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TITLE: **A PHASE 2 STUDY OF AZD1775, A WEE1 INHIBITOR, IN PATIENTS WITH CCNE1 AMPLIFICATION**

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SCHEMA

This is an open-label phase II study of AZD1775, a Wee1 kinase inhibitor in patients with advanced solid tumors harboring CCNE1 amplification. This study follows a two-stage design to assess anti-tumor activity according to RECIST version 1.1, and toxicity profile according to NCI-CTCAE 5.0.

The primary endpoint is the objective response rate, and the secondary endpoints are safety, tolerability, and survivals. As shown in Figure 1, patients will be treated with AZD1775 at 300 mg PO daily for 5 days each week for 2 weeks (one cycle of therapy is 21 days). Blood and tumor specimens will be collected for translational research.

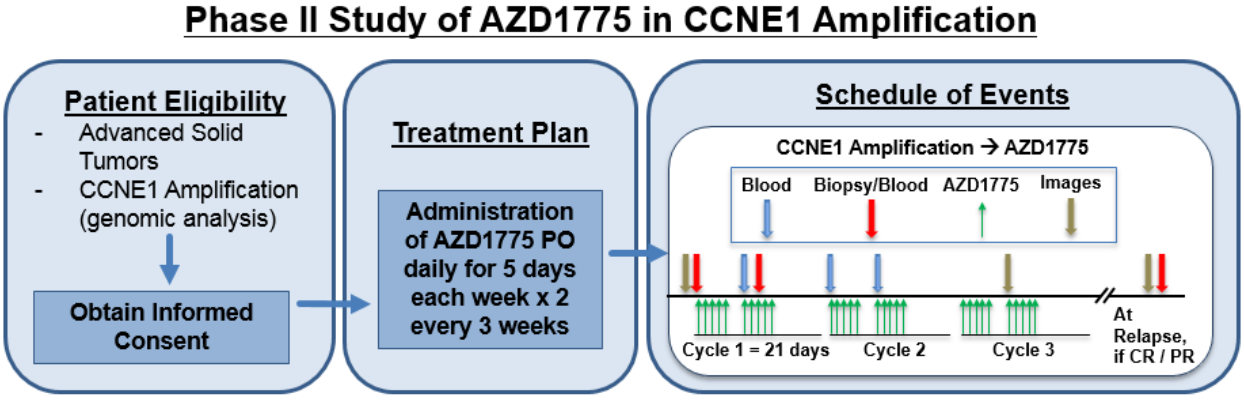

Figure 1. Study Schema

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1. OBJECTIVES

1.1 Primary Objectives

- To evaluate the proportion of patients with the objective response rate (ORR) to AZD1775 in patients with advanced refractory cancers with CCNE1 amplification.

1.2 Secondary Objectives

- To evaluate the proportion of patients alive and progression free at 6 months of treatment with AZD1775 in patients with advanced refractory cancers with CCNE1 amplification.

- To evaluate proportion of patients with extended time to progression (time to progression on AZD1775/ time to progression on last line of therapy ≥ 1.3).

- To evaluate time until death or disease progression.

- To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned or resistance mechanisms using additional genomic, RNA, protein and imaging-based assessment platforms.

2. BACKGROUND

2.1 Study Disease(s)

The study diseases include all histologically advanced solid tumors harboring CCNE1 amplification.

2.2 AZD1775: an oral, potent Wee1 inhibitor

AZD1775 is a potent, highly selective, ATP-competitive, small-molecule inhibitor of Wee1 kinase, displaying *in vitro* and *in vivo* preferential sensitization of tumor cells (relative to normal cells) to various DNA-damaging anticancer agents and modalities while sparing normal tissues from radiation- and chemotherapy-induced toxicity [1, 2]. Wee1 phosphorylates and inhibits cyclin-dependent kinases 1 (CDK1) and 2 (CDK2), and is involved in regulation of the intra-S and G2 cell cycle checkpoints [3]. Proper functioning of these checkpoints is essential for the DNA metabolism and the DNA damage response. The gene expression profile induced by Wee1 inhibition revealed dose-dependent inhibition of direct substrate pCDK1 and changes of genes regulating S-G_2 cell cycle progression or checkpoints, which are consistent with the mode of action of Wee1 inhibitors [4]. Inhibition of WEE1 is expected to release a tumor cell from DNA damage-induced arrest at the G2/M boundary, so that un-repaired DNA damage may be taken into mitosis (M-phase). Since cancer cells exhibit higher levels of endogenous damage than normal cells, as well as exhibiting loss of one or more DNA damage response capabilities, this is expected to preferentially enhance cancer cell death through mitotic catastrophe compared to normal cells. Also, inhibition of WEE1 is expected to cause aberrantly high CDK2 activity in S-phase cells that will have multiple effects for cancer cells that already have G1/S checkpoint aberrations. These include de-regulated replication origin firing before sufficient deoxynucleotides are available, resulting in a higher degree of replication stress and ultimately replication fork collapse where endonucleases generate DNA damage, which leads to apoptosis.

CDK1 (also called cell division cycle 2, or CDC2) activity drives a cell from the G2 phase of the cell cycle into mitosis. In response to DNA damage, WEE1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). Inhibition of WEE1 is expected to release a tumor cell from DNA damage-induced arrest at the G2/M boundary, so that un-repaired DNA damage may be taken into mitosis (M-phase). Since cancer cells exhibit higher levels of endogenous damage than normal cells, as well as exhibiting loss of one or more DNA damage response (DDR) capabilities, this is expected to preferentially enhance cancer cell death through mitotic catastrophe compared to normal cells.

[redacted]

CDK2 activity drives a cell into, and through the DNA synthesis (S-phase) of the cell cycle in which the genome is duplicated in preparation for cell division. An important aspect of CDK2 regulation of replication is the control of replication origin firing. WEE1, under normal circumstances, regulates CDK2 to provide sufficient time to generate the optimum environment for DNA synthesis, such as the generation of a sufficient pool of deoxynucleotide triphosphates (dNTPs), the building blocks of DNA. Inhibition of WEE1 is expected to cause aberrantly high CDK2 activity in S-phase cells that will have multiple consequences for cancer cells that already have G1/S checkpoint aberrations such as p53 mutations or CDKN2A deletions [5]. These include de-regulated replication origin firing before sufficient dNTPs are available, resulting in a higher degree of replication stress (already greater in cancer cells). The resulting increase in levels of replication stress will result in replication fork stalling, the generation of unstable DNA

replication structures and ultimately replication fork collapse where endonucleases generate DNA damage. [redacted]

In sarcoma cell lines, AZD1775 treatment at clinically relevant concentrations led to unchecked entry into mitosis associated with increased phosphorylated $CDK1^{Tyr\text{-}15}$ and histone 3 ($pH3^{Ser\text{-}10}$); DNA damage associated with phosphorylated $\gamma\text{-}H2AX^{Ser\text{-}139}$; and initiation of apoptosis associated with cleaved caspase-3 [6]. Clonogenic survival and tumor xenograft analyses showed that AZD1775 abrogated radiation-induced G_2 blockade by accelerating the progression of cells harboring radiation-induced DNA lesions into premature mitosis and inducing apoptosis in p53-defective tumor cells but not in p53-wt cell lines [7]. AZD1775 selectively sensitizes p53-deficient tumor cells to DNA-damaging agents such as gemcitabine, carboplatin, cisplatin, pemetrexed, doxorubicin, camptothecin, mitomycin C, and 5-fluorouracil [8-11]. Further investigation showed that AZD1775 displayed single-agent activity and enhanced the response of HPV-positive HNSCC to cisplatin both *in vitro* and *in vivo*, which was associated with G2 checkpoint abrogation, persistent DNA damage, and apoptosis induction through decreased expression of the anti-apoptotic proteins MCL-1 and XIAP [12]. The therapeutic effects of AZD1775 as single agent or combination with other agents are actively being evaluated in more than 30 clinical trials across multiple tumor types. A phase I study of 25 patients with a refractory solid tumor showed that single-agent AZD1775 can be safely administered as 225 mg twice per day orally over 2.5 days per week for 2 weeks every 21 days, and confirmed partial responses were observed in two patients carrying a *BRCA* mutation (one with head and neck cancer and one with ovarian cancer), providing preliminary clinical evidence of its preferential cytotoxicity to DNA damage repair–deficient cancer cells [13].

[redacted]

2.3 Clinical experience with AZD1775

AZD1775 has been administered to patients in 12 AstraZeneca-sponsored or Merck-sponsored clinical studies, 6 of which are ongoing. As of 11 November 2016, a total of approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. Of these 551 patients, 103 received AZD1775 monotherapy, 407 patients received AZD1775 in combination with cytotoxic chemotherapy agents and the remaining 41 patients

received AZD1775 in combination with targeted therapies MEDI4736 or olaparib.

These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy. In addition, approximately 350 patients have also received AZD1775 as part of externally-sponsored scientific research.

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 was terminated early due to portfolio prioritization in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.

- PN008 (NCT01076400): a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritization in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. The Phase IIa part was not initiated.

- PN011 (Investigator Sponsored Study): 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 multicenter, 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 multicenter Phase II study of AZD1775 plus either paclitaxel, gemcitabine, carboplatin, or pegylated liposomal doxorubicin in patients with platinum-resistant epithelial 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.

- NCI130032 (NCT01748825): AZD1775 for Advanced Solid Tumors (CTEP Sponsored study)

In Study PN001, of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients (AZD1775 Investigator's Brochure[IB])In Study PN001, 9 patients received AZD1775 monotherapy. Single ascending doses of AZD1775 up to 1300 mg were well tolerated; the maximum tolerated dose (MTD) was not established.

No complete responses (CRs) or PRs were observed in either of Studies PN005 or PN008 at the time that they were terminated.

In Study PN011, patients received single-agent AZD1775 PO BID over 2.5 days per week for 2 weeks in 3-week treatment cycles. Twenty-five patients were enrolled to determine the MTD using a 3+3 design. The MTD was established at 225 mg by mouth (PO) BID for 5 doses on

Weeks 1 and 2 of a 3-week schedule. Six patients with BRCA-mutated solid tumors were enrolled at the MTD. Partial responses were confirmed in two of the patients carrying BRCA mutations (ovarian cancer patient and head/neck cancer patient). Paired tumor biopsies were obtained from 5 patients treated at the MTD at baseline and after the 5th AZD1775 dose to determine the levels of pY15-Cdk and γH2AX. The biopsies showed a decrease in pY15-Cdk levels (2/5 paired biopsies). The same biopsies were analyzed for increases in γH2AX, an indicator of DNA damage. Three of the 5 biopsy pairs showed an increase in γH2AX levels. DNA damage response was observed in this study through provided paired tumor biopsies.

In Study D6011C00001, 32 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with docetaxel (75 mg/m2 IV) administered on Day 1 followed by pegfilgrastim on Day 4 of each 21-day cycle. The 3 patients (9.4%) that achieved PR by RECIST v1.1 had TP53 mutations. Twenty-one patients (65.6%) had SD and 10 (47.6%) of these patients had TP53 mutations. The planned Interim Analysis of 32 patients in the single cohort lead-in (Part A) suggested that toxicities associated with AZD1775 given in combination with docetaxel were greater in frequency and severity than with docetaxel alone. Additionally, the analysis revealed that it was very unlikely the target response rate would be reached in this study and a decision was made to terminate enrolment.

In Study D6011C00002, 14 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with pemetrexed 500 mg/m2 IV and carboplatin AUC 6 IV, both administered on Day 1 of each 21-day cycle. Enrolment was stopped because of the introduction of new therapies for the treatment of first-line NSCLC, such as immunotherapy, which resulted in challenges in patient recruitment. In addition, the planned Interim Analysis of Study D6011C00001 revealed that it was very unlikely that the target response rate would be reached, and increased gastrointestinal and hematologic toxicities associated with AZD1775 were observed.

In study NCI130032, the MTD was determined to be 300mg daily on days 1-5 and 8-12 every 21 days (EORTC poster, Oct 2017). In monotherapy studies carried out by AstraZeneca, a similar dosing regimen was also determined to be the MTD (data on file at AstraZeneca), therefore it will be the selected starting dose for this study.

2.4 AZD1775 Pharmacokinetics

The pharmacokinetic (PK) data of AZD1775 following a single oral administration (Study PN001) showed a moderate rate of absorption with a time of maximum concentration (Tmax) occurring at 3 to 4 hours, 2 and 4 hours on day 1 and 3 respectively (IB v15 p. 119). Post-peak plasma concentrations declined essentially in a mono-exponential manner with a terminal elimination half-life (t1/2) between 9.02 to 12.3 hours 13.2 hours at the 225 mg PMF dose (IB v15 p. 119). Exposure as measured by maximum plasma drug concentration observed (Cmax) and area under the curve $AUC_{(0-\infty)}$ increased in a dose-proportional manner over the dose range of 325 to 1300 mg.

Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg once daily [QD]) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. Preliminary investigation of drug-drug interactions (DDIs) in Study PN001 suggest a ~40% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor) on both Day 1 and Day 3 of dosing, but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers). Preliminary studies also suggested that the Pre-marketed Oral Formulation of AZD1775 was similar to that of the Fit-For-Purpose formulation.

Based on the preliminary comparison of the results of AZD1775 PK parameters at the 225 mg dose, PK estimates in Asian patients were higher than in Western patients. After single dose administration on Cycle 0 Day 1 (monotherapy), Cmax and AUC at the 225 mg dose were 45% and 35% higher, respectively, in the Asian population as compared to the Western population (Study PN011). At steady state (Cycle 3 Day 1), a similar trend of higher exposure in Asian patients was observed. Additional analysis/investigation will be conducted based on the emerging data to understand the exposure differences between the populations.

2.5 AZD1775 Safety

Overall risks and benefits support the administration of oral AZD1775 according to this clinical protocol. The identified risks (expected events) for AZD1775 are described in section 5.4 (Emerging Safety Profile) of the IB. Section 6.4 (Risk Management) of the IB.

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies, adverse drug reactions to AZD1775 monotherapy include [redacted]

Based on information emerging during the clinical development program of AZD1775, potential risks with AZD1775 monotherapy include [redacted]

2.6 Cyclin E encoded by CCNE1 is a critical G1/S transition regulator

Human cyclin E1 was initially discovered as one of several substitutes (cyclins A, B1, B2, C, D, and E) for G1 cyclin genes in yeast, and accumulated periodically through the cell cycle, initiating the G1 to S transition [14]. CCNE1 encodes the full-length 50-KD E1 protein that interacts with cyclin-dependent kinases 1 and 2 (CDK1 and CDK2) to activate their kinase activity, a requirement for G1-S transition [15]. In normal dividing cells, cyclin E1 is highly cell cycle-dependent, peaking in late G1 and reaching its nadir in G2-M and early G1 phases [16]. Early in the G1 phase, increases in c-Myc levels promote cyclin D transcription, which activates CDK4 and CDK6 to phosphorylate their target protein, such as retinoblastoma (Rb) and its complex partners (p130 and p107) [17]. Activated Rb acts as a tumor suppressor to maintain cells in the G1/G0 phase through binding the inhibiting E2F in the absence of cyclin E/CDK complex. Upon Rb hyperphosphorylation by cyclin D/CDK complexes, E2Fs are released from its inhibitory complex and can initiate CCNE1 expression [18]. Once activated, cyclin E1/CDK2 becomes independent of mitogenic stimuli and can further upregulate its own expression by increased phosphorylating and dissociating Rb/E2F complexes, triggering the G1-S transition. Cyclin E1/CDK complexes can be silenced by CCNE1 promoter silencing, protein inhibition by $p21^{Cip1}$ and $p27^{Kip1}$, degradation by the SCF^{Fbw7} tumor suppressor pathway [19], and microRNA-mediated inhibition (miR-15a, miR-15b, miRNA-16) [20].

The function for cyclin E1 to induce S phase entry depends on its interactions with CDK1 and CDK2 [21], mediating cell cycle progression from G1 to S phase; DNA replication and transcription; centriole duplication, centrosome separation, and endoreduplication; activating BRCA1/2 transcription via E2F transcription factors to trigger important components of the homologous recombination pathway for DNA repair and confer relative chemotherapy resistance; and many other biological processes such as apoptosis, pre-mRNA splicing, synaptic function and epigenetic silencing, as described in Figure 2 [22].

Cyclin E demonstrates high oncogenic potential and their amplification can induce tumor formation both in vivo and in vitro [23-26]. CCNE1 is frequently amplified in many human tumors, with the frequency of amplification ranging from 2 to 40% [27]. CCNE1 amplification results in cyclin E1 overexpression, which play an important role in cancer progression, and correlates with worse overall survivals [28-34], as well as disease survival as shown in Figure 3 (data from Dr. K. Keyomarsi's laboratory).

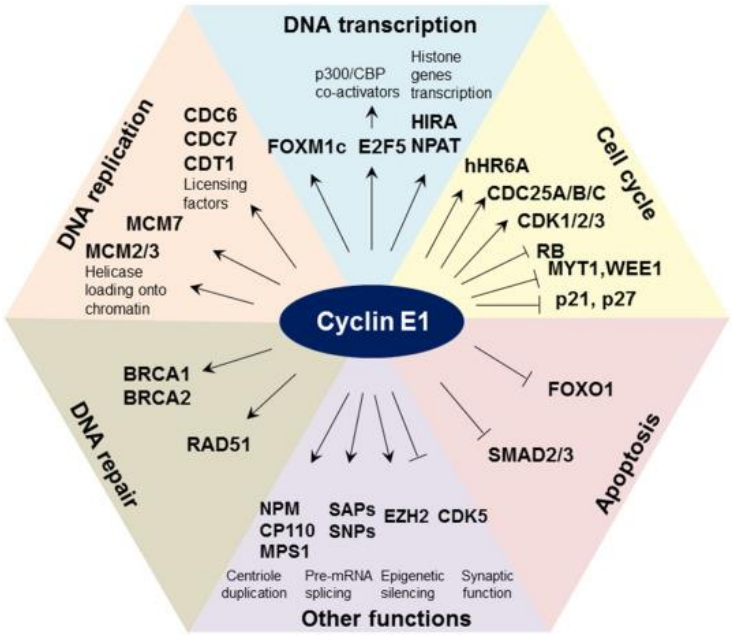


Figure 2. Summary of cyclin E1 functions. Cyclin E1 functions in cell cycle progression, inhibition of apoptosis, and DNA transcription, replication, and repair. Less characterized functions may include centriole duplication, pre-mRNA splicing, and epigenetic silencing. Kanska J et al: Gyn Onc, 2016

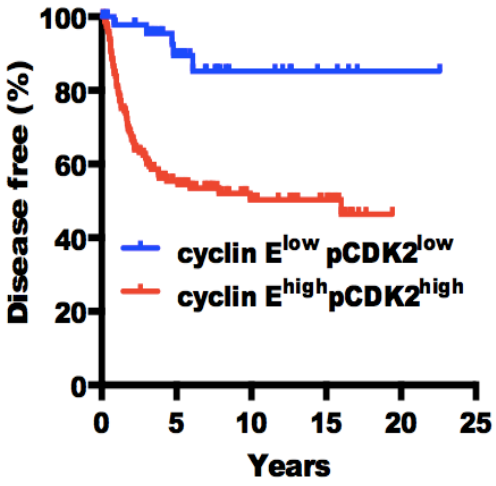


Figure 3: Overexpression of cyclin E and pCDK2 was associated with worse disease-free survival in patients with triple negative breast cancer. (Chen X et al: unpublished data).

2.7 CCNE1 Amplification Sensitizes Cancer Cells to AZD1775

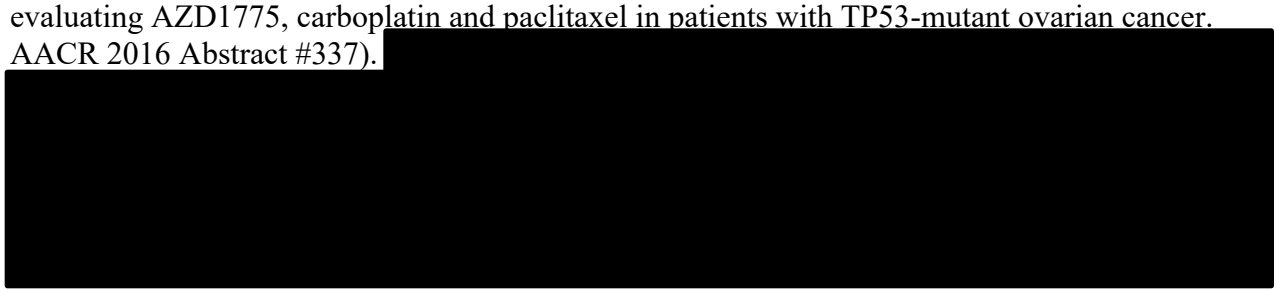
Overexpression of cyclin E has been shown to promote genomic instability by causing DNA replication stress and deregulating the G1 to S transition [35-37]. Wee1 kinase, which prevents premature mitotic entry by inhibiting CDKs, may be essential when cyclin E is overexpressed in order to prevent massive DNA damage and cell death [38-40]. Recent findings from a genome-wide knockout screen revealed that absence of CDK2 decreases sensitivity to Wee1 kinase inhibition [41]. Furthermore, Dr. Khandan Keyomarsi and her group at MD Anderson have shown that overexpression of cyclin E is significantly associated (85%; $p<0.001$) with active CDK2 (phoshpo-CDK2) in tumor samples from 1,678 breast cancer patients [28, 42].

Collectively, these studies suggest that overexpression of cyclin E could predict response to Wee 1 kinase inhibition. To test this hypothesis, we initially evaluated the sensitivity of

[redacted]

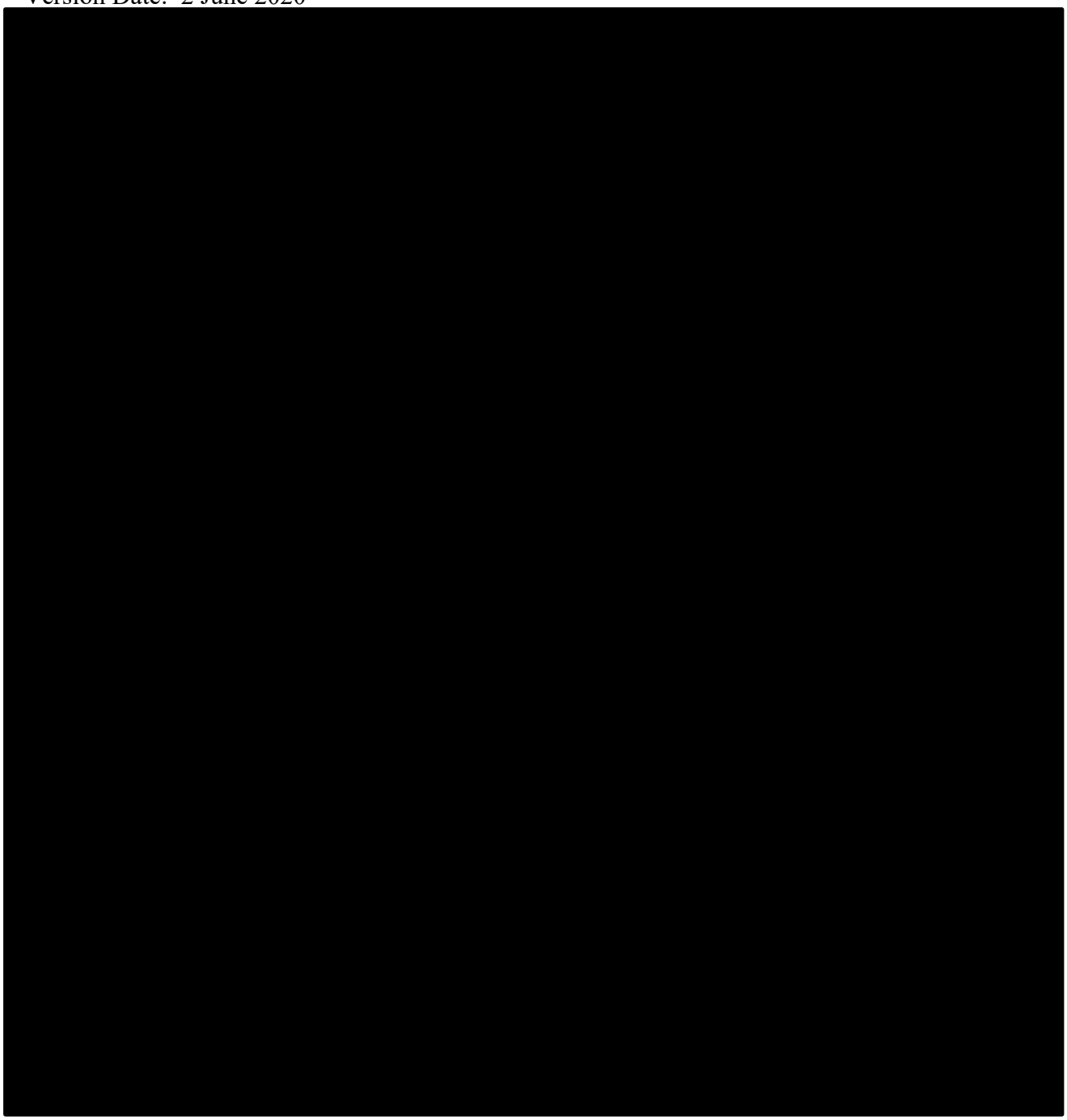
The clinical data to use AZD1775 in patients with advanced solid tumors is emerging from the ongoing phase I study (NCT02482311; AstraZeneca Study D6015C00001; REFMAL 383), which is a single agent AZD1775 study. In a phase II trial PN004 that investigated the combination of AZD1775 and platinum-containing chemotherapy for the treatment of patients with TP53 mutant recurrent platinum-sensitive ovarian cancer (NCT01357161), enrollment

started with 15 patients for open-labeled safety run-in study (Part A) followed by 121 patients (Part B) who were randomized to receive AZD1775 plus paclitaxel and carboplatin or placebo plus paclitaxel and carboplatin (Laing N et al: Genetic analysis of tumors from a Phase II trial evaluating AZD1775, carboplatin and paclitaxel in patients with TP53-mutant ovarian cancer. AACR 2016 Abstract #337).



2.8 The Feasibility to Conduct a Phase II Basket Study in CCNE1 Amplified Solid Tumors

The above preclinical studies have provided the mechanistic and preclinical evidence to support the use of cyclin E a biomarker of response to AZD1775 in TNBC [43].



Overexpression of cyclin E has been shown to promote genomic instability by causing DNA replication stress and deregulating the G1 to S transition. Wee1 kinase, which prevents premature mitotic entry by inhibiting CDKs, may be essential when cyclin E is overexpressed in order to prevent massive DNA damage and cell death. [redacted]

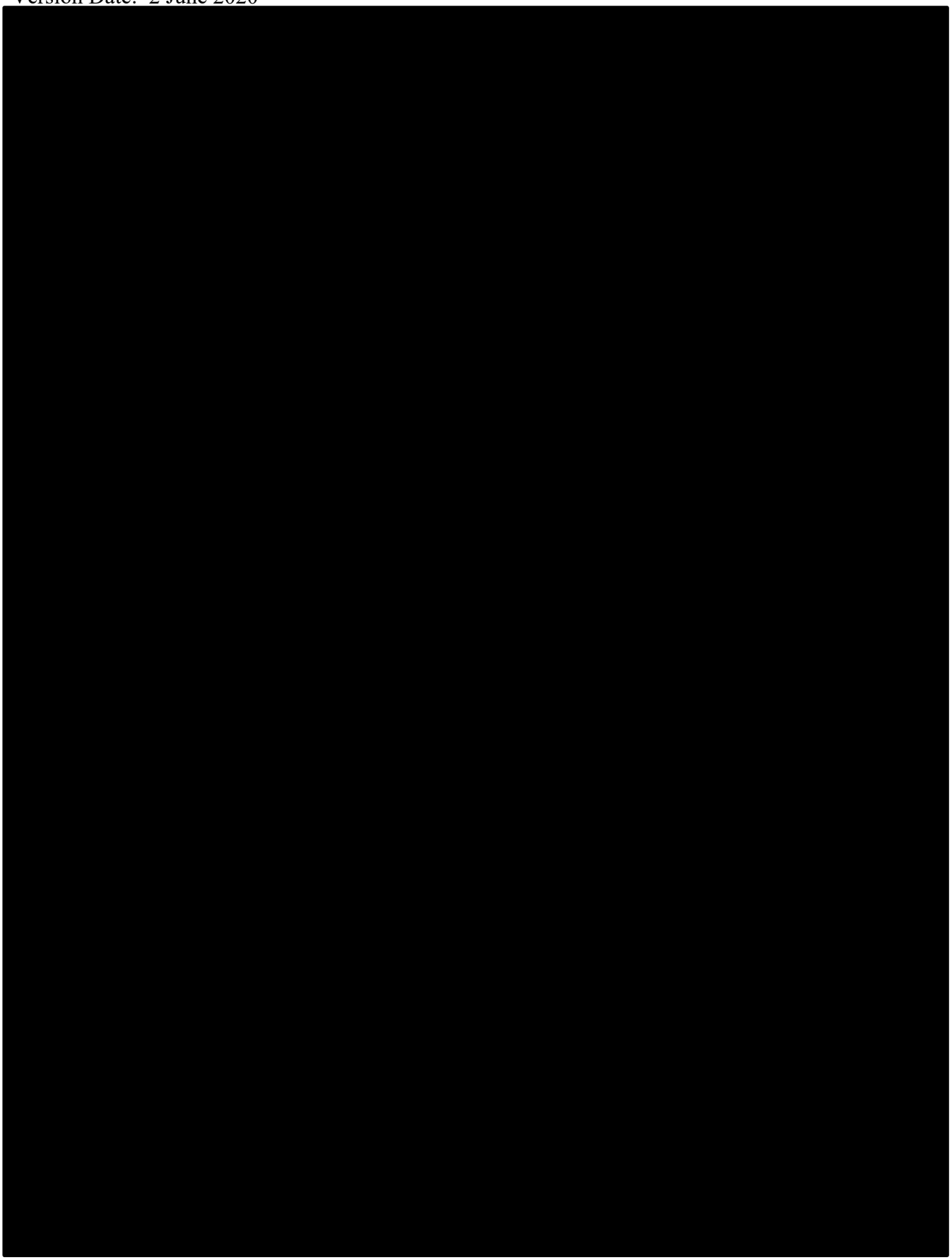
2.9 Correlative Studies – Background and Rationale

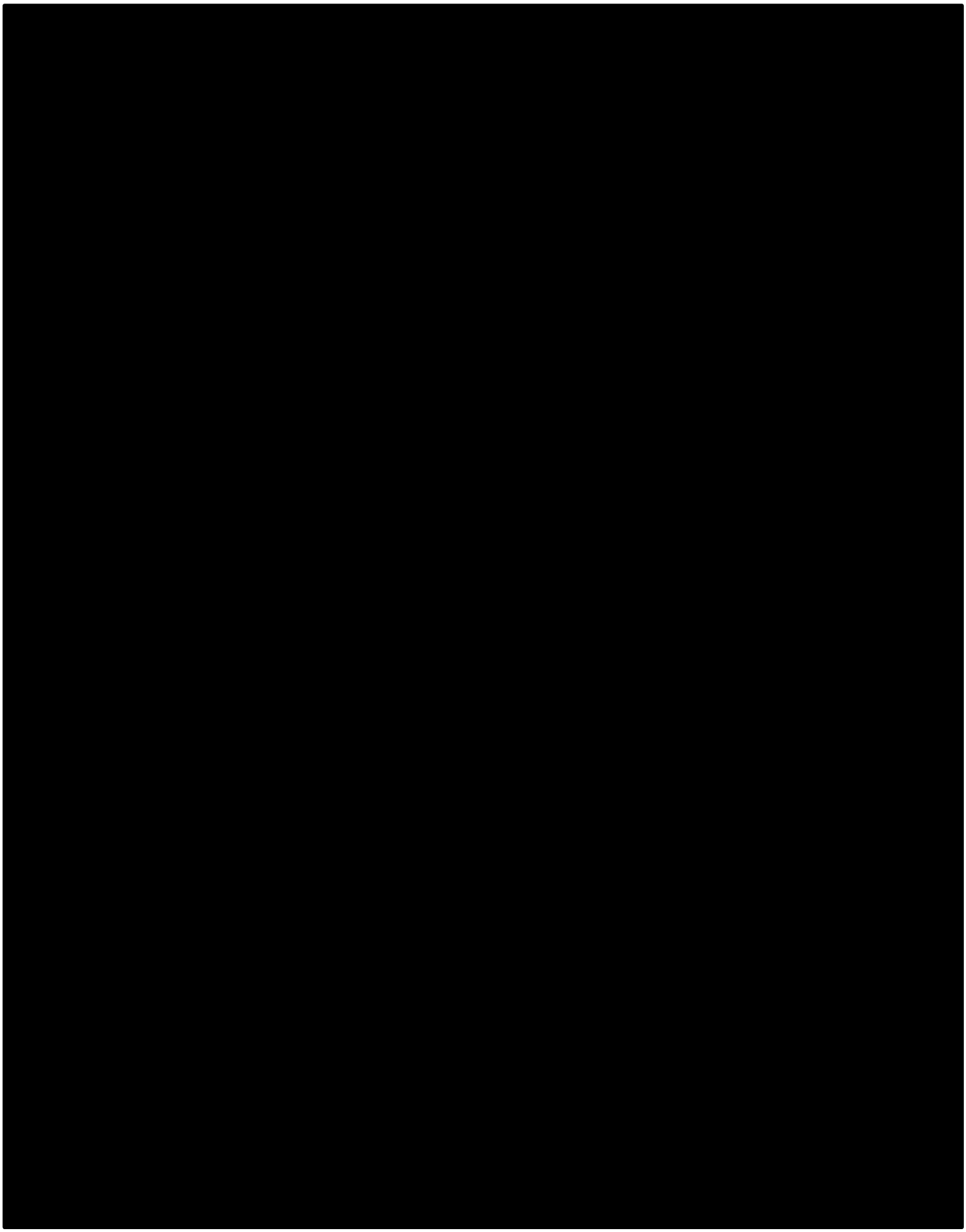
Introduction

Overexpression of cyclin E has been shown to promote genomic instability by causing DNA replication stress and deregulating the G1 to S transition. Wee1 kinase, which prevents premature mitotic entry by inhibiting CDKs, may be essential when cyclin E is overexpressed in order to prevent massive DNA damage and cell death. [redacted] We will test this hypothesis in this clinical study with the help of the following correlative studies.

In order to further define the molecular environment of CCNE1 amplification along with Wee1 inhibition, [redacted]

[redacted]





3. PATIENT SELECTION

3.1 Patient Inclusion Criteria

To be eligible for this trial, patients must meet all of the following eligibility criteria.

1. Patients must have one of the histologically advanced solid tumors harboring CCNE1 amplification: Their diseases are refractory to, or do not have, standard-of-care therapy; or they declined standard-of-care therapy. CCNE1 amplification is defined in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory: CCNE1 Amplification > 7 based on targeted custom Ampliseq panel on the Ion Torrent PGM; or CCNE1 amplification on alternate CLIA platforms such as Foundation One, UW-OncoPlex – Cancer Gene Panel, MSK-IMPACT, Solid Tumor Genomic Assay (Life Technologies), etc. will also be eligible to be treated after PI approval. Patients with known CCNE1 amplification on local or commercial platforms can start treatment after planned biopsy or submission of recent archival sample. Central NGS CCNE1 and FISH testing will be performed to confirm the result.

2. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

3. Male or female sex and age ≥18 years

4. Has read and understands the informed consent form (ICF) and has given written ICF prior to any study procedures. Patients with Impaired Decision Making Capacity (IDMC) must have a close caregiver or Legally Authorized Representative (LAR).

5. Any prior radiation must have been completed at least 7 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of study treatment.

6. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-1.

7. Baseline laboratory values within 14 days of study drug(s) initiation:

   - Absolute neutrophil count (ANC) ≥1500/ μL
   - Hemoglobin (Hgb) ≥ 9g/dL for mono-therapy
   - Platelets ≥ 100,000/μL
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN) or ≤ 5 x ULN if known hepatic metastases.
   - Serum bilirubin < ULN or < 1.5 x ULN in patients with liver metastases; or total bilirubin < 3.0 x ULN with direct bilirubin WNL in patients with well documented Gilbert's Syndrome. Serum creatinine ≤ 1.5 x ULN, or calculated creatinine clearance (CrCl) ≥ 45 mL/min as calculated by the Cockcroft-Gault method or 24-hour measured urine CrCl ≥ 45 mL/min.

     CrCl (glomerular filtration rate [GFR]): [a] where F= 0.85 for females and F=1 for male
     = (140-age) x (weight/kg) x F[a] / (72 x serum creatinine mg/dL)

8. Female patients who are not of child-bearing potential and 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, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to the start of study treatment (see Appendix D). 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 (see Appendix D).

9. Willingness and ability to comply with study and follow-up procedures.

10. Ability to take oral medications without medical history of malabsorption or other chronic gastrointestinal disease, or other conditions that may hamper compliance and/or absorption of the study agent.

11. No prior treatment with Wee1 kinase inhibition.

12. Provision of an archival tissue block, or 10 formalin-fixed paraffin-embedded (FFPE) slides, if available, and having biopsiable disease and agreeing to pre-treatment and on-study biopsies.

3.2 Patient Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for the study.

1. Use of anti-cancer treatment drug ≤ 21 days or 5 half-lives (whichever is shorter) prior to the first dose of AZD1775. For drugs for which 5 half-lives is ≤ 21 days, a minimum of 10 days between termination of the prior treatment and administration of AZD1775 treatment is required.

2. Previous radiation therapy completed ≤ 7 days prior to the start of study drugs.

3. Major surgical procedures ≤ 28 days of beginning AZD1775, or minor surgical procedures ≤ 7 days. No waiting period required following port-a-cath or other central venous access placement.

4. Unresolved Grade 2 toxicity from prior therapy (except alopecia or anorexia).

5. Patient has an inability to swallow oral medications. Note: Patient may not have a percutaneous endoscopic gastrostomy (PEG) tube or be receiving total parenteral nutrition (TPN).

6. No other anticancer-therapy (chemotherapy, immunotherapy, hormonal anti-cancer therapy, radiotherapy [except for palliative local radiotherapy]), biological therapy or other novel agent is to be permitted while the patient is receiving study medication. Patients on LHRH analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the Investigator.

7. Known malignant central nervous system (CNS) disease other than neurologically stable, treated brain metastases – defined as metastasis having no evidence of progression or hemorrhage for at least 2 weeks after treatment. Must be off any systemic corticosteroids for the treatment of brain metastases for at least 14 days prior to enrolment.

8. Patient has had prescription or non-prescription drugs or other products known to be sensitive to CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors/inducers of CYP3A4 which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug. Co-administration of aprepitant or fosaprepitant during this study is prohibited. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin, is also prohibited in this study

9. 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.

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

AZD1775.

11. Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2.
    - Unstable angina pectoris
    - Congestive heart failure
    - Acute myocardial infarction
    - Conduction abnormality not controlled with pacemaker or medication
    - Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

12. Mean resting corrected QTc interval using the Fridericia formula (QTcF) >450 msec/male and >470 msec/female (as calculated per institutional standards) obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart at study entry, or congenital long QT syndrome.

13. Pregnant or breastfeeding women.

14. Serious active infection at the time of study entry, or another serious underlying medical condition that would impair the ability of the patient to receive study treatment.

15. Symptomatic and uncontrolled metastasis in the central nervous system or leptomeningeal or lymphangitic carcinomatosis.

16. Presence of other active invasive cancers that do not harbor CCNE1 amplification.

17. Grade 2 or higher peripheral neuropathy.

18, Human immunodeficiency virus requiring HAART treatment due to unknown drug-drug interactions or has known active hepatitis B (e.g., HBsAg reactive or C virus (e.g., HCV RNA (quantitative) is detected) infection

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

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

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

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

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

4.2 Site Registration

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

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

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

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

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

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

Downloading Regulatory Documents

Site registration forms may be downloaded from the 10136 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select *LAO-TX035*, and protocol *10136.*

• Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

Requirements For NCI 10136 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Local informed consent document

Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office

1818 Market Street, Suite 3000

Philadelphia, PA 19103

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

Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

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

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

the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
  - To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN

tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *10* days.* Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

5. TREATMENT PLAN

Cycles are 21 days long. **5.1 Agent Administration**
Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

AZD1775 Administration
Oral AZD1775 will be given 300 mg once daily for 5 days a week for 2 weeks every cycle (QD days 1 to 5, and 8 to 12). One cycle of therapy will be 21 days: therefore, 10 doses each cycle. Dose escalation will not be permitted. Appropriate dose modifications and interruptions will be allowed. Other investigational or commercially available agents specifically for cancer control will be prohibited. Patients will continue the treatment until they experience tumor progression, prohibitive toxicity or withdraw from the study by themselves.

Table3. Regimen Description

Agent	***Premedications; Precautions****	***Schedule***	***Cycle Length***
AZD1775	5-HT3 antagonist (ondansetron 8 mg PO or granisetron 1 mg PO) prior to each dose of AZD1775; taken with 8 ounces of water approximately 2 hours before or 2 hours after food	Days 1-5, week 1 Days 8-12, week 2	21 days (3 weeks)

*Dexamethasone (oral or intravenous) or the 5-HT3 antagonist (intravenous) may be given for better symptom control as indicated. Prophylactic anti-emetic therapy with aprepitant or fosaprepitant is prohibited.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food. If a patient misses the daily dose according to the schedule, the dose should be taken as soon as possible, but not more than 12 hours after the missed dose was scheduled. If greater than 12 hours, the missed dose should be skipped and the patient should take the next dose when scheduled. If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

2.7 5.2 Study Procedures

All patients will be evaluated and study procedures will be performed in Figure 1. Dosing, laboratory tests, imaging studies, and office visits will occur per protocol (within ± 4 days) unless patients' medical or logistical issues necessitate adjustment.

Pretreatment Evaluations
To be completed within 4 weeks before initiation of therapy:
- Medical history, including list of current medications
- Tumor markers, if applicable
- Imaging studies, as appropriate for specific types of cancers
- ECG and ECHO or MUGA, and then as clinically indicated
- Mandatory biopsy
- Urinalysis, to be repeated as clinically indicated
- For women of childbearing potential, blood or urine pregnancy test at baseline and then periodically as clinically indicated
- Obtainment of the informed consent document

To be completed within 7 days before initiation of therapy:
- Physical examination
- ECOG performance status determination
- Complete blood count with leukocyte differential and platelet count
- Serum chemistry analysis, including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, ALT, TSH, and free T_4

On-Study Evaluations
To be obtained weekly during the first cycle and then as clinically indicated:
- Complete blood count and leukocyte differential and platelet count
- Serum chemistry, including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, AST, and ALT

To be obtained once in every cycle of therapy (once every 3 weeks):
- Medical history and physical examination
- ECOG performance status
- Assessment of treatment-related and treatment-unrelated toxic effects
- Complete blood count with leukocyte differential and platelet count
- Serum chemistry, including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, AST and ALT

To be obtained for tumor responses:
- Evaluation of the tumor: the same imaging technique used during the initial evaluation or more sophisticated studies will be performed about once every 9 weeks ± 7 days for six months, then once every 12 weeks ± 7 days, or sooner if clinically indicated
- Tumor markers, if applicable, once with each imaging study, or more frequently as indicated

Sample Collection for Correlative Studies
Correlative studies will be performed by Dr. Robert Kinders at the NCI-Frederick National Laboratory for Cancer Research, Dr. K. Keyomarsi, in the Department of Experimental

Radiation Oncology, and Dr. F. Meric-Bernstam in the Department of Investigational Cancer Therapeutics. Patients who experience CR/PR will be encouraged to enroll into the Unusual Responders protocol (F. Meric-Bernstam) at MD Anderson.

Blood Sample Collections:
After the informed consent is obtained, blood samples (~10 mL each) will be obtained at each of the following time-points:

1. Prior to the initiation of treatment (pre-study), and cycle 1 day 8 (C1D8)
2. Prior to the initiation of cycle 2 (C2D1) and cycle 2 day 8 (C2D8)
3. At the end of the study, if available

Tumor Sample Collections:
After informed consent is obtained, tumor samples will be collected as follows:
1. Ten 5 μm-thick FFPE slides, or tumor block – all patients if available
2. Pre-treatment core biopsy – mandatory for all patients
3. Tumor core biopsy on C1D10 at 4 hours (± 2 hours) post dose– mandatory for all patients if clinically feasible
4. Tumor core biopsy at relapse – optional for all patients.

The time of drug administration and the time of biopsy will be documented.

Please refer to Section 9 and Appendix D for more details.

2.8 5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of AZD1775 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions.

Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.

All concomitant medications received within 14 days before the first dose of study medication and 30 days after the last dose of study medication should be recorded. Concomitant medications must be recorded in the appropriate sections of the CRF.

Mandatory prophylactic anti-emetics will be required for all patients. Treatment with the anti-emetics aprepitant [Emend] and fosaprepitant are excluded because of known drug-drug interactions. In addition, loperamide (Imodium) is required at the first onset of diarrhea according to ASCO guidelines. Oral loperamide (Imodium) 4mg should be administered at the first onset of diarrhea and then 2mg every 2 hours until diarrhea-free for at least 12 hours. The first dose of loperamide could be lowered to 2mg if the diarrhea is recurrent and if, in the opinion of the treating physician, the diarrhea is not severe.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab).
- Patients requiring therapeutic warfarin or coumarin-derivative anticoagulants will be monitored with international normalized ratio (INR) and prothrombin time (PT) as clinically indicated.
- Low molecular weight heparin (LMWH), rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated.
- Patients may receive treatment with megestrol acetate when prescribed for appetite stimulation.

2.9 5.4 Restrictions during the study

The following restrictions are considered the minimum standards for each study within the project. Additional restrictions may be included depending on individual study requirements.

- AZD1775 should be taken with 8 ounces of water approximately 2 hours before or 2 hours after food.

- In once a day dosing if a patient misses the daily dose according to the schedule, the dose should be taken as soon as possible, but not more than 12 hours after the missed dose was scheduled. If greater than 12 hours, the missed dose should be skipped and the patient should take the next dose when scheduled

- If vomiting occurs after a patient takes the AZD1775 dose, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the patient should contact the Investigator.

- Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for two weeks before study entry, for the duration of the treatment with the study drug and for 1 month after the last dose of AZD1775

- WoCBP defined as: Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

- All WoCBP must have a negative pregnancy test within 3 days prior to study entry and prior to starting each treatment cycle.

- Male patients who are involved in the study must agree to avoid procreative and unprotected sex and must not donate sperm during the study and for 3 months after the last dose of AZD1775. Where the female partner is pregnant or not using effective birth control, men should be advised to abstain while in the study and for 3 months after the last dose of AZD1775.

- Female partners, who are of child-bearing potential, of men participating in clinical studies of AZD1775 will also be required to use effective contraceptive measures (detailed in Appendix D) while their partner is on study drug and for 3 months thereafter.

- Male patients will be advised to arrange for the freezing of sperm samples prior to the start of the study should they wish to father children while on AZD1775 or during the 3 months after stopping AZD1775.

Prohibited concomitant medications

The following treatments and the medications listed in Appendix D are prohibited or should be used with caution while in AZD1775 studies. Any further questions regarding concomitant treatments should be referred to a Medical Monitor.

- No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance. Therefore, concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.

  Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interactions (DDI) becomes available. The use of sensitive substrates of CYP3A4, such as atorvastatin, simvastatin and lovastatin, is prohibited in this study. As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking AZD1775.

- In vitro data suggests that AZD1775 may also be a weak reversible inhibitor of CYP2C19. Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range; refer to Appendix D for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range.

- AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro with a maximum measured response between donors of 39.9% to 93.1% (at 10 μM) and 18.6% to 32.5% (at 5 μM) of the positive control omeprazole (50 μM). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

- In vitro studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein (P-gp). Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775 (see Appendix D).

- *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC50 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be

administered with caution, dose modification considered or substituted by an alternative drug.

- Metformin should be used with caution. AZD1775 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of AZD1775.

2.10 5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy

  All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

  The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor

- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF). A patient that decides to discontinue investigational product (IP) should be asked about the reason(s) and the occurrence of any AEs.

2.11 5.6 Duration of Follow Up

- Patients will be followed for 4 weeks after discontinuing study treatment or until death, whichever occurs first.

- Patients who discontinue the study treatment for reasons other than disease progression, will continue to undergo radiographic tumor assessment until radiographic documentation of disease progression every 12 weeks, or earlier clinically indicated, or start of new therapy, or until overall study completion, whichever occurs first.

- Patients who discontinue the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event, or until radiographic documentation

2.12 5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Siqing Fu, MD, PhD at 713-404-1141 (Pager).

6. DOSING DELAYS/DOSE MODIFICATIONS

The principal investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.**6.1 Definition of adverse events**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

Dose Modification

Toxicity will be assessed utilizing the NCI CTCAE v5.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified.

Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. A maximum of 2 dose reductions for AZD1775 will be allowed. Patients requiring >2 dose reductions will be discontinued from the study drug.

Table 5 AZD1775 Dose Level Reductions for Toxicity

Dose Level	**AZD1775**	**Schedule 21-day cycle**
Starting Dose	300 mg QD PO	Days 1-5 and 8-12
Dose Level -1	250 mg QD PO	Days 1-5 and 8-12
Dose Level -2	200 mg QD PO	Days 1-5 and 8-12

Any patient requiring a toxicity-related dose delay of more than 21 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the Medical Monitor for the patient to continue.

2.13 Dose modifications due to hematologic toxicity

Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment cycle (Day 1). If hematologic toxicity occurs (see Table6 and Table 7), treatment should be held and ANC and platelets should be monitored weekly (or more often as clinically indicated) until recovery.

Table 6: Day 1 Hematologic Dose Modifications

Treatment Day Blood Counts and Toxicity			
ANC		**Platelets**	**Action**
≥1000/μL	And	≥75,000/μL	No dose modification or interruption
<1000/μL	Or	<75,000/μL	Delay by 1 week intervals until recovery

If hematologic toxicity parameters do not recover within 21 days, the patient should be removed from the study treatment.

Table 7: Neutropenia, Infection, Febrile Neutropenia Dose Modifications and Management

Any Day	
Grade 3 neutropenic fever (ANC <1000/μL + Temperature ≥101°F [38.5°C]) or neutropenic infection **Documented infection with Grade 3 neutropenia** (ANC <1000/μL) **Grade 4 neutropenia** (ANC <500/μL >7 days **Grade 4 thrombocytopenia** (platelet count <25,000/μL >7 days)	**Hold dose until recovery.** **Then, upon resuming dosing, reduce AZD1775 to the next lower dose level[a].**
Grade 4 febrile neutropenia or Grade 4 infection with neutropenia (both defined as septic shock) **Thrombocytopenic haemorrhage** (gross occult bleeding) associated with a platelet count <50,000/μL	**Discontinue treatment is recommended, and follow for disease progression.** **However patient may continue after dose reductions only when treating physician, the study chair and the patient concur.**

[a] No more than two dose reductions will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

2.14 Dose modifications due to non-hematologic toxicity

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of investigational product, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treatment physician.

Dose reductions of AZD1775 should be considered only if toxicity is considered to be related to AZD1775. Dose re-escalation is not permitted.

In general, if a patient experiences a Grade 1 / Grade 2 non-hematological toxicity, no dose modification is required (except QTc prolongation, see Table 8in). If a patient experiences a G3 or G4 toxicity which is not attributable to the disease or disease related processes under investigation, dosing will be interrupted and/or the dose reduced and supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-hematologic toxicity that does not resolve to ⩽ Grade 1 within 21 days should be removed from the study treatment unless approved by the Medical Monitor.

Dose modification for QTc interval prolongation
Table 8: AZD1775 dose modifications for QTc interval prolongation

Electrocardiogram QT corrected interval prolonged	
QTc Value	AZD1775
QTc 450-480 ms (males) or 470-480 (females)	Hold. Once QTc interval has returned to pre-treatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level.
QTc 481-500 ms	Hold. Seek cardiologist advice.
QTc ≥ 501 ms	Discontinue treatment
Shift from baseline of ≥ 60ms	Discontinue treatment

2.15 Recording of adverse events

Time period for collection of adverse events
Adverse events will be collected throughout the study, from informed consent until 30 days after the end of the last investigational product administration.

SAEs will be recorded from the time of informed consent and should be reported to CTEP.

Follow-up of unresolved adverse events
Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF.

If an Investigator learns of any SAEs, including death, at any time after a patient has completed the study and he/she considers there is a reasonable possibility that the event is related to AZD1775, the Investigator should notify CTEP.

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- The maximum intensity or intensity or changes in intensity
- CTCAE grade/max CTAE grade/changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason AE is serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to module-specific combination treatments
- Description of AE.

The grading scales found in the revised CTCAE Version 5.0 will be utilized for all events with

an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria should be utilized that converts mild, moderate, and severe events. A copy of the current CTCAE version can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 7.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms
All AEs spontaneously reported by the patient, reported in response to the open question from the study personnel, or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of a diagnosis is preferred (when possible) to the recording of a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

They do not include metastases of the original cancer.

Adverse Events based on examinations and tests
The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of the study treatment unless clearly due to the progression of disease under study.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).
Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

Hy's Law
Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN may need to be reported as SAEs.

Disease progression
Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. *(For example, the progression of existing metastasis to the primary cancer under study)* should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers
The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB. For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately.

Laboratory safety assessment
Blood and samples for determination of clinical chemistry, haematology, coagulation, and PD will be performed at the times indicated in the Study Plan (Table 12).

Additional safety samples may be collected as clinically indicated and at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry and haematology will be performed at a CLIA-certified laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the study centre.

The following laboratory variables will be measured as a minimum (some of these variables may be measured at baseline only):

Table 12: Laboratory Safety Variables

Hematology (2.7 mL whole blood sample)	**Clinical chemistry (2.7 mL serum or plasma sample)**
B-Hemoglobin	S/P-Albumin
B-Leukocyte	S/P-Alanine transaminase (ALT)
B-Hematocrit	S/P-Aspartate transaminase (AST)
B-Red blood cell count	S/P-Alkaline phosphatase (ALP)
B-Absolute leukocyte differential count	S/P-Bilirubin, total
Neutrophils	S/P-Calcium, total
Lymphocytes	S/P-Creatinine
Monocytes	S/P-Chloride
	S/P-Glucose
	S/P-Magnesium
Basophils	S/P-Potassium
Eosinophils	S/P-Sodium
B-Platelet count	S/P-Urea nitrogen or blood urea nitrogen
	S/P-TSH
Coagulation (1.8 mL sample)	S/P-Free T_4
	S/P-CO2
	S/P-BUN
B-PT or INR with PTT	
Pregnancy test (Blood or urine)	

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to starting study treatment, and a confirmatory test before treatment before each treatment period and each subsequent check-in prior to administration of study treatment in the next period. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.
The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

NB. In case a patient shows an AST **or** ALT ≥3 x ULN (upper limit of normal) **and** total bilirubin ≥2 x ULN please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE. Performance status will be assessed using the ECOG performance status criteria.

ECG

Resting 12-lead ECG

A triplicate 12-lead safety ECG (paper ECG printout of 10 seconds for Investigator review) will be taken at screening and prior to dosing of each study cycle, and as clinically indicated.

At any other time the Investigator deems necessary for safety during the administration period, triplicate ECG recordings should be taken within an approximate 5-minute period. Additional ECGs may be taken. The patients will rest for at least 10 minutes before the start of each recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at the recording time point.

The Investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the patient's completed source documents. Only overall evaluation (normal/abnormal) will be recorded in the eCRF. If there is a clinically significant abnormal unscheduled ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes.

Attention should be paid to any detected increases in QTc interval. Patients who develop a single resting value of QTc interval of >450 msec/male and >470 msec/female or a shift from baseline of 60ms should stop taking AZD1775. Dosing can be resumed at a reduced dose (see section 3.4.2.1) after return of the resting QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made.

Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline, but stays below the above limits, a cardiologist's advice should be sought.

The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The 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/adverse_effects.htm for further clarification.

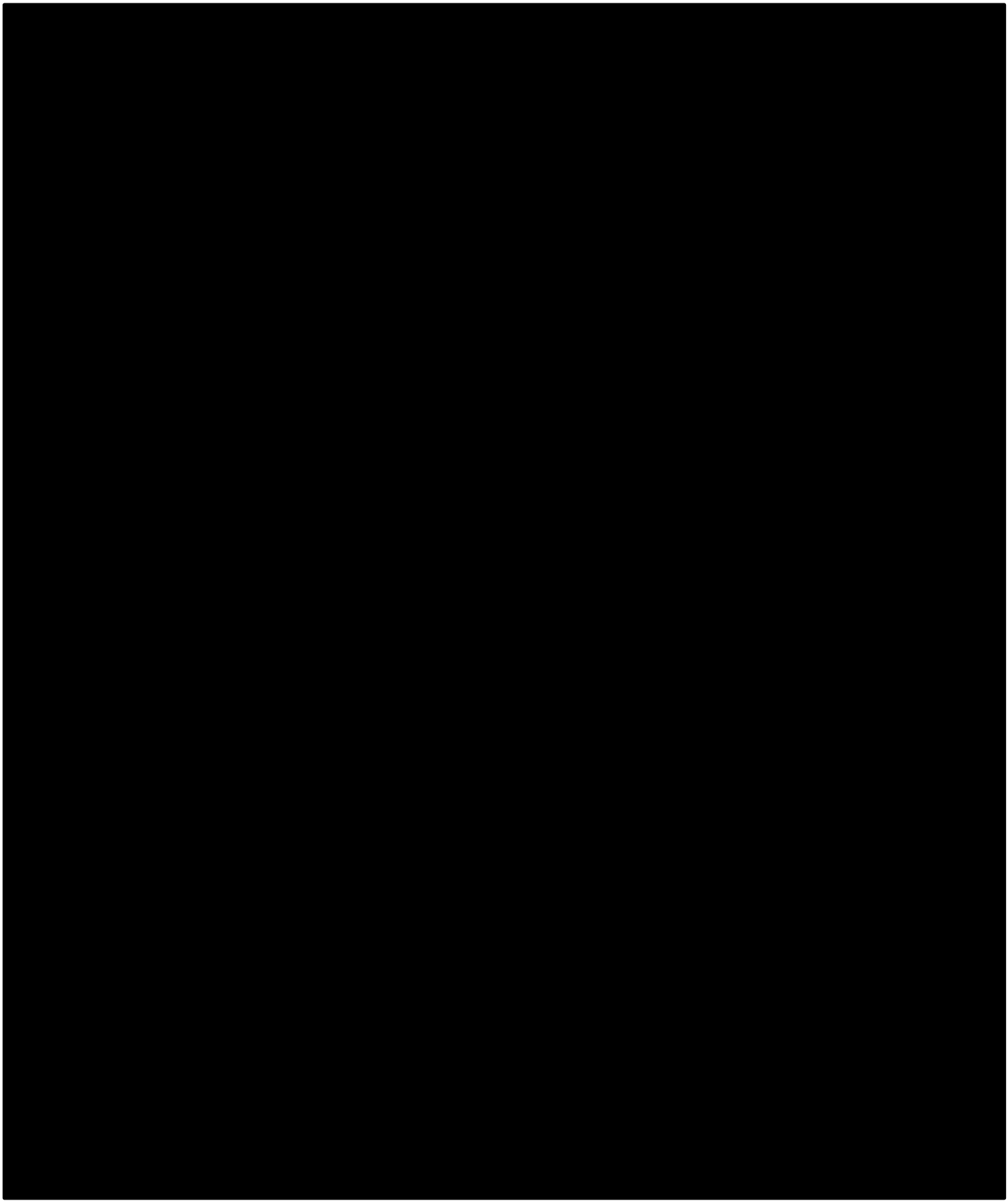
NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the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

7.1.1 CAEPR for AZD1775

Comprehensive Adverse Events and Potential Risks list (CAEPR) for AZD1775 (adavosertib, NSC 751084)

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

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



[redacted]

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

[redacted]

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the AZD1775 that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the NCI Protocol #: 10136 that do not require expedited reporting are outlined in section 7.3.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Table 14).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports (Table 14).

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Table 14: 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 electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 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 submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
○ "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 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 10 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

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

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. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

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

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

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

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

Indicate form for reporting in Rave, timeframes, and if loading of the pathology report is required.

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.

8.1 AZD1775 (NSC #751084)

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

Classification: Inhibitor of Wee1-kinase

CAS: 955365-80-7

Molecular Formula: $C_{27}H_{32}N_8O_2 \cdot H_2O$ **M.W.:** 518.623

Mode of Action: AZD1775 is an inhibitor of the Wee1-kinase. Wee1 is a tyrosine kinase upstream of CDC2 thereby involved in regulation of cell cycle checkpoints, particularly the G2 checkpoint. As the majority of human cancers harbor abnormalities in the p53 pathway they become more dependent on S- and G2-phase checkpoints. In preclinical models, AZD1775 selectively enhanced chemotherapy-induced death of cells deficient in p53 signaling.
Description: AZD1775 is a crystalline, non-hygroscopic, monohydrate of the neutral drug. It dehydrates upon heating leading to formation of a crystalline anhydrate.

How Supplied: AZD1775 is supplied by AstraZeneca and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as capsules available in 25 mg (yellow color, size 2 gelatin capsule) and 100 mg (orange color, size 2 gelatin capsule) strengths. The dry-filled capsules consist of a roller-compacted granule of drug substance, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. Each high-density polyethylene (HDPE) bottle contains 20 capsules.

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

Storage:

Store at 2 to 30˚C (36 to 86˚F). Do not freeze.

If a storage temperature excursion is identified, promptly return AZD1775 to between 2-30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf life studies of AZD1775 are on-going.

Route of Administration: Oral administration. Take AZD1775 at least two hours before or two hours after a meal.

Potential Drug Interactions: AZD1775 is primarily metabolized by CYP3A4 and is a weak, time-dependent inhibitor of CYP3A4. Avoid concomitant CYP3A4 moderate or strong inhibitors/inducers, and sensitive substrates with a narrow therapeutic index. AZD1775 is also a weak inhibitor of CYP2C19. Caution should be exercised with concomitant administration of sensitive substrates or substrates with a narrow therapeutic index.

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

Contraindications: Treatment with AZD1775 is contraindicated in subjects with hypersensitivity to any component of the drug. Developmental and reproductive toxicity studies of AZD1775 have not been performed. AZD1775 is not to be given to women who are pregnant or breast feeding.

Availability AZD1775 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. AZD1775 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and DCTD, NCI.

8.2 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.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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.

8.3 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 Identity and Access Management (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.

8.4 Useful Links and Contacts

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/index.jsp

CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

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)

9. BIOMARKER, CORRELATIVES AND SPECIAL STUDIES

9.1 Collection of Specimens

Table 15: Summary of Specimen Requirements

Time Point	Specimen and Quantity	Send Specimens to:
Baseline		
	• 2 tissue cores snap-frozen	PADIS Laboratory, NCI-Frederick
	• Archival FFPE tumor block or 10 5-micron unstained slides • 1-2 cores snap-frozen • 10 mL blood in purple top EDTA tube • 10 mL blood in green top (sodium heparin) tube	Keyomarsi Laboratory
	○	
	○	
C1D8		
	○ 10 mL blood in purple top EDTA tube ○ 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
C1D10 – 4h post dose (+/- 1 h)		
	○ 2 tissue cores, snap frozen	PADIS Laboratory, NCI Frederick
	○ 1-2 tissue cores, snap forzen	Keyomarsi Laboratory
C2D1		
	○ 10 mL blood in purple top EDTA tube ○ 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
C2D8		
	○ 10 mL blood in purple top EDTA tube ○ 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
Progression/Relapse		
	○ 2 tissue cores, snap frozen ○ 10 mL blood in purple top EDTA tube ○ 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory

Time Point	Specimen and Quantity	Send Specimens to:
Baseline		
	• 2 tissue cores snap-frozen	PADIS Laboratory, NCI-Frederick
	• Archival FFPE tumor block or 10 5-micron unstained slides • 1-2 cores snap-frozen • 10 mL blood in purple top EDTA tube • 10 mL blood in green top (sodium heparin) tube	Keyomarsi Laboratory
04h post dose 5		
	• 2 tissue cores, snap-frozen	PADIS Laboratory, NCI-Frederick
	• 1-2 tissue cores, snap-frozen	Keyomarsi Laboratory
C1D8		
	• 10 mL blood in purple top EDTA tube • 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
C1D10 – 4h post dose (+/- 1 h)		
	• 2 tissue cores, snap frozen	PADIS Laboratory, NCI Frederick
	• 1-2 tissue cores, snap forzen	Keyomarsi Laboratory
C2D1		
	• 10 mL blood in purple top EDTA tube • 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
C2D8		
	• 10 mL blood in purple top EDTA tube • 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory
Progression/Relapse		
	• 2 tissue cores, snap frozen • 10 mL blood in purple top EDTA tube • 10 ml blood in green top (sodium heparin) tube	Keyomarsi Laboratory

Due to the nature of the correlative analysis, fresh biopsies are necessary. A minimum of four core biopsy samples (18 gauge cores) should be attained. Please see Appendix D for detailed instructions and request sample shipment kits directly from NCI. Biopsy costs are covered for all ETCTN sites.

Note that if any site is unable to send flash frozen biopsy tissue, please contact Dr. Siqing Fu and Dr. Robert Kinders for a case by case discussion prior to collection of the samples.

Collaborating labs should collect 10ml of whole blood in lavender/purple top Vacutainer tube (EDTA) and 10ml in green top Vacutainer tube (sodium heparin). After sample collection, gently invert tubes 5-10 times to mix the blood with the tube additive. All tubes should be labelled with the patient's study ID. Ship whole blood to the address below for Dr. Keyomarsi's laboratory on the day the biospecimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) and shipped within 24 hours.

Dr. Keyomarsi's labs will isolate DNA for NGS sequencing and PBMCs and plasma. PBMCs and plasma will be isolated using Ficoll density gradient and cryopreserved in liquid nitrogen in 10% DMSO and 90% human AB serum at 10×10^6 cells/vial. Plasma will be stored at -70°C (0.5-1 mL/vial) until later analysis.

2.169.2 Shipping Information

1. Two cores per time point should be sent to the Pharmacodynamics Assay Development & Implementation Section (PADIS) laboratory at NCI, where they will be embedded. Monthly batch shipment is allowed.

   The shipping address is listed in the SOP under sections 8.3 and 8.4

   Attention: Dan Danner
   NCI-F/FNLCR
   1073 Beasley Street, Building 1073
   Fort Detrick
   Frederick, MD 21701
   Phone: 301-846-5748

Please notify Rachel Andrews, Dr. Robert Kinders and Dr. Siqing Fu by email before sending a shipment. A separate email with FedEx shipping information will be sent to the research nurse for shipment.

Note that FedEx packages should not be shipped any later than Thursday mornings for overnight to the facility, and should not be shipped to arrive on Federal holidays because the receiving docks are closed on weekends and holidays.

Robert Kinders: kindersr@mail.nih.gov
TEL: 301-846-6410
Sr. Principal Scientist
Head, Pharmacodynamics Section
Clinical Pharmacodynamics Program

Rachel Andrews: Rachel.andrews@nih.gov
TEL: 240-344-5697.

2. Two additional cores, along with pharmacodynamics blood samples should be sent to Dr. Khandan Keyomarsi's laboratory at MD Anderson Cancer Center. Please contact Dr. Siqing Fu should you have any questions.

Khandan Keyomarsi
Zayed Building for Personalize (Z6.3012)
1515 Holcombe Blvd.
Unit 0066
Houston, TX 77030
kkeyomar@mdanderson.org

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy (Table 15).

Table 16: Phase II Study of AZD1775 in CCNE1 Amplified Patients

Assessment Tool	Screening[a]	Baseline[b]	Cycle 1[p]			Cycle 2, 3, 4, …[p]			End of Study[c]
			Week			Week			
			1	2	3	1	2	3	
AZD1775[d]			X	X		X	X		
Medical history	X								X
Physical exam		X	X			X			X
ECOG performance status[e]		X	X			X			X
CBC with differential		X	X	X	X	X			X
Serum chemistries(electrolytes, hepatic and renal function tests)		X	X	X	X	X			X
Pregnancy test[f]	X		X			X			X
Triplicate ECG[g]	X		X			X			
ECHO/MUGA[h]	X								
Urinalysis[i]	X								X
Tumor markers, if available[j]	X								X
Radiological evaluations (CT, MRI or PET as appropriate)[k]	X								X
Pharmacodynamics (blood)[l]			X	X		X	X		X
Tumor specimens[m]		X		X					
Adverse event assessment[n]	X								

Concurrent medications	X			
DLT assessment [o]			X	

a) Screening visit to occur within 4 weeks prior to initiation of therapy
b) Baseline visit to occur within 7 days prior to initiation of therapy
c) End of study visit to occur within 30 days of the last dose of study agents, if feasible
d) This agent is administered orally daily from D1 to D5 (Week 1) and D8-D12 (Week 2), there will not be agent administration for Week 3 of each cycle. One cycle is 21 days in length
e) To be obtained at the screening, on Day 1 of each cycle of therapy and at EOT
f) To be tested in women of child-bearing potential prior to the enrollment, on Day 1 of each cycle of therapy and at EOT
g) Triplicate 12-lead ECGs at screening and during the study. Triplicate ECGs will be performed on Day 1 of each treatment cycle. The mean QTcF interval for all 3 ECGs must be <450 msec for male patients and <470 msec for female patients. Triplicate 12-lead ECGs will be conducted approximately 2-5 minutes apart prior to dosing
h) To be obtained at screening and then as clinically indicated
i) To be obtained at screening then periodically as indicated clinically
j) To be tested at screening and with each restaging if abnormal at baseline, or more frequently as appropriate
k) To be performed at screening, once approximately at 9 weeks, another at 18 weeks and also at 27 weeks +/- 7 days or sooner if clinically indicated, and then every 12 weeks or sooner if clinically indicated
l) To collect pharmacodynamics blood samples (20 mL each collection: plasma and peripheral blood monocytes): mandatory on cycle 1 day 1 pre-dose and optional on cycle 1 day 8, cycle 2 day 1, cycle 2 day 8, and at the end of study, if feasible. Optional blood (about 10 mL) will be collected with optional tumor biopsy on C1D10 or at relapse.
m) Mandatory tumor biopsy pre-study and archived tumor tissues (ten 5 µm-thick slides), if available. Additional mandatory tumor biopsy on C1D10 at 4 hours (± 2 hours) post dose. Optional biopsies will be collected at relapse if a patient has achieved a partial remission or complete remission.
n) Adverse events to be assessed at all study visits and/or over the phone as clinically indicated
o) DLT assessment to occur with 21 days of the first dose
p) Assessments should occur within +/- 4 days of each scheduled visit

11. MEASUREMENT OF EFFECT

Although the clinical benefit of this drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *9* weeks or sooner as clinically indicated. In addition to a baseline scan, confirmatory scans will also be obtained *4* weeks following initial documentation of an objective response.

Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *9* weeks. In addition to a baseline scan, confirmatory scans should also be obtained *4* (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [51]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD1775.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which

circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a

method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol

and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

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

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

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

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

depend on the achievement of both measurement and confirmation criteria (Tables 15 and 16).

Table 17: For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

∗See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 17: For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

∗'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that

recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase I trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after 03/01/2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

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 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 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 NCI, 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 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 Agent.

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

12.5 Genomic Data Sharing Plan

N/A

12.6 Safety Monitoring

The site investigators will meet by teleconference at a weekly frequency for approximately 30 minutes. The site investigator(s) and research staff involved with the conduct of the protocol are required to attend. During the weekly teleconference, the investigators will discuss:

- Safety of protocol participants (AEs and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual (eligible and ineligible participants)
- Retention of participants, adherence to the protocol, and protocol violations
- Protocol amendments

12.7 Data Safety Monitoring Plan

The MD Anderson Cancer Center Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The MD Anderson DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol at a minimum of once every six months. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by RAVE/Theradex which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

The MD Anderson Cancer Center Office of Investigational New Drug/Device (the MD Anderson IND Office) will audit the trial at least annually or as determined by the MD Anderson DSMC. The overall principal investigator, study coordinator and/or data manager may request access to all source documents and other study documentation for on-site or remote monitoring, audit or inspection.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint is objective response rate (ORR), defined as a CR or PR within 6 months of start of treatment, which is defined as consistent with RECIST version 1.1 criteria for solid tumors. The ORR rate will be compared against a null benchmark value of 5%. A maximum of 29 patients will be treated. If at least 4 patients have a response, it will then be concluded that the agent is promising and worthy of further testing. Allowing for 10% ineligibility or dropout rate, we will accrue 32 patients to obtain 29 evaluable patients.

13.2 Sample Size/Accrual Rate

The ORR rate will be compared against a null benchmark value of 5%. If the observed objective response rate is ≥ 4/29 (14%), it will then be concluded that the agent is promising and worthy of further testing. Allowing for 10% ineligibility or dropout rate, a total of 32 patients will need to be accrued in order to obtain 29 evaluable patients (Table 17). If a response has been observed in a particular tumor type, then the study may be expanded to include a total of 14 participants with that tumor type.

In order to accrue 29 evaluable patients, we will use a 2-stage design with 10 patients in the first stage. If at least one of these 10 patients has a response, we will continue to a second stage of 19 patients. The proposed design has the following operating characteristics: power is 80% to conclude an agent is promising if the true ORR is 0.2; type 1 error rate (one-sided) is 6% (this is the probability to conclude that a given agent is promising if the true ORR is 0.05). If the true ORR is 0.05, there is a 49% chance of stopping after the first stage.

Table 18: PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	0	1	**3**
Asian	1	1	1	0	**3**
Native Hawaiian or Other Pacific Islander	1	0	1	1	**3**
Black or African American	1	1	1	1	**4**
White	4	3	3	3	**13**
More Than One Race	2	1	1	2	**6**
Total					**32**

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13.3 Stratification Factors

No stratification factor is applied in this study.

13.4 Analysis of Secondary Endpoints

All patients will be evaluated for toxicity and efficacy from the time of their first treatment. All patients must be assessed for response to treatment to be assigned one of the following categories, even if there are major protocol treatment deviations or if they are ineligible.

1) Complete response

2) Partial response
3) Stable disease
4) Progressive disease
5) Early death from malignant disease
6) Early death from toxicity
7) Early death because of other cause
8) Unknown (not assessable, insufficient data)

Categorization of response will be based on RECIST 1.1. All of the patients who meet the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-8 as above should be considered as failing to respond to therapy (disease progression). A patient will be determined as having a response if he/she has CR or PR; a patient will be determined as a non-response if there is no evidence of response by 6 months during this study. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

The method of Thall, Simon, and Estey [52] will be employed to perform interim safety monitoring. We will assume a Beta (.3, .7) prior distribution for the DLT rate, and target a 30% DLT rate and we will terminate enrollment into the trial if Pr{DLT rate > 30%| data} > 0.9. That is, if at any time during the study we determine that there is more than a 90% chance that the DLT rate is more than 30% we will stop enrollment. We will monitor at 10 and 20 patients with a possible maximum of 32 patients. Stopping boundaries corresponding to this probability criterion are to terminate the trial if [# of patients with DLT/ # of patients evaluated] ≥5/10, 8/20. The operating characteristics of this rule in the trial are shown in Table 18.

Table 19: Operating Characteristics for Safety Monitoring Rule

True DLT Rate	Probability of Early Termination (PET)	Mean number of patients
10%	0%	32.0
20%	5%	31.0
30%	28%	27.1
40%	63%	20.7
50%	89%	15.1

Calculations performed using MultcLean Desktop Version 2.1.0.

Descriptive summary statistics will be used to assess demographics, safety, and antitumor activity. Categorical data will be summarized as percentages. Continuous data will be summarized by means, medians, ranges, coefficients of variation, and standard deviations. Differences in categorical variables will be assessed using the Fisher exact test. PFS and OS will be estimated using the Kaplan-Meier method. In correlative mechanism studies, we will focus on the association between clinical responses and potential biomarkers and on comparison of biomarkers before and after treatment. Statistical inferences will be based on 2-sided tests at a significance level of $P<0.05$. In 20 patients with paired blood samples or biopsies for comparing biomarker levels before and after treatment, the study will have 80% power for a paired *t*-test to

detect a 0.7 standard deviation mean difference, assuming a 2-sided alpha 5% level. To compare biomarker levels between responders and non-responders, the study will have 80% power for a 2-sample *t*-test to detect a 1.5 standard deviation mean difference, using a 2-sided 5% alpha level if the response rate is 25% and N = 20. Non-parametric analogs of the *t*-tests will be used if the data violate the assumptions of the *t*-test.

13.5 Stopping Rules

An interim futility monitoring analysis will be conducted after the enrollment of 10 evaluable patients. If no objective response is observed, the trial should be terminated for futility. If one or more objective responses are observed, this study will continue the enrollment of additional 19 evaluable patients.

Patients who meet a stop rule may remain on study only in their own best medical interest. Otherwise patients will be removed from the study for one of the following stop rules:

- Any uncontrolled side effect affecting quality of life.
- Intercurrent illness that prevents further administration of treatment.
- At least 20% increase in tumor burden compared with nadir.
- Patient chooses to withdraw. Patients can stop participating at any time.
- The researcher may decide to take a patient off under several circumstances: discontinuing is in the participant's medical best interest, funding is stopped, agent supply is insufficient, patient's condition worsens, or new information becomes available

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: 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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **AZD1775.** 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 healthcare provider need to know:
AZD1775 interacts with certain specific enzyme(s) in your liver* and certain transport proteins that help move drugs in and out of cells**.

*The enzyme(s) in question is/are CYP3A4, CYP3A, CYP2C19, CYP1A2 and AZD1775 is broken down by CYP3A4, CYP3A and is affected by strong and moderate inhibitors and inducers of CYP3A4. AZD1775 is also a possible weak inhibitor of CYP2C19 and inhibits CYP3A4 and may increase levels of other drugs that are cleared by these enzymes. AZD1775 induces CYP1A2 enzyme that may result in decreased level of other drugs that are cleared by these enzymes.

The protein(s) in question is/are P-glycoprotein (P-gp),** multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and breast cancer resistance protein (BCRP). AZD1775 requires P-gp to move out of cells and concomitant administration of strong P-gp inhibitors and inducers should be avoided. AZD1775 inhibits BCRP, MATE1 and MATE2K transporters and has the possibility of inducing P-gp and that may affect the transport of other drugs that depend on these proteins to move out of cells. Use caution when taking substrates of these transporters, such as statins.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.
AZD1775 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 any 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, pharmacists) you are taking part in a clinical trial.

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

AZD1775 must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4, CYP3A, CYP2C19, CYP1A2, P-gp, MATE1, MATE2K and BCRP

- 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.

- Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking AZD1775.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- 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 _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug AZD1775. This clinical trial is sponsored by the NCI.

_____ may interact with drugs that are processed by your liver, or use certain transport proteins in your body. 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.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

AZD1775 interacts with specific liver enzymes called CYP3A4, CYP3A, CYP2C19, CYP1A2, transport protein, P-gp, MATE1, MATE2K and BCRP and must be used very carefully with other medicines that interact with these enzymes and transporter proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are prohibited.
- Before prescribing new medicines, your regular health care providers 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 _____.

APPENDIX C: MEDICATION DIARY

Study Name: A Phase II Study of AZD1775, a WEE1 Inhibitor, in Patients with CCNE1 Amplification.

CTEP Study ID: 10136

Patient Initials: _____

Patient Identification Number: _____

Instructions to the patient:

PLEASE complete and return this dosing diary along with any unused AZD1775 and the container(s). You will receive a new dosing diary for each treatment cycle. Thank you for your participation in the very important study!

You will take: AZD1775

Each time you take the AZD1775 study medication, your dose is _____ mg and is made up of:
_____ 100mg capsules

_____ 25mg capsules

How to store your AZD1775 study medication
The AZD1775 study medication must be stored at room temperature (below 30ºC/86ºF) at all times. Please read the medication label for additional storage instructions.

How to take your AZD1775 study medication

- The AZD1775 study medication dose indicated above is to be taken once daily for five (5) consecutive days at the start of Week 1 (Days 1, 2, 3, 4 and 5) and Week 2 (Days 8, 9, 10, 11 and 12) of each cycle.
- Each dose is taken orally (by mouth) 2 hours before or 2 hours after food and at approximately the same time each morning or evening.
- You will take 10 doses in each cycle of 21 days.

If you miss the daily dose according to the schedule,

- the dose should be taken as soon as possible, but not more than 12 hours after the missed dose was scheduled.
- If greater than 12 hours, the missed dose should be skipped and you should take the next dose when scheduled.

How to fill-in your AZD1775 dosing diary
It is very important that you complete this dosing diary as accurately as possible and bring it completed along with all remaining study medication (used and unused containers) to your next clinic visit.

Please fill-in this dosing diary each day that you are scheduled to take study medication.

Write the date in the box marked Date. Please record the exact time you took your study medication and how many capsules taken. (number of 100mg and/or number of 25mg)

It is important that you do not miss any of your study medication, but if you do please provide a reason in the Comments box along with any other comments you would like the doctor to know.

Cycle number: _____

Start date: _____

Patient Signature: _____

DAY	Date			Time capsules taken	Number of capsules taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						

Technical Reviewer: Yvonne A. Evrard Date: Feb 11, 2015

NCTVL Reviewer: Jiuping Ji Date: Feb 11, 2015

IQC Approval: Katherine V. Ferry-Galow Date: 2/11/15

LHTP Approval: Ralph E. Parchment Date: Ralph E. Parchment -S (Affiliate)

DCTD OD Approval: Joseph E. Tomaszewski Date: 03/23/2015

Change History

Revision	Approval Date	Description	Originator	Approval
F	2/11/2015	Updated contact shipping address and process for advance notification of	KFG	REP
E	7/3/2013	Updated tube-type to 1.5-mL conical bottom screw cap tubes to allow for broader use in DCTD assays and minimize the need to transfer biopsies during sample extraction steps. Decreased maximum time from biopsy	YAE	REP
D	1/8/2013	Update handling in surgical suite including details on halving of biopsy. Record total time elapsed from biopsy collection to freezing.	YAE, MM	JJ
C	12/29/2010	Update sample snap freeze to dry ice/ethanol bath or liquid nitrogen.	YAE	JJ
B	7/24/2009	Updated SOP format and prepared for publication to the DCTD Biomarkers Web site	YAE	JJ
A	10/13/2006	Revision with New Shipping Address	YZ	JJ
--	8/25/2006	New Document	YZ	JJ

Please check for revision status of the SOP at

http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm

and be sure to use the current version.

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2.171.0 PURPOSE

Standardize the method for collecting and handling frozen needle tumor biopsies to enable specimen use for measurement of pharmacodynamic (PD) markers following treatment with anticancer agents.

2.182.0 SCOPE

This procedure applies to all personnel involved in the collection and handling of frozen needle tumor biopsies for use in PD marker assays during clinical trials. The goal of this SOP and associated training is to ensure consistency in tumor needle biopsy collection and handling between clinical sites.

2.193.0 ABBREVIATIONS

DCTD	=	Division of Cancer Treatment and Diagnosis
ELISA	=	Enzyme-Linked ImmunoSorbent Assay
FNLCR	=	Frederick National Laboratory for Cancer Research
ID	=	Identification / Identifier
IQC	=	Internal Quality Control
LHTP	=	Laboratory of Human Toxicology and Pharmacology
NCTVL	=	National Clinical Target Validation Laboratory
PADIS	=	Pharmacodynamics Assay Development & Implementation Section
PD	=	Pharmacodynamic
SOP	=	Standard Operating Procedure

2.204.0 INTRODUCTION

Specimen handling, shipping, and storage procedures (pre-analytical variables) can have a significant impact on the reliability of biomarker measurements in the laboratory. Following detailed steps for sample collection and handling procedures and recording any deviations from this procedure allows retrospective identification of artifactual changes in biomarker readout and increases the reliability of the data and validity of the analytical results.

5.0 ROLES AND RESPONSIBILITIES

Laboratory Director/Supervisor — The Laboratory Director/Supervisor, directs laboratory operations, supervises technical personnel and reporting of findings, and is responsible for the proper performance of all laboratory procedures. Oversees the personnel who follow the SOPs in the laboratory and is responsible for ensuring the personnel are certified and have sufficient experience to handle clinical samples.

Certified Assay Operator and/or PK/PD Support Lab Personnel

A Certified Assay Operator and/or PK/PD Support Lab personnel may be a Laboratory Technician/ Technologist, Research Associate, or Laboratory Scientist who has been certified through DCTD training on this SOP. Work under the guidance of the Laboratory Director/Supervisor. This person performs laboratory procedures and examinations in accordance with the current SOP(s), as well as any other procedures conducted by a laboratory, including maintaining equipment and records and performing quality assurance activities related to performance.

5.1 It is the responsibility of the Laboratory Director/Supervisor to ensure that all personnel have documented training and qualification on this SOP prior to the actual handling and processing of samples from clinical trial patients. The Laboratory Director/Supervisor is responsible for ensuring the Certified Assay Operator running the SOP has sufficient experience to handle and analyze clinical samples.

5.2 It is the responsibility of the Certified Assay Operator and/or PK/PD Support Lab personnel to confirm scheduled specimen collection time points, pre-print all labels and data collection sheets in advance, check documentation for accuracy, and verify that the required collection tubes, supplies, and equipment are available for successful collection and handling of biopsy samples.

5.3 The Certified Assay Operator and/or PK/PD Support Lab personnel responsible for conducting the specimen collection and handling procedures are to follow this SOP and complete the required tasks and associated documentation. The Batch Record (Appendix 1) must be completed in ***real-time*** for each experimental run, with each page ***dated and initialed*****,** and placed with the clinical sample information.

5.4 The responsible personnel are to check the DCTD Biomarkers Web site (http://dctd.cancer.gov/ResearchResources/ResearchResources-biomarkers.htm) to verify that the latest SOP version is being followed.

6.0 MATERIALS AND EQUIPMENT REQUIRED

6.1 Stop watch, total time in minutes and seconds required
6.2 1.5-mL Sarstedt o-ring screw cap, conical bottomed tubes (Sarstedt, Cat#: 72.703.416)
6.3 Disposable, fine-tipped tweezers (e.g., VWR, Cat#: 83009-010). Tweezer tips need to easily fit to bottom of a 1.5-mL Sarstedt tube
6.4 Printable microcentrifuge tube labels or BSI labeling system
6.5 81-place freezer boxes (e.g., Fisher Scientific, Cat#: 12-565-182)
6.6 Thermoflask cooler or polystyrene foam container
6.7 Ice bucket
6.8 Liquid nitrogen or dry ice/ethanol bath
6.9 Wet ice
6.10 -80°C freezer (or lower)

7.0 OPERATING PROCEDURES

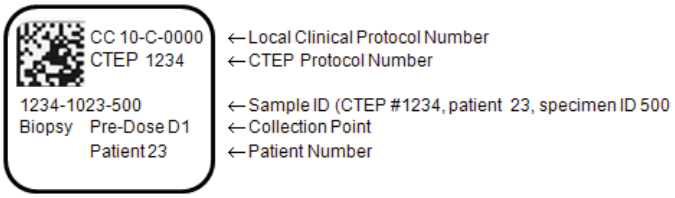
7.1 Record the name and certification number of the Certified Assay Operator and/or PK/PD Support Lab personnel performing the SOP, the facility/clinic collecting the specimens, the Patient/Sample ID, and the clinical protocol number in the Batch Record (Appendix 1).

- The Batch Record for this SOP is sufficient for collection of a **single** patient's biopsy samples; if collecting biopsy samples for more than one patient, prepare a separate Batch Record for each patient.

7.2 Prepare enough pre-printed specimen labels for each whole or halved biopsy sample to be collected and frozen as defined in the Pharmacodynamic/Correlative Study section of the Clinical Protocol; be sure to coordinate with the clinical center if they prepare the labels for sample collection.

If two passes are collected from one tumor, the labels would be identical except that the specimen ID would be followed by a lower case a/b to designate pass number. The specimen ID includes the CTEP protocol number followed by a unique patient identifier and a specimen series ID.

NCI tumor biopsy specimen IDs for PD sampling are series 500 with consecutive numbers identifying the collection time point as defined in the Clinical Protocol. Sample pre-printed label:



7.3 Of the pre-printed labels prepared for each sample, one label will go on each 1.5-mL Sarstedt tube, one on the Batch Record (Appendix 1), and the last will be given to the research nurse to place into the patient record sheet.

7.4 Tumor Needle Biopsy Collection and Handling

7.4.1 The research nurse is to notify the laboratory of scheduled PD sample collections, preferably giving at least 24-h notice. Arrive at the biopsy collection site early enough to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of specimens to the laboratory for placement at -80ºC (or lower) after collection.

7.4.2 Bring all necessary lab supplies including: disposable tweezers, a minimum of two 1.5-mL Sarstedt tubes (one for each whole biopsy core) pre-cooled on liquid nitrogen or dry ice/ethanol in an insulated bucket, and one pre-printed specimen label to give to the research nurse for the patient record.

Note: Pre-chill additional 1.5-mL Sarstedt tubes for specimen collection in case the interventional radiologist collects additional passes, or one of the other tubes is compromised prior to collection.

7.4.3 The total time elapsed between biopsy collection and placement into the pre-chilled tube is of **key importance** to biomarker analysis; biopsies should be frozen within **2min** of collection. The interventional radiologist will eject the biopsy onto a sterile slide (for optimal analyte recovery the slide should be pre-chilled). Start a stop watch (or note the time) at this point (Appendix 1, Section 1) and immediately walk the slide to the sample preparation table.

Note: The preferred method of collection, when whole biopsies are collected, is for the interventional radiologist to eject the biopsy directly into the pre-chilled tube (next step). This minimizes the time between collection and fixation of analytes.

7.4.4 Indicate if a full or halved biopsy, as defined in the Pharmacodynamic/Correlative Study section of the Clinical Protocol, is prepared in the Batch Record (Appendix 1, Section 1).

7.4.4.1 For whole biopsies: Uncap an empty, prechilled 1.5-mL Sarstedt tube and using disposable tweezers, pick up the freshly collected needle biopsy with the tweezers at one end, and touch the opposite end of the biopsy to the inner surface of the prechilled 1.5-mL Sarstedt tube. This should attach the tissue to the tube, allowing it to be dropped into the tube while releasing the tissue from the tweezers without sticking. Dispose of the tweezers in the appropriate biohazardous waste container(s).

7.4.4.2 For halved biopsies: Use 1-2 disposable tweezers and cut/shear the biopsy in half cross-wise while it is on the slide (do not pull or stretch the biopsy longitudinally). Use the tweezers to transfer the halved biopsies to sterile pre-chilled tubes as indicated above.

7.4.5 Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath.

7.4.6 Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of **minutes and seconds** elapsed in the Batch Record (Appendix 1, Section 1).

7.5 If biopsy procedure details can be obtained from the interventional radiologist or research nurse, record them in the Batch Record (Appendix 1, Section 2.). Some information may not be available until a later time from the clinical staff.

During **first-in-human** PD sample collection studies, information such as type of anesthesia and time-lag between biopsy needle withdrawal and sample freezing need to be tracked in order to determine the optimal sample collection procedure for the clinical community.

7.6 Return to the sample processing laboratory and transfer the frozen biopsy specimen(s) to -80°C (or lower) for storage until shipment to the PD processing laboratory. Record the date and time specimens are placed at -80ºC (or lower; Appendix 1, Section 3).

7.7 Review and finalize the Batch Record and document **ANY** and **ALL** deviations from this SOP in the Batch Record (Appendix 1, Section 5).

7.8 The Laboratory Director/Supervisor should review the Batch Record and sign to affirm the data contained within are correct (Appendix 1, Section 6).

8.0 SHIP TO FNLCR FOR ANALYSIS (OPTIONAL)

If shipping to a location other than FNLCR, use the following steps as a guide.

8.1 FedEx return shipment labels will be provided to each approved site sending frozen shipments to FNLCR PD Specimen Central Receiving.

8.1.1 To request return shipment labels send an e-mail to NCI_PD_Support@mail.nih.gov and state "*Protocol Name* Shipment Labels Requested" in the subject line. Specify the address to which the shipment labels should be provided and the number of shipment labels requested. Shipment labels will be provided within 6 business days.

8.2 Once a tumor biopsy has been collected from a patient and placed at -80ºC (or lower), FNLCR PD Specimen Central Receiving should be notified that the specimens are ready for shipment.

8.3 Send an e-mail to FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) to advise that biopsy samples are being prepared for shipment. State "*Protocol Name* PD Specimens Ready for Shipment" in the subject line. Request a confirmation e-mail that personnel will be available on the expected delivery date and time. Personnel are generally available to receive frozen shipments Tuesday through Friday, exclusive of government holidays. If needed, FNLCR PD Central Receiving can be contacted directly at 240-344-5697.

8.4 Use the PD Sample Shipping Manifest template in Appendix 2 to generate a shipping list containing pertinent sample information and FNLCR PD Specimen Central Receiving shipping address.

Attention: Dan Danner
NCI-F/FNLCR

1073 Beasley Street, Building 1073 Fort Detrick

Frederick, MD 21701

Phone: 301-846-5748

8.5 Make a copy of the Shipping Manifest and specimen Batch Records so one copy can be sent to FNLCR with the biopsy samples and one can be maintained at the collection site for internal records.

8.6 Day of Shipment

8.6.1 Just prior to shipment, place specimen tubes into an 81-place freezer box and then in a shipping container with sufficient dry ice to maintain the samples at -20°C for at least 72 h. All weekly processing specimens are recommended to ship out via FedEx on the following Monday afternoon for delivery by 10 AM Tuesday (FedEx First Overnight).

8.6.2 **Verify** the contents of the package match the Shipping Manifest and sign and date the bottom of both copies of the Shipping Manifest. Place one copy of the Shipping Manifest inside the shipping box along with copies of the completed Batch Records for all specimens.

8.6.3 Seal the box and print and attach the shipping address onto the outside of the shipping container; be sure the container is labeled as containing biohazardous specimens.

8.6.4 Record the shipping date, time, tracking number, and shipping information in the Batch Record (Appendix 1, Section 4).

8.6.5 E-mail FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) a shipment notification. State "*Protocol Name* PD Specimen Shipment" in the subject line and reference the tracking number in the e-mail.

8.6.6 Once specimens arrive at the receiving laboratory, they should be immediately placed at -80ºC (or lower) pending delivery to the processing laboratory for protein extraction.

APPENDIX 1: BATCH RECORD

Place PD Specimen Label Here

A **separate** Batch Record should be started for **each patient sample**.

Note: A pre-dose and post-dose sample from the same patient would have the same Patient ID, but different Specimen ID numbers.

Note: Record times using **military time** (24-h designation); for example, specify 16:15 to indicate 4:15 PM.

Certified Assay Operator: _____

Certification Number: _____

☐ Check here if PK/PD Support Lab Personnel

Facility/Clinic Collecting Specimens: _____

Clinical Protocol Number: _____

Patient ID: _____

1. Biopsy Collection

	1st Pass	2nd	3rd	4th s
Specimen ID				
Biopsy size prepared for PD or histological analysis:	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved
Required: Time elapsed from collection to placement in tube	min sec	min sec	min sec	min sec
Time biopsy collected (opt)	:	:	:	:
Time biopsy placed in tube (opt)	:	:	:	:

2. Biopsy Procedure Details

Specimen ID	
Time local anesthesia administered	:
Dose of local anesthetic	mg
Name of local anesthetic used (from Research Nurse)	
Time of skin incision	:
Needle Type (e.g., Temno)	
Needle diameter	gauge
Needle Length	cm
Time guide needle introduced	:
Time guide needle placement confirmed	:
Time biopsy needle introduced	:

3. Biopsy Storage

Date/time biopsy specimen(s) placed at
-80°C (or lower) ____/__/____ ____:____ _____ºC

4. Shipping to FNLCR (optional)

Date and time samples shipped _____ _____:_____
Tracking information _____

****Attach copy of Shipping Manifest**

5. Notes, including any deviations from the SOP:

6. Laboratory Director/Supervisor Review of Batch Record

Laboratory Director/Supervisor:_____(PRINT)
_____(SIGN)

Date: ____/____/_____

APPENDIX 2: PD SAMPLE SHIPPING MANIFEST

From: **Phone:** **E-mail:**	**PD Sample Shipping Manifest**	

In Package	Item No	Patient/Specimen ID	Clinical Protocol	Description	Time Point Scheduled	
	Example	*1234-1023-500*	*12-C-0000*	*Full biopsy*	*Pre-dose D1*	
	Example	*1234-1023-501*	*12-C-0000*	*Half biopsy*	*Cycle 1, D8*	
☐	1					
☐	2					
☐	3					
☐	4					
☐	5					
☐	6					
☐	7					
☐	8					
☐	9					
☐	10					

Verification of Contents **Signature**

Contents Verified Collection Laboratory

_____

Contents Verified FNLCR PD Central Receiving

_____