK-1775)

NSC#751084;

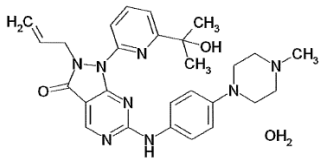
9.1.1 Structure and molecular weight

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 AZD1775 (MK-1775):



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

9.1.3 Formulation

9.1.4 Storage

; dispense in the original container.

9.1.5 Administration

Patients will take AZD1775 (MK-1775) orally based on assigned dose. AZD1775 (MK-1775) will be administered orally once each day it is assigned directly after that day's radiation therapy fraction.

If a dose is vomited it should not be repeated; resume administration with the next regularly scheduled dose.

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 213 patients.* Below is the CAEPR for AZD1775 (MK-1775).

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 2.5, April 18, 2018[1]

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

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

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

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

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

Adverse events reported on AZD1775 (MK-1775) trials but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD1775 (MK-1775) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Febrile neutropenia; 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; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Flatulence; Gastric ulcer; Gastritis; Hemorrhoids; Lower gastrointestinal hemorrhage; Oral pain; Rectal hemorrhage; 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; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased; Weight loss
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 cramp; 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; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Paresthesia; Peripheral neuropathy[4]; Presyncope; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury[5]; 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; 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 (MK-1775) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2 Agent Ordering and Agent Accountability

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.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

9.3 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.

9.4 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 the 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.

9.5 Investigator Brochure Availability

The current versions of the IB for the agent 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 IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.6 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
- Registration and Credential Repository (RCR):
  https://ctepcore.nci.nih.gov/rcr/
- PMB email:
  PMBAfterHours@mail.nih.gov
- IB Coordinator:
  IBCoordinator@mail.nih.gov

- PMB phone and hours of service:
  (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

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 planned therapy on Day 42.
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) (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during radiation therapy should continue to have the required observations in Section 8.1 until the originally planned end of treatment 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 off protocol therapy are to be followed as described in Section 8.2 until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Serious adverse events that occur during the follow-up period (more than 30 days after the last administration of investigational agent) and have an attribution of possible, probable, or definite require reporting per Footnote 1 of Table A. Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Death
b) Lost to follow-up
c) Withdrawal of consent for any further required observations or data submission.
d) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

A minimum of 2 evaluable patients 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 DIPG may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Review of the enrollment rate into a recent COG study of DIPG, ACNS0927, indicates that 1-2 patients per month are available, which will permit completion of the study within 20-38 months if all dose levels are studied with 6 evaluable patients. A maximum of 65 patients is anticipated, which accounts for potential expansion to 12 patients at each dose level (see Section 11.2) and an inevaluability rate of 20%.

As of Amendment #4, 26 patients have enrolled onto the study. An additional 24 evaluable patients may be required to evaluate Dose Levels 5-7, which will permit completion of the study within 12-24 months if these dose levels are studied with 6 evaluable patients each and an additional 6 patients are required for PK analysis. Up to 51 additional patients may be enrolled, which accounts for potential expansion to 12 patients at each dose level (see Section 11.2) and an inevaluability rate of 20%. This would be expected to be completed within 26-51 months. The maximum accrual for the study will increase from 65 to 77 patients.

11.2 Definitions

Evaluable For Adverse Effects

Any patient who experiences DLT at any time during protocol therapy is considered evaluable for Adverse Effects. Patients without DLT who receive at least 85% of the prescribed dose of AZD1775 (MK-1775) and radiation therapy within 8 weeks of starting protocol therapy 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.

Maximum Tolerated Dose

The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.4) during therapy. In the event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients will be considered if all of the following conditions are met:

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

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

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study.[29] Due to the

unknown pharmacokinetics of AZD1775 (MK-1775) after prolonged administration, the age requirement of the first patient enrolled on dose level 1 will be ≥ 7 years. The study will be temporarily closed to accrual until PK analysis of this patient is completed. Pending results, the study will either open a slot to another patient 7 years of age or older, or to children greater than 3 years of age. Upon agreement from the study team, the rolling six design may then be utilized: Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

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

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

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

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

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

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

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

11.4 Inclusion of Children, Women and Minorities

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

11.5 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 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).

Biologic activity of AZD1775 (MK-1775) will be explored using expression of p-CDC2, p-HH3 and γ-H2AX in PBMCs before and after administration of AZD1775 (MK-1775) using paired analysis methods.

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 criteria outlined in Section 12.0, and will be reported descriptively. Progression-free survival and overall survival will also be summarized using the Kaplan-Meier method and including 95% confidence intervals. Both measurements of survival will be measured from the time of study entry.

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 website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

12.2 **Methodology to Determine Tumor Measurement**

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

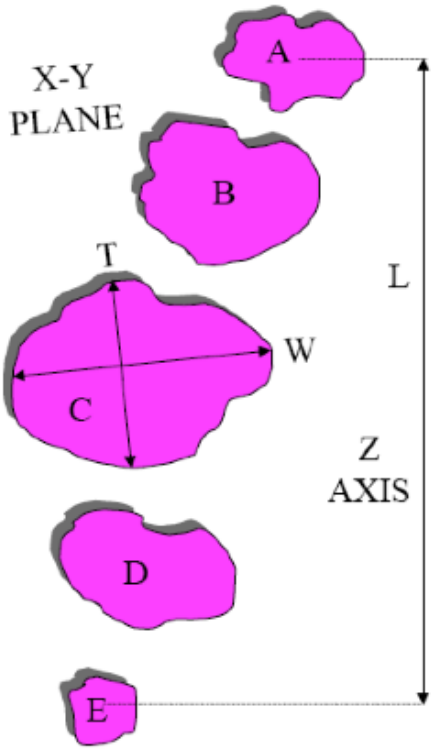
Tumor response criteria for this study are to be determined by changes in size using the maximal 2-dimensional cross-sectional tumor measurements, T x W (product of the longest diameter of the tumor [width (W)] and its longest perpendicular diameter [transverse (T)], using either T1 or T2 weighted images (which ever gives the best estimate of tumor size). This will allow comparison with historical studies as outlined in the statistical design section, such as CCG-9941, ACNS0126, and ACNS0927 which used cross-sectional measurements in their determination of response status.

Tumor length (L), perpendicular to the T x W plane should also be measured and recorded, since this will provide historical data for future studies that will rely exclusively on volumetric response determinations. However, for the current study, 3-dimensional tumor volume change will not be used to determine response status.

The following section describes the methodology.

(See drawing below for illustration)

1. For MRI imaging, the longest diameter can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups.
2. The longest measurement of the tumor (or width, W) should be determined.
3. The 2 perpendicular measurements should be determined (transverse (T) measurement-perpendicular to the width in the selected plane, and the length (L) tumor extent in the plane perpendicular to the selected plane).
4. Leptomeningeal tumor spread is not a target lesion, as its presence at diagnosis would make the patient ineligible for this brainstem glioma study. The presence and location of leptomeningeal tumor spread at relapse should be noted.



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

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

12.3 **Selection of Target and Non-Target Lesions**

For intrinsic pontine brainstem gliomas, only one lesion/mass is present at diagnosis, and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. (Patients with multiple target lesions at diagnosis are considered to have disseminated disease and would be ineligible for this study).

If other non-target lesions develop at relapse (including CSF positive for tumor cells), their location should be noted, although they do not need to be measured.

12.4 **Response Criteria for Target Lesions**

For this study, comparison of maximal 2-dimensional measurements, T x W (product of the longest diameter [width (W)] and its longest perpendicular diameter [transverse (T)] will be used for Response Criteria for Target Lesions.

Complete Response (CR): The disappearance of all abnormal signal within the brainstem and return to normal size of the brainstem.

Partial response (PR): ≥50% decrease in the sum of the products of the two perpendicular diameters of the target lesion, taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the products of the two perpendicular diameters of the target lesion to qualify for PR (taking as reference the initial baseline

measurements), nor sufficient increase in the target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started).

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

12.5 Overall Response Assessment

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

Target Lesion	**New Lesions**	**Overall Response**
CR	No	**CR**
PR	No	**PR**
SD	No	**SD**
PD	Yes or No	**PD**
Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease

12.6 Best Response

Two objective status determinations of disease status, by MRI, obtained on two consecutive determinations, separated by at least a 4 week time period, are required to determine the patient's overall best response. Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after treatment has been administered) will have a best response of progressive disease. Best response is unknown if the patient does not qualify for a best response of progressive disease and if all objective statuses after the first determination and before progression are unknown.

1st Status	**2nd Status**	**3rd Status**	**Best Response**
Progression			Progressive disease
Stable, PR, CR	Progression		Progressive disease
Unknown	Progression		Progressive disease
Stable	Stable	Progression	Stable
Stable, Unknown	PR, CR	Progression	Stable

Stable, Unknown	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

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

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

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 during the follow-up period (see Section 10.2) more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

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

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

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

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period. **Effective Date: May 5, 2011**

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or

prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

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

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.
- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD 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.

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 http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet

connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

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

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System CTEP-AERS that can be found at 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 ADVL1217 COG 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 case report forms and do not alter the guidelines for CTEP-AERS reporting.

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.

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

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

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."

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

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

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).

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.

Note: The AML/MDS Secondary Reporting form is no longer available on the CTEP website. In lieu of this form, AML/MDS events are now to be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either:

1) Leukemia secondary to oncology chemotherapy,
2) Myelodysplastic syndrome, or
3) Treatment-related secondary malignancy.

Non-treatment related cases of AML/MDS for CTCAE v4.0 should be reported using "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify".

To grade a non life-threatening event for "Myelodysplastic syndrome", use "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify" where the specified term is MDS.

Note: If a patient has been enrolled in more than one NCI-sponsored study, the CTEP-AERS report must be submitted for the most recent trial.

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

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. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event"

section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as **Grade 3** ***"Pregnancy, puerperium and perinatal conditions - Other (Pregnancy)"*** under the ***"Pregnancy, puerperium and perinatal conditions"*** SOC.
- There is a possibility that the sperm of male patients treated on studies involving possible teratogenic agents may have been damaged. For this reason, pregnancy in partners of men on study should also be reported and followed as described in this section.
- 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 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 recognizes any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE 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 Grade 4 "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 as 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 case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. **Note**: If this study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If this study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

This is not a responsibility of institutions participating in this trial.

14.3 CRADA/CTA/CSA

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

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential

information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that

Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

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 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.

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.

15.0 RADIATION THERAPY GUIDELINES

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities.

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

15.0.1 General Guidelines

This is a dose escalation, Phase 1 study of the selective Wee1 kinase inhibitor AZD1775 (MK-1775) in combination with radiation in patients with newly diagnosed diffuse intrinsic pontine glioma (DIPG). All patients will receive radiation therapy on this protocol with the targeted volume based on the extent of disease defined by neuroimaging prior to radiation therapy. This study specifies a 1 cm clinical target volume margin and mandates the use of CT-MR registration to define the target volume. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons and electronic data submission is required. Proton therapy is not allowed.

15.0.2 Treatment Planning Specifics

The guidelines for this study were developed based on the performance of COG investigators when executing the guidelines in prior COG trials. The goal of the treatment planning process is to develop a plan to deliver a uniform dose to the planning target volume that includes all known tumor plus the specified clinical target volume margin. The protocol-specified total dose is 54 Gy using conventional fractionation. Because the total dose does not exceed the recommended dose limits for the spinal cord and optic chiasm, volume reductions are not required nor recommended.

15.0.3 Required Benchmark and Questionnaires

Radiation therapy will be administered using photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; sites using IMRT and not previously credentialed for use of IMRT in COG trials must irradiate the IMRT Head and Neck Phantom available from the IROC Houston QA Center (RPC) and update their Facility Questionnaire on the IROC Houston website (http://rpc.mdanderson.org/rpc). All centers participating in this protocol must complete the CT/MR image fusion benchmark. Benchmark materials and questionnaires may be obtained from IROC Rhode Island (www.irocri.qarc.org) and must be submitted before patients on this protocol can be evaluated.

15.0.4 Guidelines and Requirements for the Use of IMRT

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

15.1 **Indications for Radiation Therapy**

All patients enrolled on this protocol will receive concurrent AZD1775 (MK-1775) and radiation therapy.

15.2 **Timing**

15.2.1 All patients should be seen in consultation by a radiation oncologist at the time of study enrollment. The purpose of the consultation is to participate in the initial evaluation and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning. If additional imaging studies are pursued, thin section MR (T2-weighted and FLAIR) sequences should be obtained for registration to the CT data set to assist in treatment planning.

15.2.2 All patients must begin therapy no later than 7 days after study enrollment. Enrollment must be no later than 28 days after the date of radiographic diagnosis or surgery, whichever is the later date.

15.2.3 There are no contraindications to radiation therapy. There are, however, some restrictions with regard to concomitant medications and eligibility as detailed in Section 4.2.2. Patients must not be receiving enzyme-inducing anticonvulsants (see Appendix II for a list of enzyme inducing and non-inducing anticonvulsants). Within these constraints, corticosteroids and anticonvulsants should be used as clinically indicated and tapered as soon as possible. Prophylactic anticonvulsants are strongly discouraged.

15.2.4 Please see Section 5.1 and Section 5.2 for details of timing of AZD1775 (MK-1775) administration. AZD1775 (MK-1775) will be administered orally once each day it is assigned directly after each day's radiation therapy fraction.

15.3 **Emergency Irradiation**

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol and urgent irradiation is not envisioned under any circumstance.

15.4 **Equipment and Methods of Delivery and Verification**

Equipment	Photons (any energy)	IMRT (4-10MV)
Linear Accelerator	X	X

15.4.1 Treatment planning

CT (volumetric) based planning is required to optimize dose to the PTV while protecting normal tissues. Organs at risk within the irradiated volume should be contoured. A dose-volume histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues. CT section thickness should be ≤ 5mm although 2-3mm is preferred.

15.4.2 In-room verification of spatial positioning

15.4.2.1 Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are

required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

15.4.2.2 Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging.

15.5 Target Volumes

15.5.1 General comments

International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study where applicable. Although the MRI obtained immediately prior to radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after surgical resection or CSF shunting procedure. The investigators recognize that resection and shunting are unlikely for these patients. The sequence that best defines the extent of disease and post-operative tumor bed (when applicable) should be used to determine the GTV and registered to the treatment planning CT. Most patients with DIPG require a combination of MR sequences to delineate the extent of disease. MR T2 and FLAIR sequences are most likely to be those chosen for registration to the treatment planning CT data set. The GTV, CTV, PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

15.5.2 Definitions for GTV, CTV and PTV

- Gross tumor volume (GTV) is based on the most recent MRI and/or post-operative MRI examination (if resection was done) and includes gross residual tumor and the tumor bed at the primary site. In defining the GTV, the investigator should consider all imaging studies that have defined the extent of tumor and the tissues involved anatomically. The GTV in most cases will be the T2 or FLAIR abnormality on the appropriate MR sequence. Tissue defects resulting from surgical approaches, when undertaken, will not be included as part of the GTV when not previously involved by tumor. Investigators should register the immediate pre-irradiation MR imaging sequences that demonstrated tumor and contour the GTV.

- Clinical target volume (CTV) includes the GTV with an added margin of 1 cm. This is meant to treat subclinical microscopic disease and is anatomically confined (i.e., the CTV is limited to the confines of the bony calvarium, falx and tentorium where applicable or extends up to but not beyond neuroanatomic structures through which tumor extension or invasion is certain not to have occurred). The CTV may be manually moved inward to the inner table of the bony calvarium. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires treatment planning MR and/or diagnostic MR imaging data with image section thickness ≤ 5mm.

- Planning target volume (PTV) includes a margin which is added to the CTV in 3-dimensions. It is geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The

IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 3 or 5 mm. The use of a PTV margin of 3 mm requires written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system is used with weekly or more frequent imaging. For this study, IGRT is defined as 2- or 3-dimensional digital imaging positioning. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient. The PTV margin chosen by the treating investigator requires treatment planning MR and/or diagnostic MR imaging data with imaging section thickness ≤ the chosen PTV margin.

15.6 Target Dose

15.6.1 Dose Definition

Photon dose is to be specified in centigray (cGy)-to-muscle.

15.6.2 Prescribed dose and fractionation

The total dose to the isodose surface encompasses the PTV will be 5400 cGy administered in 30 fractions of 180 cGy. The patient should be treated with one fraction per day. All fields should be treated each day.

Table 15.6.2 Prescribed Doses and Fractionation

Nominal Dose by Site	Target Volume	Dose/fraction	Number of Fractions
Primary Site 5400 cGy	PTV1	180 cGy	30

15.6.3 Dose uniformity

At least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of the PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

15.6.4 Tissue heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities.

15.6.5 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. Blood product

support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size.

15.7 Treatment Technique

15.7.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissues.

15.7.2 Field Shaping

Field shaping will be done with either customized cerrobend blocking or multileaf collimation.

15.7.3 Simulation including patient positioning and immobilization

15.7.3.1 Patient positioning

Reproducible setups are critical. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter- and intra-fraction motion when using non-standard position approaches.

15.7.3.2 Immobilization devices

Standard immobilization devices for the brain or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

15.7.4 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

15.7.5 Motion Management and Margins to Account for Target Volume Changes During Treatment

Considering motion of target volumes is important. Brain tumors susceptible to cyst expansion should be monitored closely. Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele, or steroid use should be monitored carefully with repeat imaging when indicated.

If motion management techniques are used, a description of the method used and evidence of the remaining tumor motion (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT) should be submitted **on the Motion Management Reporting Form** with the Quality Assurance Documentation materials as noted in Section 15.10.

15.8 Organs at Risk

The organ at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, photon IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines.

Dose Constraints

15.8.1 Cochleae

- D50% ≤ 3500 cGy – Goal (each cochlea)
- D50% ≤ 2000 cGy – Preferred (each cochlea)
- Comment – There is no dose maximum for the cochleae.
- Structure definition - Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

15.8.2 Optic Globes

- D90% ≤ 500 cGy, D50% ≤ 1000 cGy and D10% ≤ 3500 cGy – Goal
- D90% ≤ 1000 cGy, D50% ≤ 2000 cGy and D10% ≤ 5400 cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the anterior chamber of the eye and minimize dose to the entire eye without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition - Each eye should be separately contoured on the treatment planning CT or MR as a circular structure from the most superior to inferior aspect.

15.8.3 Right and Left Optic Nerves and Chiasm

- D90% ≤ 1000 cGy, D50% ≤ 5400 cGy and D10% ≤ 5600 cGy – Goal
- D90% ≤ 5400 cGy, D50% ≤ 5600 cGy and D10% ≤ 5800 cGy – Maximum
- Comment – These parameters apply to each of the separate three structures, not the combined volume of the three structures. Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use his/her discretion to reduce target volume coverage.
- Structure definitions – The optic nerves and chiasm may be contoured on CT or MR. The contours should appear on at least two successive CT or MR images.

15.8.4 Spinal Cord

- D90% ≤ 300 cGy, D50% ≤ 2600 cGy and D10% ≤ 5700 cGy - Goal
- D90% ≤ 900 cGy, D50% ≤ 5000 cGy and D10% ≤ 5900 cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage.
- Structure Definition - For the purposes of this study, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For purposes of comparison and consistency with dose volume data, the spinal cord should be contoured on a number of images to be determined by the image section thickness (CT section thickness, n=number of images; 2mm, n=30; 2.5 mm, n=24; 3 mm, n=20). Using these guidelines, only the superior-most 6 cm of anatomic spinal cord is contoured.

15.9 Dose Calculations and Reporting

15.9.1 Prescribed Dose

The dose prescription and fractionation shall be reported on the RT-1 Dosimetry Summary Form. The total dose delivered shall be reported on the RT-2 Radiotherapy Total Dose Record. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry.

15.9.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record form. The appropriate dose-volume histograms should be submitted. If IMRT is used for the primary tumor, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

Table 15.9a Required DVH data:

Required DVH
Total Brain
Optic Nerves (L+R)
Optic Chiasm
Brainstem
Spinal Cord
Cochleae (L+R)
Unspecified Tissue

15.10 Quality Assurance Documentation

On-treatment review is NOT required for this study. Within one week of the completion of radiation therapy, detailed treatment data shall be submitted.

Digital Submission: Submission of treatment plans in digital format (DICOM RT) is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the IROC RI Web site at www.irocri.qarc.org. Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk specified in Section 15.8. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- All diagnostic imaging used to plan the target volume. This includes CT or MRI PRIOR to attempted surgical resection of the primary tumor. Digital format is preferred.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review.
- If a PTV margin of 3 mm is used, written documentation that image-guided radiation therapy (IGRT) methods are used on a daily basis or alternatively that a head fixation system or verification system was used with weekly or more frequent imaging. See Section 15.5.2.
- Motion Management Reporting Form (if applicable, see Section 15.7.5).

Forms

- RT-1 Dosimetry Summary Form.
- RT-2 Radiotherapy Total Dose Record form.

These data should be forwarded to:
IROC Rhode Island QA Center
640 George Washington Highway

Building B, Suite 201
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the dose calculations or documentation should be directed to:
COG Protocol Dosimetrist
IROC Rhode Island QA Center
640 George Washington Highway
Building B, Suite 201
Lincoln, Rhode Island 02865-4207

15.11 Definitions of Deviations in Protocol Performance

	DEVIATION	
	Minor	**Major**
Prescription Dose		
	Difference in prescribed or computed dose is 6-10% of protocol specified dose	Difference in prescribed or computed dose is > 10% of protocol specified dose
Dose Uniformity and Coverage		
	>10% PTV received > 110% of the protocol dose *or* 95% isodose covers < 100% of CTV	> 20% of PTV received >110% of the protocol dose *or* 90% isodose covers < 100% of CTV
Volume		
	CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	GTV does not encompass MR-visible residual tumor
Organs at Risk		
	Dose to any OAR exceeds the goal dose stated in 15.8	Dose to any OAR exceeds the maximum dose stated in 15.8

REFERENCES

1. Hargrave D, Bartels U, Bouffet E: Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol 7:241-8, 2006
2. Pollack IF, Finkelstein SD, Woods J, et al: Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 346:420-7, 2002
3. Grill J, Puget S, Andreiuolo F, et al: Critical oncogenic mutations in newly diagnosed pediatric diffuse intrinsic pontine glioma. Pediatric blood & cancer 58:489-91, 2012
4. Goi K, Takagi M, Iwata S, et al: DNA damage-associated dysregulation of the cell cycle and apoptosis control in cells with germ-line p53 mutation. Cancer Res 57:1895-902, 1997
5. Reinhardt HC, Aslanian AS, Lees JA, et al: p53-deficient cells rely on ATM- and ATR-mediated checkpoint signaling through the p38MAPK/MK2 pathway for survival after DNA damage. Cancer Cell 11:175-89, 2007
6. Manke IA, Nguyen A, Lim D, et al: MAPKAP kinase-2 is a cell cycle checkpoint kinase that regulates the G2/M transition and S phase progression in response to UV irradiation. Mol Cell 17:37-48, 2005
7. Lee J, Kumagai A, Dunphy WG: Positive regulation of Wee1 by Chk1 and 14-3-3 proteins. Mol Biol Cell 12:551-63, 2001
8. Rothblum-Oviatt CJ, Ryan CE, Piwnica-Worms H: 14-3-3 binding regulates catalytic activity of human Wee1 kinase. Cell Growth Differ 12:581-9, 2001
9. Stanford JS, Ruderman JV: Changes in regulatory phosphorylation of Cdc25C Ser287 and Wee1 Ser549 during normal cell cycle progression and checkpoint arrests. Mol Biol Cell 16:5749-60, 2005
10. Hirai H, Iwasawa Y, Okada M, et al: Small-molecule inhibition of Wee1 kinase by MK-1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents. Mol Cancer Ther 8:2992-3000, 2009
11. Hirai H, Arai T, Okada M, et al: MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer biology & therapy 9:514-22, 2010
12. Kreahling JM, Gemmer JY, Reed D, et al: MK1775, a selective Wee1 inhibitor, shows single-agent antitumor activity against sarcoma cells. Molecular cancer therapeutics 11:174-82, 2012
13. Rajeshkumar NV, De Oliveira E, Ottenhof N, et al: MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. Clinical cancer research : an official journal of the American Association for Cancer Research 17:2799-806, 2011
14. Porter CC, Kim J, Fosmire S, et al: Integrated genomic analyses identify WEE1 as a critical mediator of cell fate and a novel therapeutic target in acute myeloid leukemia. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, U.K, 2012
15. Mir SE, De Witt Hamer PC, Krawczyk PM, et al: In silico analysis of kinase expression identifies WEE1 as a gatekeeper against mitotic catastrophe in glioblastoma. Cancer Cell 18:244-57, 2010
16. Bridges KA, Hirai H, Buser CA, et al: MK-1775, a novel Wee1 kinase inhibitor, radiosensitizes p53-defective human tumor cells. Clinical cancer research : an official journal of the American Association for Cancer Research 17:5638-48, 2011
17. Mizuarai S, Yamanaka K, Itadani H, et al: Discovery of gene expression-based pharmacodynamic biomarker for a p53 context-specific anti-tumor drug Wee1 inhibitor. Mol Cancer 8:34, 2009
18. Mueller ea: WEE1 Is a Promising Molecular Target for the Treatment of Pediatric High-Grade Gliomas. Presented at the Annual Meeting of the Society of Neuro-Oncology 2011, Los Angeles, 2011
19. Caretti V, Hiddingh L, Lagerweij T, et al: WEE1 Kinase Inhibition Enhances the Radiation Response of Diffuse Intrinsic Pontine Gliomas. Mol Cancer Ther 12:141-50
20. Paugh BS, Qu C, Jones C, et al: Integrated molecular genetic profiling of pediatric high-grade

gliomas reveals key differences with the adult disease. J Clin Oncol 28:3061-8
21. Nicolaides TP, Li H, Solomon DA, et al: Targeted therapy for BRAFV600E malignant astrocytoma. Clin Cancer Res 17:7595-604, 2011
22. Sanai N, Li J, Boerner J, et al: Phase 0 trial of AZD1775 in patients with first-recurrence glioblastoma. J Clin Oncol 34 (suppl; abstr 2008), 2016
23. Schwartz GJ, Gauthier B: A simple estimate of glomerular filtration rate in adolescent boys. . J Pediatr 106(3):522-6, 1985
24. 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.,
25. Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.,
26. Acute kidney injury includes renal impairment and acute renal insufficiency.,
27. Rash may include rash, erythema, eczema, and rash maculo-papular.,
28. Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.,
29. Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26(2):190-5, 2008

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 IV: PATIENT DIARY: RADIATION PHASE

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

Complete each day with the time and dose of AZD1775 (MK-1775) given, and circle AM or PM. 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***. 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 each week. Your institution will upload this document into RAVE weekly. Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

EXAMPLE				***Number of capsules***			***Comments***
WEEK 1	***Date***	***Time***		***10 mg***	***25 mg***	***100 mg***	
Day 1: MONDAY	*1/15/14*	*8:30*	*AM*		*2*	*1*	*He felt nauseated an hour after taking the drug but did not vomit.*

Cycle #: _____ Dose: _____ Start Date: |__/__|__/__|__/__| **End Date:** |__/__|__/__|__/__|

WEEK 1	**Date**	**Time**		**10 mg**	**25 mg**	**100 mg**	**Comments**
Day 1:_____			**AM/ PM**				
Day 2:_____			**AM/ PM**				
Day 3:_____			**AM/ PM**				
Day 4:_____			**AM/ PM**				
Day 5:_____			**AM/ PM**				
Day 6:_____			**AM/ PM**				
Day 7:_____			**AM/ PM**				
WEEK 2	**Date**	**Time**		**10 mg**	**25 mg**	**100 mg**	**Comments**
Day 8:_____			**AM/ PM**				
Day 9:_____			**AM/ PM**				
Day 10:_____			**AM/ PM**				
Day 11:_____			**AM/ PM**				
Day 12:_____			**AM/ PM**				
Day 13:_____			**AM/ PM**				
Day 14:_____			**AM/ PM**				
WEEK 3	**Date**	**Time**		**10 mg**	**25 mg**	**100 mg**	**Comments**
Day 15:_____			**AM/ PM**				
Day 16:_____			**AM/ PM**				
Day 17:_____			**AM/ PM**				
Day 18:_____			**AM/ PM**				
Day 19:_____			**AM/ PM**				
Day 20:_____			**AM/ PM**				
Day 21:_____			**AM/ PM**				

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

WEEK 4	Date	Time		10 mg	25 mg	100 mg	Comments
Day 22:_____			AM/ PM				
Day 23:_____			AM/ PM				
Day 24:_____			AM/ PM				
Day 25:_____			AM/ PM				
Day 26:_____			AM/ PM				
Day 27:_____			AM/ PM				
Day 28:_____			AM/ PM				
WEEK 5	**Date**	**Time**		**10 mg**	**25 mg**	**100 mg**	**Comments**
Day 29:_____			AM/ PM				
Day 30:_____			AM/ PM				
Day 31:_____			AM/ PM				
Day 32:_____			AM/ PM				
Day 33:_____			AM/ PM				
Day 34:_____			AM/ PM				
Day 35:_____			AM/ PM				
WEEK 6	**Date**	**Time**		**10 mg**	**25 mg**	**100 mg**	**Comments**
Day 36:_____			AM/ PM				
Day 37:_____			AM/ PM				
Day 38:_____			AM/ PM				
Day 39:_____			AM/ PM				
Day 40:_____			AM/ PM				
Day 41:_____			AM/ PM				
Day 42:_____			AM/ PM				

Notes: _____

_____

_____

_____

_____

APPENDIX V-A: AZD1775 (MK-1775) DOSING NOMOGRAM

AZD1775 (MK-1775) Dose Assignment: 50 mg/m^2/day*
(Dose Levels -1, 1, 2, and 3)

BSA (m^2)	Total Daily Dose (mg/day)
0.35-0.44	20
0.45-0.54	25
0.55-0.64	30
0.65-0.74	35
0.75-0.84	40
0.85-0.94	45
0.95-1.04	50
1.05-1.14	55
1.15-1.29	60
1.30-1.44	70
1.45-1.60	75
1.61-1.84	85
1.85-2.14	100
2.15- ≥ 2.30	110

*Dose Level -1: Days 1, 3, 5,15,17,19,29,31,33
Dose Level 1: Days 1-5, 15-19, 29-33
Dose Level 2: Days 1-5, 8, 10, 12, 15-19, 22, 24, 26, 29-33, 36, 38, 40
Dose Level 3: Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40

Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

AZD1775 (MK-1775) Dose Assignment: 95 mg/m^2/day* (Dose Level 4)

BSA (m^2)	Total Daily Dose (mg/day)
0.35-0.39	35
0.40-0.44	40
0.45-0.49	45
0.50-0.55	50
0.56-0.60	55
0.61-0.68	60
0.69-0.76	70
0.77-0.86	75
0.87-0.97	85
0.98-1.10	100
1.11-1.23	110
1.24-1.36	125
1.37-1.49	135
1.50-1.63	150
1.64-1.76	160
1.77-1.97	175
1.98-2.15	200
2.16-2.28	210
2.29- ≥ 2.30	225

*Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40

Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

AZD1775 Dose Assignment: 130 mg/m^2/dose (Dose Level 5)

BSA (m^2)	AZD1775 Dose (mg/dose)
0.30-0.32	40
0.33-0.36	45
0.37-0.40	50
0.41-0.44	55
0.45-0.51	60
0.52-0.55	70
0.56-0.59	75
0.60-0.63	80
0.64-0.69	85
0.70-0.80	100
0.81-0.88	110
0.89-0.94	120
0.95-1.01	125
1.02-1.09	135
1.10-1.13	145
1.14-1.21	150
1.22-1.26	160
1.27-1.32	170
1.33-1.38	175
1.39-1.48	185
1.49-1.57	200
1.58-1.65	210
1.66-1.71	220
1.72-1.84	225
1.85-2.05	250
2.06-2.21	275
2.22-2.30	300

- For dose reduction due to toxicity, please refer to dose assignment 100 mg/m^2/dose below

AZD1775 Dose Assignment: 100 mg/m^2/dose

BSA (m^2)	AZD1775 Dose (mg/dose)
0.30-0.32	30
0.33-0.37	35
0.38-0.42	40
0.43-0.47	45
0.48-0.52	50
0.53-0.57	55
0.58-0.67	60
0.68-0.72	70
0.73-0.77	75
0.78-0.82	80
0.83-0.90	85
0.91-1.05	100
1.06-1.15	110

1.16-1.22	120
1.23-1.32	125
1.33-1.42	135
1.43-1.47	145
1.48-1.57	150
1.58-1.65	160
1.66-1.72	170
1.73-1.79	175
1.80-1.92	185
1.93-2.05	200
2.06-2.15	210
2.16-2.22	220
2.23-2.30	225

Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

AZD1775 Dose Assignment: 160 mg/m^2/dose (Dose Level 6)

BSA (m^2)	AZD1775 Dose (mg/dose)
0.30-0.34	50
0.35-0.44	60
0.45-0.52	75
0.53-0.57	85
0.58-0.66	100
0.67-0.73	110
0.74-0.81	125
0.82-0.85	135
0.86-0.91	145
0.92-0.97	150
0.98-1.04	160
1.05-1.17	175
1.18-1.28	200
1.29-1.36	210
1.37-1.51	225
1.52-1.64	250
1.65-1.79	275
1.80-1.95	300
1.96-2.14	325
2.15-2.29	350
2.30	375

Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

AZD1775 Dose Assignment: 200 mg/m^2/dose (Dose Level 7)

BSA (m^2)	AZD1775 Dose (mg/dose)
0.30-0.34	60
0.35-0.39	75
0.40-0.44	85
0.45-0.52	100
0.53-0.57	110

0.58-0.65	125
0.66-0.71	135
0.72-0.81	150
0.82-0.91	175
0.92-1.04	200
1.05-1.17	225
1.18-1.28	250
1.29-1.41	275
1.42-1.58	300
1.59-1.64	325
1.65-1.79	350
1.80-1.93	375
1.94-2.04	400
2.05-2.14	425
2.15-2.29	450
2.30	475

Refer to Appendix V-B for scheduling guidelines based on the day of the week XRT is initiated.

APPENDIX V-B: GUIDELINES FOR AZD1775 (MK-1775) DOSING SCHEDULE

Please refer to the tables below for scheduling guidelines based on the day of the week XRT is initiated.

Dose Level -1: AZD1775 50 mg/m²/dose daily Mon-Fri QOD, alternating weeks

Monday Start Date for XRT

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 50mg/m²	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-
PK	x	x		x	x			x																																		
PD	x				x			x																																		

Tuesday Start Date for XRT

	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 50mg/m²	x	-	x	-	-	-	x	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-
PK														x	x		x	x			x																						
PD														x				x			x																						

Wednesday Start Date for XRT

	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 50mg/m²	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-
PK						x	x		x	x			x																														
PD						x				x			x																														

Thursday Start Date for XRT

	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 50mg/m²	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-
PK					x	x		x	x			x																															
PD					x				x			x																															

Friday Start Date for XRT

	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 50mg/m²	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-	-	-	-	x	-	x	-	x	-	-	-	-	-	-
PK				x	x		x	x			x																															
PD				x				x			x																															

X = treatment; "-" = no treatment

Dose Level 1: AZD1775 (MK-1775) 50 mg/m^2/dose daily Mon-Fri, alternating weeks

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
Monday Start Date for XRT																																										
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 50mg/m^2	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-
PK	x	x		x	x			x																																	
PD	x				x			x																																	
Tuesday Start Date for XRT																																										
	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 50mg/m^2	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	x	-	-	-	-	-	-	-
PK														x	x		x	x			x																					
PD														x				x			x																					
Wednesday Start Date for XRT																																										
	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 50mg/m^2	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-
PK						x	x		x	x			x																													
PD						x				x			x																													
Thursday Start Date for XRT																																										
	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 50mg/m^2	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	x	x	x
PK					x	x		x	x			x																														
PD					x				x			x																														
Friday Start Date for XRT																																										
	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 50mg/m^2	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	-	-	x	x	x	x
PK				x	x		x	x			x																															
PD				x				x			x																															

"x" = treatment; "-" = no treatment

Dose Level 2: AZD1775 (MK-1775) 50 mg/m^2 daily Mon-Fri every other week, alternating with weeks of QOD dosing

Monday Start Date for XRT

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 50mg/m^2	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-
PK	x	x		x	x			x																																		
PD	x				x			x																																		

Tuesday Start Date for XRT

	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 50mg/m^2	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x
PK							x	x		x	x			x																													
PD							x				x			x																													

Wednesday Start Date for XRT

	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 50mg/m^2	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-
PK						x	x		x	x			x																														
PD						x				x			x																														

Thursday Start Date for XRT

	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 50mg/m^2	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x
PK					x	x		x	x			x																														
PD					x				x			x																														

Friday Start Date for XRT

	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 50mg/m^2	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-	x	-	-	x	x	x	x	x	-	-	x	-	x	-
PK				x	x		x	x			x																															
PD				x				x			x																															

"x" = treatment; "-" = no treatment

Dose Level 3: AZD1775 (MK-1775) 50 mg/m² daily Mon-Fri During Weeks 1-6

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
Monday Start Date for XRT																																										
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 50mg/m²	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
PK*	x	x		x	x			x																																	
PD*	x				x			x																																	
Tuesday Start Date for XRT																																									
	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 50mg/m²	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
PK*	B						x	x			x			x																												
PD*	B						x				x			x																												
Wednesday Start Date for XRT																																									
	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 50mg/m²	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
PK*	B					x	x			x			x																												
PD*	B					x				x			x																												
Thursday Start Date for XRT																																									
	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 50mg/m²	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
PK*	B				x	x			x			x																														
PD*	B				x				x			x																														
Friday Start Date for XRT																																									
	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 50mg/m²	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
PK*	B			x	x			x			x																														
PD*	B			x				x			x																														

"x" = treatment; "-" = no treatment

* B= The initial Baseline/Pre-study blood sample is drawn within 7 days prior to XRT start date. "PK/PD Day 1" is scheduled for the Monday of the first full week of dosing.

Dose Level 4: AZD1775 (MK-1775) 95 mg/m² daily Mon-Fri During Weeks 1-6

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
Monday Start Date for XRT																																										
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 95mg/m²	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
PK*	x	x			x			x																																		
PD*	x				x			x																																		
Tuesday Start Date for XRT																																										
	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 95mg/m²	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
PK*	B						x	x			x			x																													
PD*	B						x				x			x																													
Wednesday Start Date for XRT																																										
	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 95mg/m²	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
PK*	B					x	x			x			x																													
PD*	B					x				x			x																													
Thursday Start Date for XRT																																										
	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 95mg/m²	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
PK*	B				x	x			x			x																														
PD*	B				x				x			x																														
Friday Start Date for XRT																																										
	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 95mg/m²	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
PK*	B			x	x			x			x																														
PD*	B			x				x			x																														

"x" = treatment; "-" = no treatment

* B= The initial Baseline/Pre-study blood sample is drawn within 7 days prior to XRT start date. "PK/PD Day 1" is scheduled for the Monday of the first full week

of dosing.

Dose Level 5: AZD1775 (MK-1775) 130 mg/m^2 Mon-Fri During Weeks 1-6

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
Monday Start Date for XRT																																										
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 130mg/m^2	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
PK*	x	x			x			x																																		
PD*	x				x			x																																		
Tuesday Start Date for XRT																																										
	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 130mg/m^2	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
PK*	B						x	x			x			x																													
PD*	B						x				x			x																													
Wednesday Start Date for XRT																																										
	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 130mg/m^2	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
PK*	B					x	x			x			x																													
PD*	B					x				x			x																													
Thursday Start Date for XRT																																										
	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 130mg/m^2	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
PK*	B				x	x			x			x																														
PD*	B				x				x			x																														
Friday Start Date for XRT																																										
	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 130mg/m^2	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
PK*	B			x	x			x			x																														
PD*	B			x				x			x																														

"x" = treatment; "-" = no treatment

* B= The initial Baseline/Pre-study blood sample is drawn within 7 days prior to XRT start date. "PK/PD Day 1" is scheduled for the Monday of the first full week of dosing.

Dose Level 6: AZD1775 (MK-1775) 160 mg/m^2 daily Mon-Fri During Weeks 1-6

Monday Start Date for XRT

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 160mg/m^2	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
PK*	x	x			x			x																																		
PD*	x				x			x																																		

Tuesday Start Date for XRT

	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 160mg/m^2	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
PK*	B						x	x			x			x																													
PD*	B						x				x			x																													

Wednesday Start Date for XRT

	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 160mg/m^2	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
PK*	B					x	x			x			x																														
PD*	B					x				x			x																														

Thursday Start Date for XRT

	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 160mg/m^2	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
PK*	B				x	x			x			x																														
PD*	B				x				x			x																														

Friday Start Date for XRT

	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 160mg/m^2	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
PK*	B			x	x			x			x																															
PD*	B			x				x			x																															

"x" = treatment; "-" = no treatment

* B= The initial Baseline/Pre-study blood sample is drawn within 7 days prior to XRT start date. "PK/PD Day 1" is scheduled for the Monday of the first full week of dosing

Dose Level 7: AZD1775 (MK-1775) 200 mg/m² daily Mon-Fri During Weeks 1-6

Monday Start Date for XRT

	Week 1: Days 1-7							Week 2: Days 8-14							Week 3: Days 15-21							Week 4: Days 22-28							Week 5: Days 29-35							Week 6: Days 36-42						
	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S
XRT	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
AZD1775 200mg/m²	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-
PK*	x	x			x			x																																		
PD*	x				x			x																																		

Tuesday Start Date for XRT

	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M
XRT	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
AZD1775 200mg/m²	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x
PK*	B						x	x			x			x																													
PD*	B						x				x			x																													

Wednesday Start Date for XRT

	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T
XRT	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
AZD1775 200mg/m²	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x
PK*	B					x	x			x			x																														
PD*	B					x				x			x																														

Thursday Start Date for XRT

	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W
XRT	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
AZD1775 200mg/m²	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x
PK*	B				x	x			x			x																														
PD*	B				x				x			x																														

Friday Start Date for XRT

	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th	F	Sa	S	M	T	W	Th
XRT	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
AZD1775 200mg/m²	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x	x	-	-	x	x	x	x
PK*	B			x	x			x			x																															
PD*	B			x				x			x																															

"x" = treatment; "-" = no treatment

* B= The initial Baseline/Pre-study blood sample is drawn within 7 days prior to XRT start date. "PK/PD Day 1" is scheduled for the Monday of the first full week of dosing

APPENDIX VI: CORRELATIVE STUDIES GUIDE

Correlative Study	Appendix	Blood Volume			Tube Type
		Volume per sample	Total Volume ≥ 20 kg	Total Volume <20 kg	
Pharmacokinetics	VII; X	2-3 ml	30-45 ml	16-24 ml	K_2 EDTA (lavender-top)
Pharmacodynamics	VIII	1 ml	5 ml	5 ml	Heparinized (green-top); Smart Tubes
Total Blood Volume			**35-50 ml**	**21-29 ml**	

APPENDIX VII: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ACC # _____ **Day 1 of Protocol Therapy (XRT Start Date)**: _____
Please do not write patient names on this form or on samples.

Patient weight: _____kg
Body Surface Area: _____m^2 Dose Level: _____mg/m^2 Total Daily Dose: _____mg

****Refer to Appendix V-B for PK collection based on XRT start date. ****

Blood samples (2-3 mL) will be collected in K_2 EDTA (lavender-top) tubes in patients ≥ 20 kg at the following time points (+/- 10 minutes): Baseline, PK Day 1 (pre-dose, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr and 24 hours after dose), PK Day 5 (pre-dose, 1 hr, 2 hr, 4 hr, 6 hr, and 8 hr after dose), and PK Day 8 (pre-dose).

For patients < 20 kg, samples will be collected at the following time points (+/- 10 minutes): Baseline, PK Day 5 (pre-dose, 1 hr, 2 hr, 4 hr, 6 hr, and 8 hr after dose), and PK Day 8 (pre-dose).

Blood Sample No.	Time Point**	Scheduled Collection Time**	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
0[$]	**Baseline/Pre-study**	Within 7 days prior to XRT start date	___/___/___	|__|__| : |__|__|
1[$, ^]	**Baseline/PK Day 1**	Prior to Monday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PK Day 1** **Date:**___/___/___ **Time:** |__|__| : |__|__|				
2[^]	**PK Day 1**	1 hr after Monday dose	___/___/___	|__|__| : |__|__|
3[^]	**PK Day 1**	2 hr after Monday dose	___/___/___	|__|__| : |__|__|
4[^]	**PK Day 1**	4 hr after Monday dose	___/___/___	|__|__| : |__|__|
5[^]	**PK Day 1**	6 hr after Monday dose	___/___/___	|__|__| : |__|__|
6[^]	**PK Day 1**	8 hr after Monday dose	___/___/___	|__|__| : |__|__|
7[^]	**PK Day 2**	24 (±2) hrs after Monday dose[@]	___/___/___	|__|__| : |__|__|
~~**8**~~	~~**PK Day 4**~~	~~Prior to Thursday dose~~	No Longer Collected per AMD#3	
9	**PK Day 5**	Prior to Friday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PK Day 5** **Date:**___/___/___ **Time:** |__|__| : |__|__| **Hematocrit Value on PK Day 5 (if available):** _____				
10[%]	**PK Day 5**	1 hr after Friday dose	___/___/___	|__|__| : |__|__|
11	**PK Day 5**	2 hr after Friday dose	___/___/___	|__|__| : |__|__|
12	**PK Day 5**	4 hr after Friday dose	___/___/___	|__|__| : |__|__|
13	**PK Day 5**	6 hr after Friday dose	___/___/___	|__|__| : |__|__|
14	**PK Day 5**	8 hr after Friday dose	___/___/___	|__|__| : |__|__|
15	**PK Day 8**	Prior to Monday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PK Day 8** **Date:**___/___/___ **Time:** |__|__| : |__|__|				

[$] Baseline samples should be taken at least 1 day apart, if feasible.
[^] Patients ≥ 20 kg only
****Refer to Appendix V-B for PK collection based on XRT start date.**
[@] Hold Dose until PK sample is 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 8.4.6. See Section 8.4 and Appendix XI for detailed guidelines for packaging and shipping PK samples.

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

APPENDIX VIII: PHARMACODYNAMIC STUDY FORM

COG Pt ID # _____ ACC # _____ **Day 1 of Protocol Therapy (XRT Start 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

Blood samples will be obtained from all patients (1 ml per time point) prior to treatment start (two baseline samples are required) as well as at the following time points. Every effort should be made to obtain the baseline (pre-treatment) samples on two different days, if feasible. A total of 5 time points for the PD analysis will be collected.

Blood Sample No.	Time Point**	Scheduled Collection Time**	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1*	**Baseline/Pre-study**	Within 7 days prior to XRT start date	___/___/___	|__|__| : |__|__|
2*	**Baseline/ PD Day 1**	Prior to Monday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PD Day 1		**Date:**___/___/___	**Time:** |__|__| : |__|__|	
3	**PD Day 1**	6-8 hr after Monday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PD Day 5		**Date:**___/___/___	**Time:** |__|__| : |__|__|	
4	**PD Day 5**	6-8 hr after Friday dose	___/___/___	|__|__| : |__|__|
5	**PD Day 8**	Prior to Monday dose	___/___/___	|__|__| : |__|__|
AZD1775 (MK-1775) Dose on PD Day 8		**Date:**___/___/___	**Time:** |__|__| : |__|__|	

*Baseline samples should be taken at least 1 day apart, if feasible.
****Refer to Appendix V-B for PD collection based on XRT start date.**

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 8.5.5. See Section 8.5 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: PD SAMPLE COLLECTION GUIDELINES

Required Items:

- Whole blood collection at required PD time points as outlined in Appendix VIII
- 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 (i.e. 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 8.5.5. Samples should NOT be shipped on a Friday or before a holiday.

APPENDIX X: 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 SGPT 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 SGOT 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 XI: PREPARATION OF PLASMA SAMPLES FOR AZD1775 (MK-1775) PK ASSESSMENT

I. Biosafety

It is essential that universal precautions be taken while working with these specimens. However, you are encouraged to wear gloves and a lab coat/gown at all times to ensure safe handling of samples. If you should tear a glove, remove the torn one and replace it immediately.

II. General Instructions

Collect venous blood in a purple-topped vacutainer containing K_2EDTA.

III. Sample Preparation:

Material Needed:

1. Purple-topped vacutainer evacuated blood collection tubes (containing K_2EDTA)
2. 3.6 mL NUNC internal thread round bottom cryotubes (NUNC Part #366524) for plasma

Collection of Blood

For specific time points of sample collection, please refer to Appendix VII and Appendix V-B.

Procedure

1. Samples in the blood collection tube will be centrifuged at between 1000-1300 RCF (x g) at between 4°C to 10°C for 10 minutes. If the samples cannot be centrifuged immediately, the tubes should be kept on ice and centrifuged within 30 minutes of collection.
   Note: *RCF varies according to the centrifuge rotor radius. The formula for computing RCF from rotation speed and centrifuge radius is RCF = 11.2r (RPM/1000)^2, where r is rotor radius, in cm, and RPM is the rotations per minute setting of the centrifuge.*
2. Immediately after separation of the whole blood, carefully transfer the plasma **(about 0.5 - 1.0 mL)** using a plastic pipette into a labeled 3.6 mL internally-threaded NUNC cryotube and store at -20°C until shipment on DRY ICE.
   Note: *In the event that the whole blood samples cannot be processed immediately the samples should be kept on ice. No more than 60 minutes should elapse between blood draw and the freezing of plasma samples.*

IV. Laboratory Contact and Shipping Instructions

It is the responsibility of the primary investigator to ensure that all staff personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

1. AZD1775 (MK-1775) plasma shipments will be made in freezer boxes containing at least 10 kg DRY ICE.
2. Please include the PK Study Form (Appendix VII) with each shipment.
3. Shipments should be sent via overnight Federal Express, Monday through Wednesday to assure receipt by Friday. All samples should be shipped to the address in Section 8.4.6.

APPENDIX XII: POTENTIAL DRUG INTERACTIONS WITH AZD1775 (MK-1775)

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)**
• **Some heartburn medications (cimetidine, omeprazole, lansoprazole, rabeprazole)**
• **Some cholesterol lowering medications (atorvastatin, pravastatin, rosuvastatin, simvastatin)**
• **Several other specific agents, including the following:**
  ○ **Aprepitant/fosaprepitant**
  ○ **Amiodarone**
  ○ **Barbiturates**
  ○ **Diazepam**
  ○ **Diltiazem**
  ○ **Imatinib**
  ○ **Metformin**
  ○ **Mifepristone**
  ○ **Modafinil**
  ○ **Pioglitazone**
  ○ **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.*

APPENDIX XIV: INSTRUCTIONS FOR TREATING DIARRHEA

Institutional practice may be used in place of these guidelines.

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, initiate infectious evaluation including but not limited to bacterial culture, c. difficile toxin, viral infection (i.e. adenovirus, norovirus, rotavirus, enterovirus, CMV). If studies are negative, initiate loperamide (dosing below).

Any patient with diarrhea who is not already admitted to the hospital should be admitted for close monitoring for the occurrence of blood or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhea within 24 hours of using loperamide or other prescribed antidiarrheal medications.

Patients will be given **loperamide** based on body weight. Loperamide may be discontinued when diarrhea has resolved for 12 hours.

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

	2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

APPENDIX XV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

[Note to investigators: This appendix consists of an "information sheet" to be handed to the patient at the time of enrollment. Use or modify the text as appropriate for the study agent, so that the patient is aware of the risks and can communicate with their regular prescriber(s) and pharmacist. A convenient wallet-sized information card is also included for the patient to clip out and retain at all times. If you choose to use them, please note that the information sheet and wallet card will require IRB approval before distribution to patients.]

The patient _____ is enrolled on a clinical trial using the experimental study drug **AZD1775 (MK-1775)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

AZD1775 (MK-1775) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

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STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **AZD1775 (MK-1775).** This clinical trial is sponsored by the NCI**.** Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- "
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

and can be contacted at _____.