SUMMARY OF CHANGES

NCI Protocol #: 10132
Local Protocol #: PHL-087
Version # / Version Date: Initial / 11 July 2017
Amendment 1 / 20 February 2018
Amendment 2 / 15 June 2018
Amendment 3 / 28 December 2018
Amendment 4 / 28 June 2019
Amendment 5 / 03 Jun 2020

#	Section	Comments
1.	All	Updated the version date in the top left corner.

2.	7.1	Revised AZD1775 CAEPR – Version 2.6, May 14, 2019 to CAEPR version 2.7 April 27, 2020
		
		• Added New Risk:
		  • Also Reported on AZD1775 Trials But With Insufficient Evidence for Attribution: Apnea; Blood and lymphatic system disorders - Other (right leg deep vein thrombosis); Depressed level of consciousness
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on AZD1775 Trials But With Insufficient Evidence for Attribution: Muscle cramp; Weight loss
		
		Rationale: Updated CAEPR list as per Rapid Request for Amendment (RRA) from CTEP dated 21May2020.

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TITLE: A Phase I Study of the Wee 1 kinase (Wee 1) inhibitor AZD1775 in combination with Radiotherapy and Cisplatin in Cervical, Upper Vaginal and Uterine Cancers (10041848, 10008224, 10008238, 10046888, 10014735)

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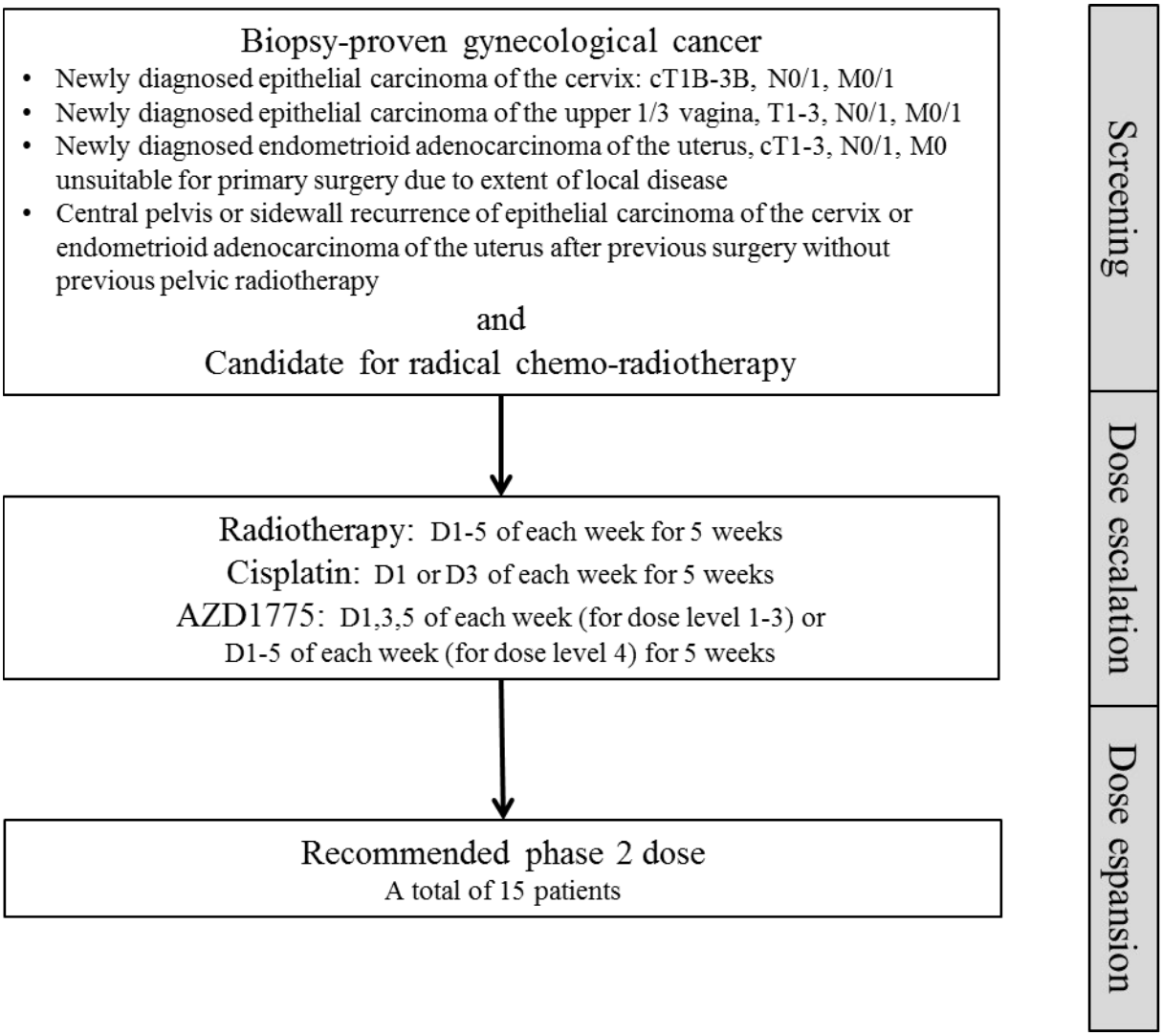
NCI Supplied Agent: AZD1775 (previously named MK-1775, NSC#751084, IND#116495)
Commercial Agent: Cisplatin (NSC#119875)

IND #: 116495
IND Sponsor: DCTD, NCI

SCHEMA


Biopsy-proven gynecological cancer
• Newly diagnosed epithelial carcinoma of the cervix: cT1B-3B, N0/1, M0/1
• Newly diagnosed epithelial carcinoma of the upper 1/3 vagina, T1-3, N0/1, M0/1
• Newly diagnosed endometrioid adenocarcinoma of the uterus, cT1-3, N0/1, M0 unsuitable for primary surgery due to extent of local disease
• Central pelvis or sidewall recurrence of epithelial carcinoma of the cervix or endometrioid adenocarcinoma of the uterus after previous surgery without previous pelvic radiotherapy
and
Candidate for radical chemo-radiotherapy
Radiotherapy: D1-5 of each week for 5 weeks
Cisplatin: D1 or D3 of each week for 5 weeks
AZD1775: D1,3,5 of each week (for dose level 1-3) or D1-5 of each week (for dose level 4) for 5 weeks
Recommended phase 2 dose
A total of 15 patients
Screening
Dose escalation
Dose espansion

STUDY SUMMARY

This will be a multi-institution, open-label, dose escalation phase I evaluating different schedules of AZD1775 administration in combination with cisplatin-based chemoradiation. Eligible patients will have one of the following biopsy-proven gynecological cancers, and a decision to treat radically with pelvic radiotherapy (total dose ≥45Gy) and concurrent cisplatin chemotherapy (RT-CT):

- Newly diagnosed epithelial carcinoma of the cervix, cT1B-3B, N0/1, M0/1**
- Newly diagnosed epithelial carcinoma of the upper 1/3 vagina, T1-3, N0/1, M0/1**
- Newly diagnosed endometrioid adenocarcinoma of the uterus, cT1-3, N0/1, M0 unsuitable for primary surgery because of the extent of local disease. These patients are eligible if a prior decision has been made to treat radically with neoadjuvant chemoradiation followed by surgery or further radiotherapy (including brachytherapy) depending on response
- Central pelvis or sidewall recurrence of epithelial carcinoma of the cervix or endometrioid adenocarcinoma of the uterus after previous surgery without previous pelvic radiotherapy

**Patient may have small volume metastatic disease in para-aortic or supraclavicular lymph nodes or at other metastatic sites as long as, in the best judgment of the treatment team, a radical course of pelvic radiotherapy is warranted to assure local disease control

Study design

This phase I dose-escalation study will determine the provisional recommended phase II dose. Once the recommended phase II dose is determined, a dose expansion will be performed.

Dose Escalation

A cohort of 3 patients per dose level are planned:

- The starting dose will be dose level (DL) 1, AZD1775 will be administered daily on Day 1, 3, and 5 of the week
- If AZD1775 is tolerable at DL1 with no DLT experienced, 3 patients enter DL2.
- If AZD1775 is tolerable at DL2 with no DLT experienced, 3 patients enter DL3.
- If AZD1775 is tolerable at DL3 with no DLT experienced, 3 patients enter DL4 of which AZD1775 will be administered Day 1-5 of the week.

If the first 2 patients enrolled in a starting dose level (DL1) experience DLT, further enrollment to that dose level will stop and a lower dose level will be explored. If the first 2 patients enrolled in the lower dose level (DL-1) experience DLT, further enrollment to that dose level will stop. The Principal Investigator will discuss with the sponsors regarding the appropriate next step.

If 1/3 patients encounter a dose-limiting toxicity (DLT), then the cohort will be expanded to 6 patients. If ≥2/6 of patients encounter DLT, then that dose level will be declared excessively toxic. A total of 6 patients will be entered into the previous dose level.

The recommended phase II dose (RPTD; also called the MTD) is defined as the dose level with $\leq$ 1/6 patients with DLT.

Dose Expansion

If no patient experiences a DLT at each dose level, dose level 4 will be declared as the provisional RPTD. Then 12 additional patients will be enrolled (make up to a total of 15 patients).

- If 1/3 patients encountered DLT, then the cohort will be expanded to 6 patients.
- If $\leq$1/6 patients encountered DLT, that dose level is declared as the RPTD, and 9 additional patients will be enrolled (make up to a total of 15 patients).
- If $\geq$2/6 of patients encounter DLT, then that dose level will be declared excessively toxic. Additional 3 patients will be entered into the lower dose level. If $\leq$1/6 patients at the lower dose level had DLT, then that level will be declared as the RPTD, and 9 additional patients will be enrolled (make up to a total of 15 patients).

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1. OBJECTIVES

1.1 Primary Objectives

- To determine the recommended phase II dose (RP2D) and safety profile of AZD1775 in combination with radiotherapy and concurrent cisplatin in patients with gynecological cancers.

1.2 Secondary Objectives

- To determine the acute and late toxicity of AZD1775 when administered to patients with gynecological cancer in combination with standard radiotherapy and concurrent cisplatin.
- To evaluate the pharmacodynamic effects of AZD1775 when administered in combination with radiotherapy and concurrent cisplatin (in particular, for the 15 patients treated in an expansion cohort at the RP2D). Pharmacodynamic biomarkers will include: pCDC2, Ki67, γH2AX, pH3, and CC3.
- To obtain preliminary information about the progression–free survival, as defined by RECIST 1.1 or clinical progression, of AZD1775 in combination with standard radiotherapy and concurrent cisplatin in women with gynecological cancer.

2. BACKGROUND

2.1 Gynecological Cancer

2.1.1 Cervical Cancer (code 10041848, 10008224, and 10008238)

Cervix cancer is the fourth most common malignant neoplasm in women worldwide. Routine screening has greatly decreased the incidence and mortality of cervical carcinoma.[1] Despite these advances, the lifetime risk of developing cervical cancer remains significant at 1 in 150 women. A subset of patients with small localized tumors (FIGO stage IA-IBI) have an excellent prognosis with either surgery or radiotherapy and achieve 5-year survival rates in excess of 90%. Unfortunately most patients present at a more advanced stage of disease where despite aggressive management, 5-year survival rates are disappointingly low (50-75%).[2]
Most patients with cervix cancer are candidates for potentially curative treatment using primary radiotherapy and concurrent cisplatin chemotherapy, based on the results of several phase III studies.[3-7] Despite delivery of adequate doses of chemotherapy and radiation, over 25% of patients with stage IB2 or II disease will have recurrence of disease and this number rises to more than 50% in patients with stage III and IVa disease.[8] In those patients whose disease recurs after failure of chemo-radiation and is not amenable to further loco-regional therapy, outlook is generally poor with a median overall survival of about one year.[9] As such, there is an urgent need to identify new treatment options to increase cure rates with primary treatment for patients with localized disease and to improve prognosis of those patients in whom primary therapy fails.

2.1.2 Vaginal Cancer (10046888)

Primary cancer of the vagina is rare and comprises three percent of all malignant neoplasms of the female genital tract. The most common histologic subtype is squamous cell carcinoma and are likely mediated by human papillomavirus (HPV) infection, as with cervical cancer.[10,11] Most women are initially diagnosed at an advanced stage and therefore carry a poor prognosis; rates of 5-year survival according to disease stage as per FIGO stage II-IV, range from 12.9-52%.[12]

2.1.3 Uterine cancer (10014735)

Uterine carcinoma is the highest incidence gynecologic malignancy and remains the 4th most common cancer diagnosis in North American women less frequent only to diagnoses of breast, lung and colorectal carcinoma. In 2015, approximately 6300 more women will be diagnosed with, and 1000 will die of this disease in Canada.[13] US statistics parallel those of Canada with an approximately 10-fold difference.[14]

The majority of women are diagnosed with early stage endometrial carcinoma and have a relatively good prognosis, with 5-year disease-free survivals of greater than 77%.[15] In the contrary, women with advanced disease (Stage III) at presentation have a poor prognosis, with survival less than 57%[15]. Factors like age > 60, depth of invasion, involvement of lower uterine segment, non-endometrioid histology and the presence of lymphovascular invasion or aneuploidy, have demonstrated importance in identifying those at a particularly high risk of failing primary therapy.[16,17]

One large retrospective analysis examining the use of intensity-modulated radiation therapy (IMRT) for patients with isolated nodal recurrence was feasible, with a median OS of 46 months [18]. Interestingly, patients who received concurrent chemoradiation (given as weekly cisplatin) had significantly longer median survival as compared to IMRT alone.

2.2 Target information: AZD1775

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[19,20]. Cell cycle checkpoints are critical in the DNA damage response, and inhibition of Wee-1 is expected to release a tumor cell from chemotherapeutically induced arrest of cell replication. In vitro experiments demonstrate that AZD1775 has synergistic anti-tumor effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action.

The tumor suppressor protein p53 regulates the G1 checkpoint. As the majority of human cancers harbor abnormalities in this pathway they become more dependent on S- and G2-phase checkpoints[21]. Thus, S- and G2-checkpoint abrogation caused by inhibition of WEE1 may selectively sensitize p53-deficient cells to anti-cancer agents

2.2.1 Non-clinical studies

AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin and topotecan, in p53- deficient cell lines. In xenograft models AZD1775 enhanced the anti- tumor effect of cisplatin, carboplatin, gemcitabine, 5-Fluoruracil, and radiotherapy.

The preclinical pharmacokinetic studies of AZD1775 revealed a short terminal half-life (1.6 and 1.1 h in rats and dogs respectively). The oral bioavailability was 59.7% in rats and 33.6% in dogs.

AZD1775 was moderately bound to plasma proteins. Metabolism was the major route of elimination of AZD1775 in rat and dog.

In preclinical toxicological studies the major organs affected were proliferation dependent organs such as lymphoid and hematopoietic organs and gastrointestinal tract. In preclinical toxicity models AZD1775 was observed to marginally prolonged QTc. AZD1775 was negative in the Microbial Mutagenesis Assay but positive in vitro Chromosomal Aberrations Assays and in vivo Micronucleus Assay. These positive results in the chromosomal aberration assay were not unexpected based on the mechanism of action of AZD1775.

2.2.2 Metabolism

The in vitro studies suggest that the major pathways of the metabolism of AZD1775 in humans involve CYP3A4, although FMO3 and FMO5 may be involved to same extent. In addition, AZD1775 was a time-dependent inhibitor of CYP3A4 in vitro in human liver microsomes. Therefore, there is a potential for drug-drug interactions when AZD1775 is co-administered with drugs that are known to be moderate or potent CYP3A4 inhibitors or inducers, and when it is co-administered with substrates of CYP3A4.

2.2.3 Clinical experience

As of 11 November 2017, a total of approximately 713 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 559 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients include those who have received single doses 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.

Adverse drug reactions to AZD1775 monotherapy include: anemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. Adverse drug reactions to AZD1775 in combination with cytotoxic chemotherapy include febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, and myalgia.

Based on information emerging during the clinical development program of AZD1775, potential risks with AZD1775 monotherapy are transaminases, asthenia/fatigue, lymphopenia/lymphocytes count decreased, leukopenia/WBC count decreased, stomatitis, myalgia, gastrointestinal hemorrhage, sepsis, febrile neutropenia. Potential risks for AZD1775 in combination with cytotoxic chemotherapy are tachycardia and pancytopenia.

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.

In Study PN001[22], 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. No complete or PRs were observed in either of Studies PN005 or PN008 at the time that they were terminated.

In the phase I clinical trial evaluating AZD1775 as single agent and in combination with cisplatin, gemcitabine and carboplatin (Study PN001), the MTD of AZD1775 was determined to be 200mg in single-dose combination with cisplatin (75mg/m^2) every 21 days; and 200mg BID x 2.5 days during week 1 with cisplatin (75mg/m^2) every 21 days. The DLT experienced were Grade 3 diarrhea, fatigue, nausea and vomiting. As limited data is available for AZD1775 in combination with chemoradiation in patients, the initial dose selected for the current protocol is 100mg every alternate days (Day 1, 3, 5) weekly for five weeks.

2.3 Radiotherapy and concurrent cisplatin chemotherapy for the treatment of locally advanced cervical cancer

Cisplatin-based chemoradiation has been considered the standard treatment in patients with cervical cancer, since 1999 when five randomized clinical trials comparing cisplatin-based chemoradiation with radiotherapy alone[3,6,22] or hydroxyurea-based chemoradiation[4,23] were published, showing an improved outcome in the cisplatin-based group.
The most recently published metanalysis[24] has shown an increased overall survival, disease free survival, locoregional free survival and distant metastasis free survival. There was a 6% absolute 5-year survival improvement (hazard ratio [HR] = 0.81, P $\leq$.001) from 60% to 66%.
Among the cisplatin based regimens, weekly cisplatin (dose 40mg/m^2) shows a better toxicity profile in comparison to the other regimens. The main toxicities observed are gastrointestinal and hematological toxicities.

Table 2-1: Main toxicities in clinical trials of radiotherapy and concurrent cisplatin 40mg/m^2

	G1-G2 toxicities (%)				G3-G4 toxicities (%)			
	Keys[3] 1999	Rose[4] 1999	Pearcey[5] 2002	Lanciano[7] 2005	Keys[3] 1999	Rose[4] 1999	Pearcey[5] 2002	Lanciano[7] 2005
Hematological	55.74	57.95	-	-	21.31	22.73	4.72	33.00
Gastrointestinal	57.92	34.09	-	-	14.21	6.82	12.60	25.00
Genitourinary	31.15	9.66	-	-	1.64	2.84	2.36	-
Cutaneous	13.66	7.39	-	-	0.00	1.14	2.36	-
Neurologic	7.65	7.95	-	-	1.09	0.57	1.57	-
Other	18.58	19.89	-	-	6.56	3.98	7.87	-

- Data not available

Several approaches have been evaluated to increase the outcome of patients with cervical cancer undergoing chemoradiation treatment, such the addition of a second chemotherapeutic agent or the addition of a targeted agent. The addition of gemcitabine concurrently with cisplatin-based chemoradiation and as part of an adjuvant regimen has been evaluated recently in a clinical trial.[25] In this clinical trial, the experimental arm showed an increased disease free survival and overall survival, with a significant increase in toxicity. Regarding targeted agents, the anti-EGFR agents erlotinib[26] and cetuximab,[27] and the anti-angiogenic multi-tyrosine kinase inhibitor sorafenib[28] has been evaluated in phase I clinical trials. The early results from two phase II clinical trials evaluating erlotinib and cetuximab respectively have been recently communicated.[27,29]

Given the rarity of vaginal cancer, treatment paradigms are mostly extrapolation of studies from cervical cancer due to the fact that they shared similar etiology. Benefit of chemoradiation in vaginal carcinoma has been demonstrated in small studies involving women who had unresectable disease.[12,30]

2.4 Rationale

2.4.1 Wee 1 inhibition and p53

The cell cycle is regulated by a number of cyclin dependent kinases. Wee1, a tyrosine kinase, blocks activity of CDK1 (also called CDC2) and CDK2 through its phosphorylation of tyrosine residue 15. The ability of Wee1 to negatively regulate CDK activity is critical to the G2-M cell cycle arrest in response to DNA damage.[19,20,31] More recently, Wee1's regulation of CDK activity was also shown to be essential in preventing DNA double strand breaks during DNA replication.[32] Therefore, inhibition of Wee1 kinase activity can override a G2 cell cycle arrest and/or result in DNA damage by disrupting replication of the genome.

The tumor suppressor protein p53 is a key regulator of the G1 checkpoint, and is the most frequently mutated gene in human cancers.[32] Tumor cells with a defective G1 checkpoint due to loss of p53 are more dependent on the S and G2 checkpoints to repair DNA damage caused by cytotoxic agents or radiotherapy.[33] Therefore, p53-deficient tumor cells treated with

inhibitors of Wee1 are expected to be particularly susceptible to DNA damage induction due to genetic and pharmacologic loss of both the G1 and G2 checkpoints, respectively.[31,34] The G2 checkpoint escape induced by inhibition of Wee1 forces the DNA-damaged tumor cells into the cell cycle causing mitotic catastrophe; however, normal cells, retaining an intact G1 checkpoint, are less affected by Wee1 inhibition, a form of synthetic lethality.

AZD1775 is a potent, highly selective, ATP-competitive, small- molecule inhibitor of Wee1. AZD1775 was shown in vitro and in vivo to preferentially sensitize tumor cells, relative to normal cells, to various DNA- damaging anticancer agents while sparing normal tissues from radiotherapy and chemotherapy-induced toxicity.

In pre-clinical models AZD1775 significantly enhanced antitumor activity of a number of cytotoxic agents including carboplatin and cisplatin in a dose- dependent manner. In xenograft models AZD1775 enhances the anti-tumor growth effect of radiotherapy preferentially in p53 mutant xenograft tumors. [34]

2.4.2 Wee 1 inhibition in cervical cancer

Characteristic of cervical cancer is the presence of high risk (HR) human papillomavirus (HPV) DNA in more than 99% of tumors. When the HR HPV genome integrates into the host genome, oncogenic E6 and E7 proteins become constitutively expressed. E7 plays an important role in the early stage of carcinogenesis by stimulating proliferation. HR HPV E6-induced proteasomal degradation of p53 hampers p53 functionality in cell cycle arrest and apoptosis. The interaction of HPV- E6 with p53 is known to be the most important event in HPV-associated carcinogenesis.[35,36] Only a small percentage of cases of cervical cancer have a p53 mutation; most cervical cancer cells have a wild-type p53, which is not detectable by immunohistochemical analysis due to its short half-life.[37] Accumulation of p53 protein is associated with aggressive behavior and recurrence of various cancers, including cervical cancer.[38,39].

In a recent series from Moon et al, 31 of 80 (38.8%)[40] samples of squamous cell carcinoma of the cervix were immunohistochemically positive for p53. p53 expression was significantly related to advanced T stage ($p = 0.001$), larger than 4 cm in the greatest dimension of the tumor ($p = 0.002$) and more than 1/2 stromal invasion of the cervix ($p = 0.005$). In this series the rate of expression varied from 27.6% from T stage 1 and 68.2% from T stage 2 cancers.[41] This compares to earlier series where expression varied from 39.1% p53 expression from stage I cancer and 80.9% expression from stage II–IV cancer.[42] Seven percent p53 expression was seen in carcinoma in situ compared to 62% p53 expression in invasive SCC, with no staining of p53 observed in cervical dysplasia, condyloma, or normal cervix was observed in another series.[40] Dysfunctional p53 is therefore a key feature of cervical cancer.

By using RNA interference (RNAi) approach, Lorns et al. showed that the WEE1 gene is over-expressed in cervical cancer cell lines (HeLa), probably as a result of an increase in the gene copy number.[43] Furthermore, WEE1 was also over-expressed at the protein level in HeLa and could be silenced by small interfering RNAs (siRNA) with higher sensitivity than cell lines that did not overexpress WEE1. Knockdown of WEE1 in cervical cancer cells, but not in normal epithelial cells, in combination with adryamicin treatment, induces G2-abrogation and results in

apoptosis.[44] In vivo, AZD1775 combined with carboplatin in cervical HeLa-luc xenografts resulted in significant reduction of tumor growth[45]. Furthermore, AZD1775 enhanced the growth inhibitory effects of cisplatin and topotecan in human papilloma virus (HPV)+/genetically p53 wild-type (HeLa, SiHa, CaSki, and ME-180) as well as HPV-/p53 mutant (C-33A and HT-3) cervical cancer cells, suggesting that HPV infection, and not only mutation or loss of the p53 loci, renders cervical cancer cells susceptible to chemosensitization by AZD1775.[46]

2.4.3 Rationale for combining AZD1775 with radiotherapy and concurrent cisplatin for cervical cancer

AZD1775 is a highly promising agent particularly for tumors with loss of functional p53. Loss of functional p53 plays a key role in cervical cancer biology. The following table summarized some loss of function p53 mutations according to the IARC TP53 database [47]:
Examples of loss of function p53 mutations:

R175H	V272M	V216M	C277F	P177L	R249T
R248Q	R280T	C275Y	P250L	R110L	Y234H
R273H	I195T	G266R	G279E	R283P	P278A
R248W	R158L	V173M	N239D	D259Y	S215R
R273C	C141Y	R280K	R249G	D281N	H179Q
R282W	C176Y	K132N	V272L	N239S	L194F
G245S	P151S	G244S	R249W	S241C	R249K
R249S	H193R	G244D	D281E	V143M	F134L
Y220C	E286K	L194R	R282G	C242S	R280S
V157F	C135Y	R249M	M246I	I195F	Y163H
M237I	C242F	E258K	C238F	A138P	C277Y
E285K	G245C	G154V	R156P	P152S	F270C

H179R	G266E	H193L	P278R	P278T	I251S
Y163C	V173L	K132R	R280G	R267W	R280I
G245D	P278S	C135F	H193Y	V274F	S215I
R273L	Y236C	G266V	D281H	C176S	K132E
Y234C	C238Y	M246V	I255F	C238S	K164E
R248L	P152L	G244C	R213L	F270L	R248G
Y205C	G245V	C242Y	P151H	S127F	Y163N
S241F	P278L	A159V	R213Q	T155N	G244V
R158H	H214R	C275F	R273P	A159P	R175G

Note: this list includes some of the most frequent loss of function mutations, but it is not a restrictive list. Many other loss of function mutations are described in the IARC TP53 database.

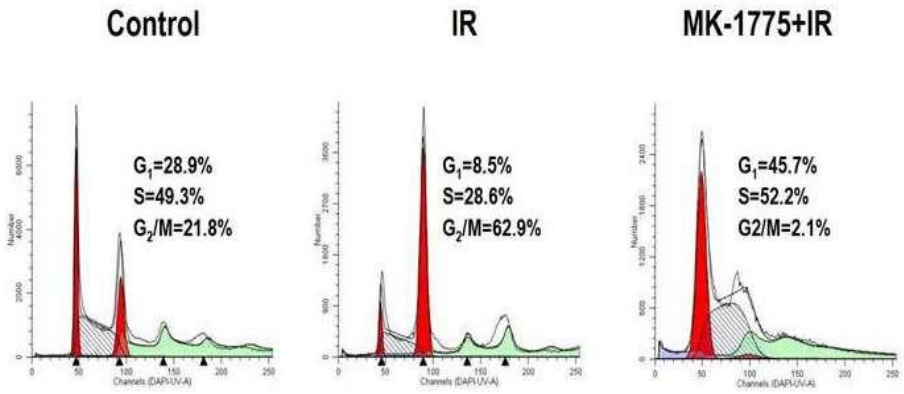
HPV interaction with p53 may in fact be another mechanism for synthetic lethality with AZD1775 in this patient population, and this study will assess this hypothesis. Pre-clinical

studies suggest AZD1775 may enhance the activity of both cisplatin and radiotherapy.

Cervical cancer is an accessible tumor particularly attractive for studies combining biological agents with chemoradiation as the availability of serial tumor biopsies allows "proof of principle" correlative studies. In this study we wanted to explore two schedules as AZD1775 is thought to enhance both the effect of cisplatin chemotherapy and the effect of radiotherapy. By scheduling AZD1775 doses around the time of cisplatin administration, we will explore both the effect of the drug on the combination of radiotherapy and concurrent cisplatin chemotherapy.

Figure 2-1: Abrogation of the G2 checkpoint by AZD1775. BxPC-3 pancreatic cancer cells show a striking increase in the G2 peak following ionizing radiation (IR), whereas irradiated cells exposed to AZD1775 continue on into mitosis.

(*Findings from D. Hedley laboratory, Princess Margaret Cancer Centre*)



2.5 Correlative Studies Background

2.5.1 Wee1 and the G2/M checkpoint

The checkpoint kinases which include ATR, CHK1 and Wee1 are important regulators of DNA damage surveillance pathways. Their normal functioning at the various transition points (G1/S, G2/M) of the cell cycle is critical in order for proliferating cells to repair DNA damage accumulated to that point from either endogenous or exogenous sources. Wee1 exerts inhibitory phosphorylation of CDC2 at Tyr14 and Tyr15 which in turn stalls cells at G2/M preventing entry into mitosis. Inhibition of wee1 therefore releases this inhibition and the decreased levels of p-cdc2 allow cells to proceed through mitosis. Cells previously exposed to DNA damaging agents and now under the pressure of wee1 inhibition would be expected to undergo mitotic catastrophe and apoptosis as a consequence of the accumulation of cytotoxic-induced DNA damage. From a molecular standpoint, effective wee1 inhibition with decreased p-CDC2 levels would be expected to result in increased p-H3 (phospho- histone 3, demonstrating entry into mitosis) and CC3 (cleaved caspase 3 indicative of apoptosis). Malignant cells with ineffective regulation of G1/S transition are therefore heavily reliant on the G2/M checkpoint to allow for repair of critical DNA damage which would otherwise promote mitotic catastrophe, triggering cells to undergo apoptosis. Given this mechanism of

action, inhibition of checkpoint kinases active at G2/M (such as wee1) is theorized to have synergistic activity with DNA damaging cytotoxics. Preclinical work in a variety of tumor models has been consistent with this hypothesis although the true relevance of functional p53 status is unclear.[45,51,52]

2.5.2 Wee1 activity during S-phase

This latter finding may be consistent with the recent description of a critical role for wee1 (acting through CDK2) during S-phase in protecting against replication stress associated DNA breakage.[32,53] Specific inhibition of wee1 activity during S-phase results in increased cdk2 activity with increased origin firing and slowed replication fork speed with an accumulation of dsDNA breaks (indicated by γH2AX) and stalling of cells in S-phase (with decreased proliferation rates indicated by ki-67).

2.5.3 Other factors potentially influencing AZD1775 activity

This study will include the analysis in archival tissue of p21, Rb and p16. Some p53 mutations induce a partial loss of function allele. These mutations failed to activate apoptotic genes, but are able to induce p21 transcription.[55] In cancers harboring these mutations, we expect to observe p21 staining. We hypothesize that in cancers expressing p21, there would be no impairment of the G1 checkpoint, thus AZD1775 could be less effective than in tumors with loss of function p53 mutations.

The Retinoblastoma (Rb) pathway is also essential regulating the G1 checkpoint. p16 blocks Rb protein phosphorylation, favoring Rb suppressor activity. Loss of Rb or dysfunction of the Rb pathway leads to chromosome instability.[56] In cervical cancer, Rb dysfunction is an expected event: HPV E7 oncoprotein disrupts the pRB/E2F transcriptional repressor complex, blocking the suppressor effect of Rb protein and releasing E2F transcription factor.[57] This E7 oncoprotein-induced loss of Rb function in cervical carcinomas, results in overexpression of p16.[58-60] The underlying mechanism for this p16 overexpression is that E2F positively regulates the transcription of p16.[61,62] It is still unknown whether changes in Rb pathway can influence the activity of AZD1775.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have one of the following biopsy proven gynecological cancer and a decision to treat with radiotherapy and concurrent cisplatin chemotherapy (RT-CT)

- Newly diagnosed epithelial carcinoma of the cervix, cT1B-3B, N0/1, M0/1**
- Newly diagnosed epithelial carcinoma of the upper 1/3 vagina, T1-3, N0/1, M0/1**
- Newly diagnosed endometrioid adenocarcinoma of the uterus, cT1-3, N0/1, M0 unsuitable for primary surgery because of the extent of local disease. These patients are eligible if a prior decision has been made to treat radically with neoadjuvant chemoradiation followed by surgery or further radiotherapy (including brachytherapy) depending on response

- Central pelvis or sidewall recurrence of epithelial carcinoma of the cervix of endometrioid adenocarcinoma of the uterus after previous surgery without previous pelvic radiotherapy

**Patient may have small volume metastatic disease in para-aortic or supraclavicular lymph nodes or at other metastatic sites as long as, in the best judgment of the treatment team, a radical course of pelvic radiotherapy is warranted to assure local disease control.

3.1.2 Patients must be planned to receive whole pelvic radiotherapy to a total dose of 45Gy or greater.

3.1.3 Patients must be able to receive weekly cisplatin.

3.1.4 Patients must be ≥18 years of age on day of signing informed consent

- Because no dosing or adverse event data are currently available on the use of AZD1775 in combination with cisplatin-based chemoradiation in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status 0 or 1 (Karnofsky ≥60%, see Appendix A).

3.1.6 Life expectancy of greater than 3 months

3.1.7 Patients must have normal organ and marrow function as defined below:

• leukocytes	≥3,000/mcL
• absolute neutrophil count	≥1,500/mcL
• platelets	≥100,000/mcL
• hemoglobin	≥9 g/dL[1]
• PT/PTT/INR	≤ 1.5 ULN
• total bilirubin	Serum bilirubin within normal limits (WNL) or ≤1.5 x ULN in patients with liver metastases; or total bilirubin ≤3.0 x ULN with direct bilirubin WNL in patients with documented Gilbert's Syndrome
• AST(SGOT)/ALT(SGPT)	Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN) or ≤5 x ULN if known hepatic metastases
• Creatinine clearance (CrCl)	≥60 mL/min as calculated by the Cockcroft-Gault method

1: Blood transfusions are allowed at any time during the screening, treatment or follow-up period, according to the center recommendations.

2: Cockcroft-Gault formula: $CrCl = \frac{(140-age)\times weight\ (in\ kg)}{72 \times serum\ creatinine\ (in \frac{mg}{dL})} \times F$;where F=0.85 for females

3.1.8 Patients must be able to swallow whole capsules.

3.1.9 The effects of AZD1775 on the developing human fetus are unknown. The preclinical Chromosomal Aberrations Assays have shown potential to induce chromosomal aberrations. In addition, cisplatin and radiotherapy are known to be teratogenic. For this reason, women of child-bearing potential must agree to use two birth control methods (two barrier methods *or* a barrier method plus a hormonal method) or abstinence prior to study entry, for the duration of study participation prior to study entry, for the duration of study participation, and for 4 months after coming off study. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

3.1.10 Females with child-bearing potential must have had a negative serum pregnancy test result ≤ 28 days prior to the first dose of study treatment.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have received any radiotherapy or chemotherapy for their current gynecological cancer.

3.2.2 Patients who received prior pelvic radiotherapy for any indication.

3.2.3 Patients who have a mean resting correct QTc interval using the Fridericia formula (QTcF) >470 msec (as calculated per institutional standards) obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart at study entry, or congenital long QT syndrome. AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

3.2.4 Patients requiring para-aortic radiotherapy.

3.2.5 Patients who are receiving any other investigational agents or anticancer therapy concurrently or within 4 weeks (ie 28 days)

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to AZD1775 or cisplatin.

3.2.7 Uncontrolled intercurrent illness including, but not limited to, myocardial infarction within 6 months, congestive heart failure, symptomatic congestive heart failure, unstable angina pectoris, active cardiomyopathy, unstable ventricular arrhythmia, uncontrolled hypertension, uncontrolled psychotic disorders, serious infections, active peptic ulcer disease, active liver disease or cerebrovascular disease with previous stroke, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because AZD1775 and chemoradiation are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AZD1775 and cisplatin, breastfeeding must be discontinued if the mother is treated with AZD1775 and cisplatin. These potential risks may also apply to other agents used in this study.

3.2.9 Patients with another uncontrolled malignancy. Patients with a previous malignancy, treated curatively and without evidence of disease relapse are eligible.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with AZD1775. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.11 History of active clinically significant bleeding.

3.2.12 History of bowel obstruction or malabsorption syndromes (within the last 3 months) which might limit the absorption of the study drug.

3.3 Inclusion of Women and Minorities

Due to the nature of the disease site, men are ineligible for this study; while women of all races and ethnic groups are eligible. This study is designed to include minorities as appropriate. However, the trial is not designed to measure differences in intervention effects. The population of Southern Ontario is ethnically diverse and the proportion of different ethnic groups in the community is provided in the table below. Universal access to health care will ensure that there is no discrimination on the basis of race or gender (Guide to Canadian Human Rights Act: www.chrc-ccdp.ca/public/guidechra.pdf). Individual hospital registries and databases do not routinely collect racial data, under the direction of the Canadian Human Rights Code.

The population demographics and distribution of minorities in Canada is included in the following table:

Table 3-1: Visible minority population by Consortium Provinces (2001 Census)

	British Columbia		Alberta		Ontario		Nova Scotia		Total	
Total population of province	3,868,870		2,941,150		11,285,550		897,570		**18,993,140**	
Visible Minorities	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**	**Population**	**%**
Black	25,465	1%	31,390	1%	411,095	4%	19,670	2%	487,620	**3%**
Asian	768,435	20%	268,660	9%	1,513,825	13%	12,630	1%	2,563,550	**13%**
Latin American (Hispanic)	23,880	1%	18,745	1%	106,835	1%	520	0%	149,980	**1%**
Visible minority, not included elsewhere	4,195	0%	4,220	0%	78,915	1%	1,170	0%	88,500	**0%**
Multiple visible minority	14,465	0%	6,910	0%	42,375	0%	535	0%	64,285	**0%**
Total Visible minority population	836,440	22%	329,925	11%	2,153,045	19%	34,525	4%	3,353,936	**18%**

Source: Statistics Canada, Census of Population.

Data from our consortium has been compiled regarding the representation of minorities on previous clinical trials, and the distribution is as follows:

Population Percentage of Minority and Gender of entering PMHC Trials			
	2010	2011	2012
Visible Minorities			
Black	0.9	2.3	1.2
Asian	10.1	10.9	11.6
Hispanic	10.1	2.3	3.5
Total	**21.1**	**15.5**	**16.3**
Women	**59.6**	**56.6**	**44.2**

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a 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.

4.1.1 CTEP Associate Registration Procedures / CTEP-I-AM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (*i.e.*, all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (*i.e.*, all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is required to access all CTEP applications and, if applicable (*e.g.*, all Network trials), all Cancer Trials Support Unit (CTSU) applications and websites.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.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: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and 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.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10132 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-11030*, and protocol #*10132.*
- 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.)

4.2.2 Requirements for *10132* Site Registration:

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

NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

4.2.3 Submitting Regulatory Documents

NCI CIRB Institutions: Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS. Sites will submit their IRB-approved local ICs and all future amended ICs to the CTSU Regulatory Office for tracking in RSS. The CTSU Regulatory Office will forward the IRB initial approval and accompanying local informed consent(s) to the Central Office (central office coordinator on protocol face page) for documentation purposes. This also applies to future amendment approvals.

Non-CIRB US Institutions: Submit model informed consent to the Central Office (central office coordinator on protocol face page) for **pre**-approval **prior** to submitting to your local IRB/REB. Once pre-approval is obtained, submit to your local IRB. Sites will submit their IRB/REB initial approval (accompanied by local IC); all future amendment approvals (accompanied by updated local IC if applicable); and continuing review approvals to the CTSU Regulatory Office for tracking in RSS. The CTSU Regulatory Office will forward the IRB initial approval and accompanying local informed consent to the Central Office (central office coordinator on protocol face page) for documentation purposes. This also applies to future amendment approvals.

Canadian Institutions: Submit model informed consent to the Central Office (central office coordinator on protocol face page) for **pre**-approval **prior** to submitting to your local IRB/REB. Once pre-approval is obtained, submit to your local IRB. Sites will submit their IRB/REB initial approval (accompanied by local IC); all future amendment approvals (accompanied by updated

local IC if applicable); and continuing review approvals to the PMP1C Central Office. The Central Office will submit copies of IRB approval documentation, ICs (and QIU and CTSI for Canadian sites) to the CTSU Regulatory Office for tracking in the RSS. This also applies to future amendment approvals.

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.

4.2.4 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

4.3.1 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.

- Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
- Central Office will receive notification via the IWRS when a slot has been reserved. An email will be sent from the Central Office to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION CHECKLIST and a copy of the signed consent to the Central Office for review and confirmation of eligibility.
- Once the Registration has been reviewed, the Central Office will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the Central Office will update the spot to 'reserved' in IWRS.
- The site can now enroll the patient into the study in OPEN

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

4.3.2 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.

4.3.3 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: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 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.

5. TREATMENT PLAN

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. 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.

5.1.1 AZD1775 administration

AZD1775 is an oral drug that should be ingested 2 hours before a meal or 2 hours after a meal. Capsules should not be broken, crushed or chewed. Missed doses should not be made up, resume dosing with the next scheduled dose. If vomiting occurs shortly after dosing, the dose should not be repeated. Patients will be instructed to bring all unused capsules and their medication diary (refer to Appendix D) to each study visit for assessment of compliance.

The study will have a dose escalation phase to determine the provisional recommended phase II dose. Once the recommended phase II dose is determined, a dose expansion will be performed. AZD1775 will be administered only during the first five weeks of treatment concurrently with external beam whole pelvis radiotherapy and concurrent cisplatin. It will not be continued beyond five weeks during brachytherapy or the delivery of additional external beam radiotherapy.

Dose Escalation

A cohort of 3 patients per dose level are planned:

- The starting dose will be dose level (DL) 1, AZD1775 will be administered on Day 1, 3, and 5 of each week
- If AZD1775 is tolerable at DL1 with no DLT experienced, 3 patients enter DL2.
- If AZD1775 is tolerable at DL2 with no DLT experienced, 3 patients enter DL3.
- If AZD1775 is tolerable at DL3 with no DLT experienced, 3 patients enter DL4 of which AZD1775 will be administered Day 1-5 of the week.

If the first 2 patients enrolled in a starting dose level (DL1) experience DLT, further enrollment

to that dose level will stop and a lower dose level will be explored. If the first 2 patients enrolled in the lower dose level (DL-1) experience DLT, further enrollment to that dose level will stop. The Principal Investigator will discuss with the sponsors regarding the appropriate next step.

If 1/3 patients encounters a dose-limiting toxicity (DLT), then the cohort will be expanded to 6 patients. If ≥2/6 of patients encounter DLT, then that dose level will be declared excessively toxic. A total of 6 patients will be entered into the previous dose level.

The recommended phase II dose (RPTD; also called the MTD) is defined as the dose level with ≤ 1/6 patients with DLT.

Dose Expansion

If excessive toxicity is not observed after exploring all dose levels, dose level 4 will be declared as the provisional RPTD. Then 12 additional patients will be enrolled (make up to a total of 15 patients).

If 1/3 patients encountered DLT, then the cohort will be expanded to 6 patients.

If ≤1/6 patients encountered DLT, that dose level is declared as the RPTD, and 9 additional patients will be enrolled (make up to a total of 15 patients).

If ≥2/6 of patients encounter DLT, then that dose level will be declared excessively toxic. Additional 3 patients will be entered into the lower dose level. If ≤1/6 patients at the lower dose level had DLT, then that level will be declared as the RPTD, and 9 additional patients will be enrolled (make up to a total of 15 patients).

Table 5-1: Dose Escalation Schedule

Dose Escalation Schedule			
Dose Level	**Dose***		
	Radiation[a] (fractions)	**Cisplatin[b] (weekly)**	**AZD1775 [c] Week 1-5**
Level -1	25 days	40 mg/m^2	100 mg, oral, QD day 3 and 5 of each week
Level 1	25 days	40 mg/m^2	100 mg, oral, QD day 1, 3, 5 of each week
Level 2	25 days	40 mg/m^2	150 mg, oral, QD day 1, 3, 5 of each week
Level 3	25 days	40 mg/m^2	200 mg, oral, QD day 1, 3, 5 of each week
Level 4	25 days	40 mg/m^2	200 mg, oral, QD day 1, 2, 3, 4, 5 of each week

[a] Radiation: External beam radiation (45-50 Gy) will be administered five days a week for five weeks.
[b] Cisplatin can be administered either on Monday or Wednesday once commenced on external beam radiation every week.
[c] AZD1775 will be administered on Monday, Wednesday and Friday of each week once commenced on external beam radiation every week.

5.1.2 Cisplatin

Cisplatin will be administered as an intravenous infusion at a dose of 40 mg/m^2 week. The time of infusion will be 1 hour ± 15min. The weekly dose should not exceed 70 mg. Five doses of cisplatin will be administered concomitantly with the external beam whole pelvis radiotherapy. Cisplatin will not be continued beyond five weeks during brachytherapy or the delivery of additional external beam pelvic radiotherapy.

5.1.3 Radiotherapy

All patients will receive whole pelvis external beam radiotherapy (EBRT) with concurrent cisplatin and AZD1775 for five consecutive weeks. Further radiotherapy may be delivered after five weeks, tailored to the specific disease site, without cisplatin or AZD1775.

Radiotherapy will adhere to the following general guidelines:

- Whole pelvis EBRT will be delivered in a uniform manner during the first five weeks of treatment using conformal, field-based techniques (four coplanar, orthogonal fields), intensity modulated radiation treatment (IMRT) or volumetric modulated arc treatment (VMAT).
- Patient management after the initial five weeks of EBRT/cisplatin/AZD1775 will vary depending on the patient cohort (cervix, upper vagina, uterus, recurrent disease) and treatment response, and may include surgery, brachytherapy, further external beam radiotherapy for residual pelvic disease, or no further treatment. To aid in interpreting

toxicity in this phase I study, detailed reporting of normal tissue radiation dosimetry will be required for the initial course of whole pelvis EBRT and for all subsequent radiotherapy courses (brachytherapy or further external beam radiotherapy) beyond five weeks. Radiotherapy after the initial five weeks will be delivered alone without concurrent cisplatin or AZD1775.

- Patient with newly diagnosed cervical cancer (cT1B-3B, N0/1, M0/1) or upper vaginal cancer (T1-3, N0/1, M0/1) will receive brachytherapy after whole pelvis EBRT/cisplatin/AZD1775 unless otherwise contraindicated.
- Patients with newly diagnosed, unresectable endometrial cancer should be re-evaluated for surgery after whole pelvis EBRT/cisplatin/AZD1775. If surgery is contraindicated, these patients should be considered for brachytherapy unless otherwise contraindicated.
- Patients with pelvic recurrences of cervical or endometrial cancer after previous surgery should be considered for brachytherapy (central pelvic recurrences), further external beam radiotherapy (pelvic sidewall recurrences) or both.

5.1.4 Whole Pelvis External Beam Radiotherapy

Whole pelvis EBRT will be delivered in a uniform manner during the first five weeks of treatment using conformal, field-based techniques (four coplanar, orthogonal fields), intensity modulated radiation treatment (IMRT) or volumetric modulated arc treatment (VMAT). Regardless of the treatment technique, the clinical target volume (CTV) and planning target volume (PTV) should be adequate to ensure coverage of clinical and subclinical primary tumor and lymph node disease extension accounting for inter- and intra-fractional target motion.

- Patients will undergo CT simulation for radiation treatment planning.
- Gross target volume (GTV) delineation: The GTV will encompass the gross primary tumor volume (GTVp), and any grossly enlarged pelvic lymph nodes (GTVn).
- Clinical target volume (CTV) delineation: The CTV will include the CTVp and the CTVn.
  - The CTVp will include the GTV, entire cervix, uterus, parametria and at least the upper half of the vagina, The lower third of the vagina should be included in the CTVp in patients with involvement of the upper vagina, at the discretion of the responsible radiation oncologist.
  - The CTVn will include the internal, external and distal common iliac lymph nodes, the upper pre-sacral lymph nodes anterior to the S1/2 vertebral bodies (CTVn) and the para-aortic lymph nodes (if clinically warranted, at the discretion of the responsible radiation oncologist). Refer to the RTOG GYN postoperative contouring atlas for lymph node delineation. The CTVn will be obtained by applying a 7 mm margin around the iliac vessels, plus extensions to include any adjacent visible lymph nodes. The presacral nodes will be contoured until the superior border of the S3 vertebral body is reached; below this point the nodal volume will be separated into two structures. The external iliac nodes will be contoured to the superior aspect of the femoral heads. The CTVn will be modified to exclude bone, muscle, and bowel.
- Organs at risk (OAR) delineation: The rectum, sigmoid, small bowel and bladder will be

delineated in all patients. Refer to the RTOG contouring atlas for normal female pelvic anatomy for OAR delineation.

- Rectum: The outer rectal wall will be contoured from the anus to the level of the sigmoid flexure.
- Sigmoid: The outer sigmoid wall will be contoured from where the rectum ends to the point of connection to the ascending colon laterally. Any sigmoid adjacent or above the uterus should be contoured.
- Small bowel: The peritoneal cavity will be contoured from the axial CT/MR slice 1 cm superior to the upper field border, and will continue to its most inferior extent in the pelvis. Individual loops of bowel should not be contoured separately. Rectum should be contoured separately from bowel.
- Bladder: The outer bladder wall in its entirety will be contoured.

- The external beam pelvic dose will be 45-50 Gy in 25 daily fractions of 1.8-2 Gy. Megavoltage radiotherapy (10 MV or greater) will be used. Treatment will be delivered daily, five fractions per week. The dose will be prescribed to an ICRU reference point in accordance with ICRU 62. All fields will be treated daily.
- Treatment verification using cone-beam CT imaging of soft tissue and bone anatomy will be performed daily on the treatment unit to ensure adequate target coverage and day-to-day reproducibility.
- EBRT dose reporting requirements: The absolute rectum, sigmoid, small bowel and bladder volumes (cm^3), and the percentages of the total delineated organ volumes, receiving ≥50% of the prescribed dose and ≥90% of the prescribed dose.

5.1.5 Brachytherapy

- Patient with newly diagnosed cervical cancer (cT1B-3B, N0/1, M0/1) or upper vaginal cancer (T1-3, N0/1, M0/1) will receive brachytherapy after whole pelvis EBRT/cisplatin/AZD1775, unless otherwise contraindicated. Patients with newly diagnosed, unresectable endometrial cancer may be considered for brachytherapy after whole pelvis EBRT/cisplatin/AZD1775 if the disease remains unresectable, unless otherwise contraindicated. Patients with central pelvic recurrences of cervical or endometrial cancer after previous surgery may be considered for brachytherapy after pelvic EBRT/cisplatin/AZD1775, unless otherwise contraindicated.
- Brachytherapy will begin after completion of whole pelvis EBRT/cisplatin/AZD1775 and will be delivered according to the usual practice at the treating institution. However, CT or MR imaging of the pelvis after placement of the brachytherapy applicator(s) with delineation of OARs and reporting of OAR doses must be done to aid in interpreting acute and late toxicity in this phase I study.
- For patients with newly diagnosed cervical, upper vaginal or endometrial cancer, brachytherapy typically will be delivered using an intrauterine applicator with a vaginal ring or ovoids. An intrauterine applicator with a vaginal cylinder may be necessary to encompass vaginal disease. Soft tissue imaging (trans-abdominal ultrasound, CT or MR) will be performed with each insertion to confirm correct positioning of the intrauterine applicator. Treatment planning (including estimation of doses to OARs) will be based on

pelvic CT and/or MR obtained after placement of the applicator. A conventional 2D dose prescription (ICRU 38 Point A) or optimized 3D volumetric planning (GEC-ESTRO recommendations or equivalent) will be allowed. The use of interstitial needles, in addition to an intrauterine/intra-vaginal applicator, is encouraged when required to assure optimal target coverage and dosimetric sparing of OARs. Treatment may be delivered using either a pulsed dose rate (PDR) or high dose rate (HDR) techniques.

- Organs at risk (OAR) delineation for brachytherapy: The rectum, sigmoid, small bowel and bladder will be delineated in all patients using axial CT and/or MR images acquired after each brachytherapy applicator insertion. OAR delineation will conform to GEC-ESTRO (or equivalent) recommendations.
  - Rectum: The outer rectal wall will be contoured from the anus to the level of the sigmoid flexure.
  - Sigmoid: The outer sigmoid wall will be contoured from where the rectum ends to the point of connection to the ascending colon laterally. Any sigmoid adjacent or above the uterus should be contoured.
  - Small bowel: The outer wall of individual small bowel loops within 3-4cm of the uterus or applicator will be contoured.
  - Bladder: The outer bladder wall in its entirety will be contoured.
- Brachytherapy reporting requirements: The following brachytherapy technique and dosimetric parameters will be reported:
  - Brachytherapy technique (PDR, HDR)
  - Total brachytherapy dose and total number of fractions
  - The ICRU 38 rectal and bladder reference point doses for each treatment fraction
  - The absolute brachytherapy dose to the maximally irradiated 2 cm^3 of rectum, sigmoid, bladder and small bowel ($D2cm^3$) for each treatment fraction

5.1.6 External Beam Pelvic Boost Radiotherapy for Residual Disease

Further external beam radiotherapy may be used at the discretion of the responsible radiation oncologist to treat residual pelvic disease not amenable to brachytherapy after the initial five weeks of whole pelvis EBRT/cisplatin/AZD1775. This may include persistently enlarged pelvic lymph nodes in patients with newly diagnosed cervical, upper vaginal or endometrial cancer, or persistent central pelvic or pelvic sidewall disease in patients with recurrence of cervical or endometrial cancer. Highly conformal IMRT or VMAT plans are encouraged to minimize the dose to adjacent OARs and potential for acute and late toxicity. The planning target volume (PTV) should be adequate to account for inter- and intra-fractional target motion.

- Organs at risk (OAR) delineation for external beam pelvic boost radiotherapy: OAR delineation for pelvic boost radiotherapy will adhere to the same guidelines as for whole pelvis EBRT:
  - Rectum: The outer rectal wall will be contoured from the anus to the level of the sigmoid flexure.
  - Sigmoid: The outer sigmoid wall will be contoured from where the rectum ends to the point of connection to the ascending colon laterally. Any sigmoid adjacent or above the uterus should be contoured.
  - Small bowel: The peritoneal cavity will be contoured from the axial CT/MR slice 1

cm superior to the upper field border, and will continue to its most inferior extent in the pelvis. Individual loops of bowel should not be contoured separately. Rectum should be contoured separately from bowel.

- Bladder: The outer bladder wall in its entirety will be contoured.

- External beam pelvic boost radiotherapy dose reporting requirements:
  - External beam pelvic boost total dose and total number of fractions
  - The absolute rectum, sigmoid, small bowel and bladder volumes (cm^3), and the percentages of the total delineated organ volumes, receiving ≥50% of the prescribed dose and ≥90% of the prescribed dose

Table 5-2: Regimen description

Regimen Description for dose level 1-3					
Agent	***Premedication; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
AZD1775	5-HT3 antagonist such as ondansetron 8mg PO daily or granisetron (Kytril) 1mg PO daily prior to AZD1775 on days not receiving cisplatin	** capsule	Oral	Once a day Day 1, 3, 5 of the week for 5 weeks	*42-56 days*
Cisplatin	IV hydration, antiemetic and steroid prophylaxis pre-medication as per institutional protocol	Infusion time: 1hour Dilute in 500 ml Normal Saline	IV	Once a week for 5 weeks (day 1 or 3)	
Radiotherapy					
External Beam Whole Pelvis Radiotherapy				5 days a week (ideally Monday to Friday) for 5 weeks	
Additional treatment (surgery, brachytherapy or additional pelvic radiotherapy) depending on patient cohort and initial response to radiation/cisplatin/AZD1775				Beginning week 6	
***Doses as appropriate for assigned dose level. Ondansetron can be substituted by any other 5HT3 inhibitor at equivalent doses if ondansetron is not available*					

Regimen Description for dose level 4					
Agent	***Premedication; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
AZD1775	5-HT3 antagonist such as ondansetron 8mg PO daily or granisetron (Kytril) 1mg PO daily prior to AZD1775 on days not receiving cisplatin	200mg capsule	Oral	once a day for 5 days a week (Mon-Fri) for 5 weeks	*42-56 days*
Cisplatin	IV hydration, antiemetic and steroid prophylaxis pre-medication as per institutional protocol	Infusion time: 1 hour Dilute in 500 ml Normal Saline	IV	once a week for 5 weeks	
Radiotherapy					
External Beam Whole Pelvis Radiotherapy				5 days a week (ideally Monday to Friday) for 5 weeks	
Additional treatment (surgery, brachytherapy or additional pelvic radiotherapy) depending on patient cohort and initial response to radiation/cisplatin/AZD1775				Beginning week 6	
Ondansetron can be substituted by any other 5HT3 inhibitor at equivalent doses if ondansetron is not available					

5.2 Definition of Dose-Limiting Toxicity

The dose limiting toxicity period will be considered from week 1 until the end of week 5 +7 days upon completing the chemo-radiation portion of the treatment. All patients evaluable for toxicity will be assessed for DLT. The following treatment related toxicities will be considered Dose-Limiting Toxicities (DLTs)[1]

5.2.1 Hematologic DLT

- Grade 4 thrombocytopenia (platelet count <25 x 10^9/L)
- Grade 3 thrombocytopenia (platelet count 25-49 x 10^9/L) with bleeding
- Grade 3 Febrile neutropenia (ANC <1.0 x 10^9/L with a single temperature of >38.3º C or ANC <1.0 x 10^9/L with a sustained temperature of ≥38 ºC for more than one hour).

5.2.2 Non-hematologic DLT

- Grade 4 vomiting, or grade 3 vomiting if persistent for longer than 48 hours despite treatment with granisetron, ondansetron or an equivalent medication.
- Grade 4 diarrhea, or grade 3 diarrhea if persistent for longer than 48 hours despite treatment with loperamide, diphenoxylate/atropine or an equivalent medication.
- Grade 3 or 4 rash
- Other grade 3 or 4 radiotherapy associated acute toxicity
- Interruption of whole pelvis radiotherapy for more than 3 days due to acute treatment toxicity
- Inability to receive at least 3 of the 5 planned doses of cisplatin
- If the patient requires an omission longer than 1 week in the administration of AZD1775 and/or cisplatin
- Any grade 3 or 4 non-hematological toxicity with the specific exception of:
    - Nausea, vomiting, diarrhea, or dehydration (all Grade 3) not optimally treated and/or lasts less than 48 hours.
    - Alopecia (of any grade)
    - Inadequately treated hypersensitivity reactions
    - Clinically non-significant, treatable or reversible lab abnormalities including, but not limited to liver function tests, uric acid, hypokalemia or hypomagnesemia.

  [Note: reversible G3 and G4 electrolyte disturbances will be considered those that improve, at least to G2, within 48h when optimally treated]

[1] An adverse event or any delay not related to the study medication will not be considered DLT

Management and dose modifications associated with the above adverse events are outlined in Section 6. Dose escalation will proceed within each cohort according to Table 5-3. Dose-limiting toxicity (DLT) is defined above in Section 5.2.

Table 5-3: Dose escalation schema

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. Once the provisional recommended phase 2 dose is found, 9-12* patients will be enrolled in the expansion cohort to confirm the safety of this dose. *The final number of patients evaluated at the recommended phase 2 dose will be 15: • If 3 patients have been previously enrolled during the dose escalation phase, 12 additional patients will be evaluated in the dose expansion phase • If 6 patients have been previously enrolled during the dose escalation phase, 9 additional patients will be enrolled in the dose escalation

5.3 General Concomitant Medication and Supportive Care Guidelines

Patients will be followed jointly during treatment by medical and radiation oncologists. General supportive care will be provided in accordance with local institutional practice. Anti-emetic and anti-diarrheal medications will be prescribed as clinically required. CBC, electrolytes, renal function studies and liver function studies will be done weekly prior to administration of cisplatin, as per routine practice. The Principal Investigator should be alerted if the patient is taking any agent known to affect QTcF prolongation. Appendix F presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.4 Duration of therapy

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

- Disease progression (clinical or radiological)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Dose limiting toxicity (see Section 5.2)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.5 Duration of follow up

Once the treatment with AZD1775 is completed, patients will have an end of treatment visit 28 days ± 7 days after their last dose of AZD1775. After that, they will be followed to evaluate toxicity or disease relapse every 4 months (± 2 weeks) for 2 years, until any of the criteria mentioned in section 5.6 apply. Patients removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for removal from study

Patient will be removed from the study when any of the following criteria listed below applies:

- Disease progression (clinical or radiological)
- Patient death
- Patient withdraws consent
- 2-year follow up complete
- Termination of study by Principal Investigator, Sponsor, or Regulatory Authorities

The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Doses of cisplatin and AZD1775 will be reduced for hematological and non-hematological toxicities. The NCI Clinical Trials Common Terminology Criteria for Adverse Events (CTCAE) will be used to grade toxicity (http://ctep.info.nih.gov/).

6.1 Dose delays/interruptions

- No more than two AZD1775 or one cisplatin dose reduction for toxicity will be permitted. If the toxicity persists despite the reductions, the patient will be removed from the trial.
- Patients will be removed from the protocol therapy for:
- Any acute toxicity that persists despite two AZD1775 or one cisplatin dose reduction

- Any acute toxicity requiring a delay in cisplatin, AZD1775 and/or radiotherapy > 2 weeks, unless approved by the Principal Investigator or Senior Protocol Investigator.
- Any acute Grade 4 non-hematological toxicity
- For electrolyte disturbances, patients will be discontinued if the electrolyte abnormality persists more than 48 hours despite optimal treatment
- Patients removed from the trial because of acute toxicity will continue treatment for cervix cancer with either radiotherapy alone or RT-CT, at the discretion of the responsible medical and radiation oncologists.
- RT is the primary therapeutic modality in this treatment regimen. There will be no delays or modifications to the planned course of radiotherapy except in exceptional circumstances, at the discretion of the treating radiation oncologist, where acute toxicity persists after appropriate cisplatin and/or AZD1775 dose reductions. For toxicity dose modifications, or delays, AZD1775 will be modified first, followed by cisplatin. Radiation will be maintained on schedule if possible. If a situation arises where dose modification or delay is necessary and not captured by the dose adjustment criteria, the decision on dose adjustment will be made by the Senior Scientific Investigator and Principal Investigator and documented.
- In case of grade 3 non-hematological DLTs or any hematological DLTs, treatment could be resumed if the toxicity is resolved to:
    - Grade 2 if the DLT was radiotherapy-induced dermatitis.
    - Tolerable grade 2 (in areas not included in the radiotherapy volume)
    - Grade 1 or baseline for the remaining DLT toxicities

  The treatment will be resumed with appropriate dose reduction(s) of the study drugs as described in section 6.2
- An exception would be made for the following grade 4 non-hematological toxicities, classically associated to cisplatin treatment after which cisplatin will be permanently discontinued, but AZD1775 could be resumed following the criteria in Table 6-9.
    - Grade 4 tinnitus
    - Grade 3 and 4 hearing loss
    - Grade 3 and 4 neurotoxicity
- In case of hematological toxicities that do not fulfill DLT criteria, but require a delay on cisplatin treatment according to our administration guidelines (grade 3 neutropenia, grade 4 neutropenia less than 7 days, grade 1 or 2 thrombocytopenia or grade 3 thrombocytopenia without bleeding), treatment with AZD1775 will be withheld. Treatment will be resumed if platelets are ≥100 x10e9/L and absolute neutrophil count is ≥1.0 x10e9/L.
- If a patient experiences several toxicities and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

6.2 Dose modifications

6.2.1 AZD1775 dose levels

Table 6-1: AZD1775 dose levels

Dose Level	Dose*
	AZD1775 ***Week 1-5 (mg)***
Level -1	100 mg, oral, QD day 3 and 5 of the week
Level 1	100 mg, oral, QD day 1, 3, 5 of the week
Level 2	150 mg, oral, QD day 1, 3, 5 of the week
Level 3	200 mg, oral, QD day 1, 3, 5 of the week
Level 4	200 mg, oral, QD day 1,2,3,4,5 of the week

6.2.2 Cisplatin dose levels

Table 6-2: Cisplatin dose levels

Dose Level	Cisplatin Dose
Reduced dose	*30 mg/m^2*
Standard dose	*40 mg/m^2*

Note: the "Reduced dose" is one dose level below the "standard dose"

6.2.3 Dose modifications for hematological toxicities

[redacted]

6.2.4 [redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
	[redacted]	[redacted]
	[redacted]	
	[redacted]	[redacted]
[redacted]		
[redacted]		

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[redacted]	[redacted]	[redacted]
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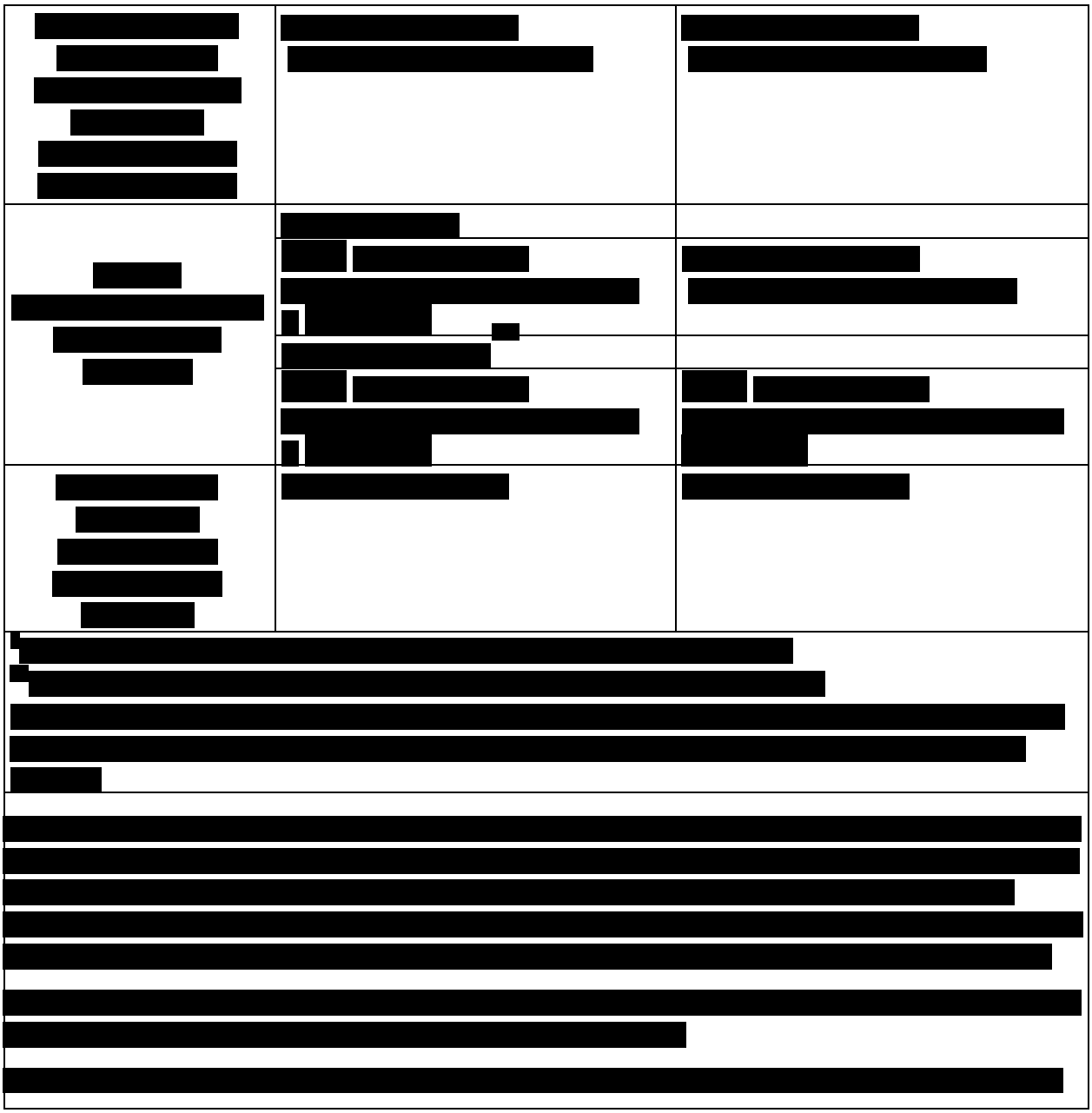

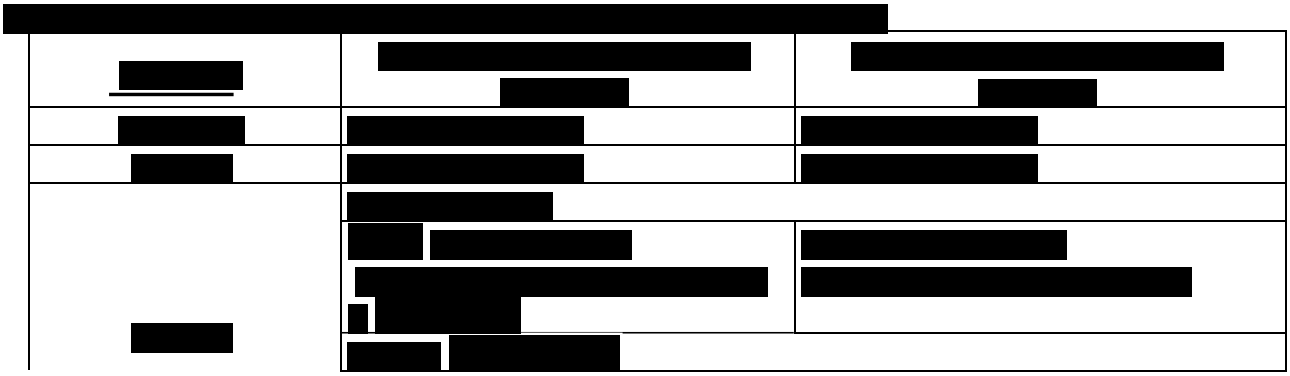

[redacted]

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 CTEP-AERS) in addition to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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).

7.1.1 CAEPRs for AZD1775

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

Version 2.7, April 27, 2020[1]

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

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

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by

contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Blood and lymphatic system disorders - Other (right leg deep vein thrombosis); Leukocytosis
Cardiac disorders - Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Ear pain; Hearing impaired; Tinnitus
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (eye swelling); Eye pain; Keratitis; Photophobia; Scleral disorder; Vision decreased; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Belching; Bloating; Cheilitis; Colitis; Colonic obstruction; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Flatulence; Gastric ulcer; Gastritis; Hemorrhoids; Oral pain; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema trunk; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation; Malaise; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)
INVESTIGATIONS - Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased

METABOLISM AND NUTRITION DISORDERS - Alkalosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Bone pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (carcinoid tumor); Tumor pain
NERVOUS SYSTEM DISORDERS - Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Paresthesia; Peripheral neuropathy[5]; Presyncope; Somnolence; Syncope
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression
RENAL AND URINARY DISORDERS - Acute kidney injury[6]; Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Reproductive system and breast disorders - Other (female genital tract fistula)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Apnea; Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin ulceration; Urticaria
VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event

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

7.1.2 Adverse Event List(s) for Cisplatin

Organ Site	Side Effect	Onset			
Auditory	Hearing impaired (31%)			D	
	Tinnitus (9%, usually reversible)			D	
	Vertigo			D	
Cardiovascular	Arterial thromboembolism		E		
	Conduction disorder (left bundle branch block, rare)	I	E		
Dermatological	Alopecia		E		
	Rash	I	E		
Gastrointestinal	Anorexia	I	E		

	Nausea, vomiting (100%) (early and delayed)	I	E		
	Diarrhea		E		
Hematological	Hemolysis (Coombs positive)		E		
	Myelosupression +/- infection, bleeding (30%)		E		
	Thrombotic microangiopathy		E		
	Hemolytic uremic syndrome		E		
Liver/Pancreas	Increased amylase		E		
	Increased LFTs (transient, rare)		E		
Metabolic/Endocrine	Abnormal electrolytes (diminished K, Na, Ca, Mg, PO4)		E		
	Increased antidiuretic hormone		E		
	Hyperuricemia (36%)	I	E		
Musculoskeletal	Muscle cramps		E		
Neoplastic	Leukemia (secondary)				L
Nervous System	Dysgeusia		E		
	Neurotoxicity (peripheral, autonomic)			D	
	Other (dorsal column myelopathy-rare)			D	
	Seizure (rare)			D	
	Encephalopathy (rare)		E	D	
Ophthalmic	Optic neuritis			D	
Renal	Nephrotoxicity (36%)	I	E		
Reproductive	Infertility				L
Respiratory	Hiccups		E		
Vascular	Peripheral ischemia (Raynaud's syndrome-rare)			D	
	Vasculitis (cerebral arteritis-rare)		E		
Hypersensitivity	Hypersensitivity	I			
Injection site	Injection site reaction (rare)	I			

I: Immediate; E: early; D: delayed; L: late From CCO monograph

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 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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 agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- Other AEs for the protocol that do not require expedited reporting are outlined

in section 7.1.

- **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 (http://ctep.cancer.gov). 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). These requirements are briefly outlined in the tables below (Section 7.3.1).

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.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. Each site will submit the electronic version of the CTEP-AERS report to the PMH Consortium Central Office. Once review by the lead group coordinator has taken place the report will be forwarded to NCI. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.1 Expedited Reporting Guidelines

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided. Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions. 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.

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

In order to ensure the timely fulfillment of both US and Canadian IND regulatory reporting requirements, all CTEP-AERS reports must be sent to the Central Office within 3 working days from the date the event was known to the investigator.

In the unlikely event that an adverse event occurs that does not meet the reporting requirements for CTEP-AERS, but does meet the definition of a Serious Adverse Event, a CTEP-AERS report must still be completed and sent to the Central Office within 3 working days of the event being known to the investigator. The event must be telephoned or e-mailed to Central Office within 1 working day.

The Central Office will be responsible for reporting to Canadian regulatory authorities all Serious Adverse Events that are both unexpected and related to study drug. The Central Office will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials as reported to the Central Office by the NCI U.S.

Investigators must notify their local Research Ethics Boards (REB/IRBs), according to their guidelines, of all SAE reports from their centre and file the report in their regulatory study binder. In addition, all reports sent out to centres by the PMH Central Office must be sent to local REB/IRBs, according to their guidelines. Documentation from the REB/IRB of receipt of these reportable events must be kept on file in each institution's regulatory binder.

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

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

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

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

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

7.3.2 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not applicable

7.4 Routine Adverse Event Reporting

All Treatment Emergent Adverse Events (TEAEs) must be reported in routine study data submissions. TEAEs reported through CTEP-AERS must also be reported in routine study data submissions.

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiotherapy or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

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 reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agent administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent

8.1.1 AZD1775

Chemical Name: 2-allyl-1-[6-(1-hydroxy-1-methyl-ethyl)-2-pyridyl]-6-[4-(4-methylpiperazin-1-yl)anilino]pyrazolo[3,4-d]pyrimidin-3-one hemihydrate

Other Names: MK-1775, Adavosertib

Classification*:* inhibitor of Wee1-kinase

CAS: 1277170-60-1

Molecular Formula: $C_{27}H_{32}N_8O_2 \cdot 0.5H_2O$ **M.W.:** 500.6

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, hemihydrate form of the drug substance.

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. [redacted]

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 two hours before a meal or two hours after a meal. Capsules should not be opened.

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 coadministered with P-gp and BCRP inhibitors/inducers, and there is potential for drug-drug interactions when coadministered with OATP1B1, OATP1B3, MATE1, MATE2K, P-gp and BCRP substrates. This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP- mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of atorvastatin when

coadministered with AZD1775 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. Women of child-bearing potential participating in clinical studies of AZD1775 must use appropriate contraception throughout the study including abstinence and double barrier methods throughout treatment. Refer to the specific protocol for more details about appropriate contraceptive methods and duration of use.

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 the DCTD, NCI (see Section 12.2).

8.1.2 Agent Ordering, Accountability, and Investigator Brochure Availability

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 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 agent received from the PMB using the NCI Investigational Agent (Drug) Accountability Record Form (DARF) for Oral Agents 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.

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

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- 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)

8.2 Cisplatin (NSC #119875)

Cisplatin is an antineoplastic agent. Please refer to the product monograph for the information regarding possible side effects and instructions, regarding formulation, preparation, handling, dosing, shelf life and storage. It will be administered at a dose of 40 mg/m^2 intravenously in 500 mL of NS. The weekly dose should not exceed 70 mg.

Product description: Commercially available supplies of cisplatin injection, 1 mg/mL.

Solution preparation: Dilute in 500 mL Normal Saline. Also see product monograph.

Route of administration: Intravenous infusion over 1 hour. Give 500 mL NS hydration post-each weekly cisplatin

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies Archival tissue

Paraffin embedded archival blocks are preferred. However, if blocks cannot be released, 20 unstained slides 4-5 microns each mounted on positively charged slides are also acceptable. An exploratory analysis of WEE1 expression by immunohistochemistry (IHC) will be performed in the archival specimens of all patients. An exploratory evaluation of the

following potential baseline predictors of response will be performed in the archival tissue if available:

- Immunohistochemistry: p53, p21, p16, Rb
- Molecular profiling using the Hi5 Panel (555 gene, including TP53 – CLIA lab Dr. Suzanne Kamel Reid) which includes the most relevant genes involved in the pathogenesis of these types of cancer (Appendix F)
- PCR–RFLP for detection and typing of HPV DNA

Please note that if blocks are provided, they will be returned to the sender at the end of the study.

If no tissue is available for this analysis, the baseline biopsy (optional) will be used for the evaluation of these biomarkers (see priority of determination in Table 9-1 at the end of this section)

9.2 Pre- and on-Treatment Fresh Tumor Tissues

Fresh tumor tissues will be collected on 2 occasions only if there is no medical contraindication:

- **Within 2 weeks prior to day 1 (Biopsy # 1)**
- **On day 2-5 post first dose of AZD1775 administered in week 1 or 2 (Biopsy # 2)**

Fresh tumor biopsies are optional. Inability to obtain fresh tumor biopsies will not render the patient ineligible to participate in the study.

Tru-cut biopsy or 14-gauge (or institutional standard) core biopsy should be performed using standard surgical techniques. If possible, 3-4 cores should be obtained at each biopsy. Labeled screw-cap cryovials, a flask of liquid nitrogen, and formalin-filled specimen containers should be brought to the room where the core biopsy is to be performed.

The disposition of the 3-4 core specimens is as follows:

1. One to two core specimen(s) should be immediately immersed in formalin for fixation and then paraffin-embedded. The following evaluations will be performed at the STTARR Spatio Temporal Targeting Lab.

a) Protein expression by immunohistochemistry: formalin fixed paraffin-embedded (FFPE) sections of tumor biopsies will be examined by four-colour immunofluorescence using DAPI to outline individual nuclei for cell by cell analysis. Tissue sections will be scanned using a multilaser scanning platform. Acquired digital images will be analyzed using semi-automated protocols developed in the Definitens Tissue Studio 3.5 semi-automatic histology image analysis platform which uses a “learn by example” algorithm to delineate and analyze regions of interest (ROI) across a sample set, scoring different parameters to allow for elucidation of co- localization relationships.

Note: Stability of analytes in FFPE
Protocols for histological staining of all of the proposed markers (apart from WEE1 and pCDC2) have already been optimized and are in common use at our institution for research purposes; good staining in FFPE samples has been demonstrated.

The following exploratory biomarkers will be assessed, but not limited to:

- WEE1 expression (baseline sample)
- pCDC2 to evaluate target engagement (baseline and on-treatment sample)
- Ki67 to investigate changes in proliferation (baseline and on-treatment sample)
- γH2AX to evaluate ds DNA damage (baseline and on-treatment sample)
- phospho-histone H3 (pH3) to delineate specific activity in S-phase vs at G2/M1 checkpoint (baseline and on-treatment biopsy)
- Cleaved caspase-3 (CC3) to evaluate apoptosis (baseline and on-treatment biopsy)

b) If the available archival tumor is not enough for the determination of p53, p21, p16 and Rb, the determination of these biomarkers will be assessed by immunohistochemistry in the baseline biopsy if patient agrees for biopsy and tissue is available.

2. One to two core specimens should be immediately transferred from the core biopsy needle directly into cryovials and embedded in O.C.T. This should then be immediately frozen in liquid nitrogen. Samples should be stored in liquid nitrogen or in a -70°C freezer. If not enough tissue available in the archival specimen, the following evaluations will be performed in these samples:
   - PCR–RFLP for detection and typing of HPV DNA (baseline)

3. In the expansion cohort one core will be immediately transferred from the core biopsy needle directly into cryovials and embedded in O.C.T. This should then be immediately frozen in liquid nitrogen. Samples should be stored in liquid nitrogen or in a -70°C freezer. Determination of AZD1775 levels in the fresh biopsy on treatment will be performed. Based on the availability of tissue, the biomarker evaluation will be performed according to the priority established in Table 9-1:

Table 9-1**:** Priority for correlative studies based on tissue availability

Priority	Assay	Sample
1	WEE1, pCDC2 and γH2AX expression	FFPE (paired)
2	Hi5 Panel molecular profiling	FFPE (archival)*
3	pH3 and CC3 expression	FFPE (paired)
4	p53, p21, p16 and Rb expression	FFPE (archival)*

5	HPV DNA determination	FFPE archival*

*If no tissue available in the archival tissue, the analysis will be performed on the baseline biopsy: p53, p21, p16, and Rb on FFPE and p53 sequencing on fresh frozen.

9.2.1 Sample Shipment

Archival samples, paraffin-embedded samples and fresh frozen biopsy for biomarker analysis For shipment of samples between facilities, fresh tumor biopsy samples that have been frozen should be sent in dry ice. Frozen samples should be buried in a large quantity of dry ice in a styrofoam container and shipped by overnight Fedex. The person shipping the samples should contact the recipient before the package is sent to ensure that the package will be handled appropriately upon arrival, and provide a Fedex tracking number.

Archival samples and paraffin-embedded samples should be sent at ambient temperature. Both kinds of specimens should be shipped to the Princess Margaret Cancer Centre Consortium at the Princess Margaret Cancer Centre (see below). Samples should only be shipped on a Monday, Tuesday or Wednesday. Samples and inventory sheet must be shipped by overnight delivery in a Styrofoam container and packaged in dry ice to ensure that they remain frozen. Shipment must be scheduled for a Monday, Tuesday or Wednesday only.

Archival and fresh tumor specimens should be shipped to:
Vanessa Speers
Correlative Studies Program
Princess Margaret Cancer Centre
610 University Avenue, Rm 7-420
Toronto, Ontario M5G 2M9
Tel: (416) 946-4501 ext 5047
Fax: (416) 946-4431
Email: Vanessa.Speers@uhn.ca

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 21 days prior to day 1, unless otherwise indicated. Scans and x-rays must be done ≤28 days prior to the start of therapy (day1). 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. All assessments can be performed up to 2 days in advance of the calendar specified timepoint.

	Pre-Study	D1	D8	D15	D22	D29	D36-43 (+12d window)	End of Treatment (28±7 days after last dose of AZD1775)	Follow-up [k]	Off Study
AZD1775[a]		X----------X [a]								
Cisplatin [b]		X----------X [b]								
Radiotherapy [c]		X----------X [c]					X [c]			
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X----------X								
Physical exam	X	X [l]	X	X	X	X		X	X	X
Vital signs	X	X	X	X	X	X		X	X	X
ECOG Performance Status	X	X [l]	X	X	X	X	X	X		
Height	X									
Weight	X	X	X	X	X	X		X	X	X
CBC w/diff, plts [d]	X	X [l]	X	X	X	X	X[n]	X	X	X
Serum chemistry [d,e]	X	X [l]	X	X	X	X	X[n]	X	X	X
Creatinine clearance [p]	X	X	X	X	X	X	X	X	X	X
Coagulation tests [d]	X									
ECG	X	X	X	X	X	X	X	X	X	X[g]
Adverse event evaluation [d]		X----------X								X
Tumor measurements [f]	X							X	X[h]	X
Chest CT, CT abdomen/pelvis, MR pelvis [d]	X							X	X[h]	X
Vaginal Exam[d]	X									
B-HCG [i]	X									
Archival tissue collection [o]	X									
Optional Tumor biopsy	X[j]	X[j]								
Assessment for Disease Progression [q]									X	X

a: AZD1775: as per dose level and schedule. Refer to Table 5-1 and Section 5.1.1
b: Cisplatin: 40 mg/m^2 IV administered over 1 hour, starting on Day 1 or 3, then weekly for a total of 5 consecutive weeks during radiotherapy. Refer to Table 5-1 and Section 5.1.2
c: Radiotherapy: 45-50 Gy external beam pelvic radiotherapy in 25 fractions, followed by brachytherapy. Refer to Table 5-1 and Section 5.1.3
d: Routine investigations for all patients with cervix cancer, uterine cancer and vaginal cancer, regardless of study participation
e: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
f: RECIST 1.1 measurements to be done using the same imaging modality for all scans at pre-study, end of treatment, 4 months after completion of radiation therapy and if patients come off study within 4 months after planned treatment.
g: To be repeated in the off-study visit in those patients with cardiac history or with clinically significant alterations in the baseline ECG.
h: Tumor measurements will be performed at radiological assessment 4 months after completion of radiotherapy. Follow-up imaging can be performed at other time points at the discretion of local investigator or standard of care at local practice. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
i: Serum pregnancy test (women of childbearing potential).
j: Optional Tumor biopsy will be performed within 2 weeks prior to day 1 and on week 1 or 2 of treatment. Refer to Section 9.2 and Table 9-1
k: Follow up assessments: every 4 months ±15 days after the End of Treatment visit, up to 2 years.
l: If completed within 7 days prior to day 1 it does not need to be repeated on day 1.
m : Only for patients who do not already have radiologically documented progression.
n: Safety blood work assessment will be performed before starting brachytherapy.
o: Collection of primary archival tissue block will be initiated at baseline.
p: Creatinine clearance will be calculated by the Cockcroft-Gault method.
q: Can be documented clinically or radiologically as per local investigator discretion.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, response rate and progression free survival are secondary endpoints. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated on every 4 months (± 15 days) of the post-treatment period for 2 years.

11.1 Antitumor Effect – Solid Tumors

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) [Eur J Ca 45:228-247, 2009]. 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.

11.1.1 Definitions

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

Evaluable for objective response. The patients will be assessed for response according to the local investigator.

11.1.2 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 by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). 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 or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non- cystic

lesions are present in the same patient, these are preferred for selection as target lesions.

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, 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.

11.1.3 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 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 or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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.

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.

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.

11.1.4 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.

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

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

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 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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD

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.

** As response rate is not the primary endpoint of the study, no confirmatory imaging evaluation is required.

*** 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.

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

11.1.5 Duration of Response

Duration of response will be assessed in patients with measurable disease.

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.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death,

whichever occurs first. Patients without an event will be censored at the end of 2 year follow-up.

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.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

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

12.2.1 Method

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.

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 three times annually (one annual site visit and two data audits). 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.

12.2.2 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 1 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 March 1, 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, as above.

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 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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Objectives

To determine the recommended phase II dose (RP2D) and safety profile of AZD1775 in combination with radiotherapy and concurrent cisplatin patients with gynecological cancer (phase I).

The proportion of patients who experience DLT will be recorded for all patients in dose escalation and dose expansion. Because toxicities can be cumulative, the proportion of patients evaluable for toxicity requiring treatment discontinuation or dose reduction/interruption at any time through the duration of therapy will also be recorded.

The first dose level will be level 1. If 1/3 patients encounter a dose-limiting toxicity (DLT), then a cohort will be expanded to 6 patients. If > 2/3 of patients encounters DLT, then that dose level will be declared excessively toxic. A total of 6 patients will be entered into the previous dose level. The recommended phase II dose (RPTD; also called the MTD) is defined as the dose level with < 1/6 patients with DLT.

13.1.2 Secondary Objectives

- To evaluate the pharmacodynamic effects of AZD1775 drugs when administered in combination with radiotherapy and concurrent cisplatin (in particular, for the 15 patients treated in an expansion cohort at the RP2D). Pharmacodynamic biomarkers will include: pCDC2, Ki67, γH2AX, pH3, and CC3.
- To obtain preliminary information about the progression–free survival of AZD1775 in combination with radiotherapy and concurrent cisplatin in women with locally advanced gynecological cancer.

- To determine the acute and late toxicity of AZD1775 when administered to patients with gynecological cancer in combination with radiotherapy and concurrent cisplatin.

13.2 Sample Size/Accrual Rate

A minimum of 9 patients and a maximum of 33 will be enrolled in this phase I study. A maximum of 24 patients for initial dose finding part and additional 9-12 patients for the expansion cohort will be enrolled. We estimate accrual as follows: 1-2 patients for dose finding per month and 1-2 patients for expansion cohort per month. Estimated study duration is 20-24 months.

13.3 Analysis of Secondary Endpoints

13.3.1 Clinical Endpoints

Summary statistics, such as the mean, median, counts and proportion, will be used to describe patients' clinical characteristics. Objective response to treatment will be assessed according to local investigator.

Predictors of clinical outcomes will be investigated using logistic regression, Cox proportional hazards regression and/or generalized estimating equations as appropriate. Potential predictors include clinical predictors and molecular correlates. Descriptive statistics and plotting of data will also be used to better understand potential relationships.

Frequency and severity of adverse events will be tabulated using counts and proportions detailing frequently occurring, serious and severe events of interest. Adverse events will be summarized using all adverse events experienced, although a subanalysis may be conducted including only those adverse events in which the treating physician deems possibly, probably or definitely attributable to one or both study treatments.

All analyses will be considered exploratory and inference will be performed with appropriate caution. For all statistical tests, two-sided tests will be performed and no p- value adjustment performed due to the exploratory nature of these tests. A p-value of 0.05 or less will be considered statistically significant.

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66. Rash may include rash, erythema, eczema, and rash maculo-papular.,

67. Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy.,

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

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

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

THESE ARE THE THINGS THAT YOU AS A PRESCRIBER NEED TO KNOW:

AZD1775 interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are ***CYP 3A4 and 2C19.*** AZD1775 is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce these enzymes. AZD1775 is an inhibitor of CYP 3A4 and 2C19 and may affect the metabolism of other drugs.
- The proteins in question are ***OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP.*** AZD1775 is a substrate of P-gp and BCRP and may be affected by other drugs that inhibit or induce these transporters. AZD1775 is an inhibitor of OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP and may affect transport of other drugs in and out of cells.

<u>TO THE PATIENT:</u> 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, remember the following:

- Include medicine you buy without a prescription (over-the-counter remedy)
- Include herbal supplements such as St. John's Wort
- It is helpful to bring your medication bottles or an updated medication list with you

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

THESE ARE THE THINGS THAT YOU AND THEY NEED TO KNOW:

AZD1775 must be used very carefully with other medicines that need certain **liver enzymes or transport proteins to be effective or to be cleared from your system.** 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 **CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, 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.
- 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. **AZD1775** 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 **CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP**, and must be used very carefully with other medicines that interact with these enzymes and 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 considered **"strong inducers/inhibitors or substrates of CYP 3A4, 2C19, OATP1B1, OATP1B3, MATE1, MATE2K, P-gp, and BCRP"**
- Before prescribing new medicines, your regular prescribers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _

  and can be contacted at_____.

APPENDIX C DATA MANAGEMENT GUIDELINES

Case Report Form Submission Schedule

Data required for the study will be collected in Case Report Forms provided by the PMH Consortium Central Office. The site will be required to complete a paper Registration Checklist at the time of patient registration. All other data will be collected on electronic case report forms (eCRFs) in the Medidata Rave system. Site staff access to Medidata Rave will be initiated at the time of site activation. The form submission schedule is outlined below.

Case Report Form	Submission Schedule
Eligibility Checklist	At the time of registration
Baseline eCRFs	Within 2 weeks of on study date
On Treatment (Cycle) eCRFs	Within 7 days of each visit
Off Treatment eCRFs	Within 2 weeks of the patient coming off-study
Short Follow-up eCRFs	Within 3 weeks of the patient coming to clinic.
Final eCRFs	Within 3 weeks from the follow-up period being complete or of the patient's death being known to the investigator unless this constitutes a reportable adverse event when it should be reported according to CTEP-AERS guidelines

Case Report Form Completion

The paper Eligibility Checklist CRF must be completed using black ink. Any errors must be crossed out so that the original entry is still visible, the correction clearly indicated and then initialed and dated by the individual making the correction.

eCRFs will be completed according to the schedule noted above and all relevant supporting documentation such as scans, progress notes, nursing notes, blood work, pathology reports, etc., will be submitted to the PMH Consortium Central Office for review. All patient names or other identifying information will be removed prior to being sent to the Central Office and the documents labeled with patient initials, study number and the protocol number.

eCRF completion guidelines are available for all sites.

Monitoring

Refer to Section 12.1 of the protocol

Patient Registration

- Refer to section 4 of the protocol

Data Safety

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study to see if there are unexpected or more serious side effects than described in the consent.

Regulatory Requirements

- Please submit all required documents to the Central Office.
- Canadian Principal Investigators must submit a completed Qualified Investigator Undertaking.
- All investigators must have a current NCI investigator number on file with the Central Office.
- All investigators must have an up-to-date CV (signed within 2 years) on file with the Central Office.
- Laboratory certification/accreditation and normal ranges are required
- Confirmation of all investigators having undergone training in the Protection of Human Research Subjects is required. It is preferred that other staff involved in the trial also undergoes such training.
- Investigators and site staff are required to complete Medidata eCRF training modules depending on delegated tasks
- OPRR assurance numbers for each institution are required
- Consent forms must be reviewed by the Central Office before submission to the local ethics regulatory board (REB/IRB) and must include a statement that 1) information will be sent to and 2) medical records will be reviewed by the Central Office.
- A Membership list of the local ethics board is required.
- A copy of the initial approval letter from the ethics board must be submitted to the Central Office.
- A completed Site Participant List/Training Log is required and must be submitted to the Central Office
- Continuing approval will be obtained at least yearly until follow-up on patients is completed and no further data is being obtained for research purposes.

APPENDIX D PATIENT DIARY TEMPLATE

STUDY: PHL-087 / NCI #10132

SUBJECT ID:

CYCLE #:

INSTRUCTIONS – Dose Level 1,2,3

For this cycle you will take _____25 mg, _____100 mg, and _____200 mg AZD1775 capsule(s) on the days indicated (_____mg total dose)

How to take the study drug capsule(s):

1. Take study drug capsules on days indicated below (blank areas of the diary). On these days, take the capsule(s) once a day, 2 hours before or 2 hours after food.
2. Swallow each capsule whole. Do not open or chew the capsule(s).
3. If you miss any of the doses or you vomit one of the capsule(s), do not take any extra dose, and call your study doctor.

Using this diary:

1. Record the date and time you took the AZD1775 capsule(s).
2. Record any comments if you notice any side effects in the "Comments" column.
3. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.
4. Please bring this form at each clinic visit.

Day	Date	Time (24hr format)	Total AZD1775 Dose (mg)	Comments
1				
2				
3				
4				
5				
6				
7				
8				

9				
10				
11				
12				
13				
14				
15				
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Physician's Office will complete this section:

The above information has been reviewed with the patient.

Physician/Nurse Signature: _____ Date: _____

STUDY: PHL-087 / NCI #10132

SUBJECT ID:

CYCLE #:

INSTRUCTIONS – Dose Level 4

For this cycle you will take _____25 mg, _____100 mg, and _____200 mg AZD1775 capsule(s) on the days indicated (_____mg total dose)

How to take the study drug capsule(s):

1. Take study drug capsules on days indicated below (blank areas of the diary). On these days, take the capsule(s) once a day, 2 hours before or 2 hours after food.
2. Swallow each capsule whole. Do not open or chew the capsule(s).
3. If you miss any of the doses or you vomit one of the capsule(s), do not take any extra dose, and call your study doctor.

Using this diary:

1. Record the date and time you took the AZD1775 capsule(s).
2. Record any comments if you notice any side effects in the "Comments" column.
3. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.
4. Please bring this form at each clinic visit.

Day	Date	Time (24hr format)	Total AZD1775 Dose (mg)	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				

10				
11				
12				
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Physician's Office will complete this section:

The above information has been reviewed with the patient.

Physician/Nurse Signature: _____ Date: _____

STUDY: PHL-087 / NCI #10132

SUBJECT ID:

CYCLE #:

INSTRUCTIONS – Dose Level -1

For this cycle you will take _____25 mg, _____100 mg, and _____200 mg AZD1775 capsule(s) on the days indicated (_____mg total dose)

How to take the study drug capsule(s):

1. Take study drug capsules on days indicated below (blank areas of the diary). On these days, take the capsule(s) once a day, 2 hours before or 2 hours after food.
2. Swallow each capsule whole. Do not open or chew the capsule(s).
3. If you miss any of the doses or you vomit one of the capsule(s), do not take any extra dose, and call your study doctor.

Using this diary:

1. Record the date and time you took the AZD1775 capsule(s).
2. Record any comments if you notice any side effects in the "Comments" column.
3. In case of errors, please place a single slash mark through the error and initial it. Please do not white out any error or scribble it out with ink. Please do not write the correct information directly over the error, but on a separate line next to the error.
4. Please bring this form at each clinic visit.

Day	Date	Time (24hr format)	Total AZD1775 Dose (mg)	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				

10				
11				
12				
13				
14				
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Physician's Office will complete this section:

The above information has been reviewed with the patient.

Physician/Nurse Signature: _____ Date: _____

APPENDIX E HI5 PANEL

Somatic Mutation Genes (555)

ABL1	CCND1	EPHA5	GNA11	LPP	NOTCH1	RAD21	SUZ12
ABL2	CCND2	EPHA7	GNA13	LRP1B	NOTCH2	RAD50	SYK
ACTG1	CCND3	EPHB1	GNAI3	LTF	NOTCH4	RAD51	SYNE1
ACVR2A	CCNE1	EPHB4	GNAQ	LTK	NPM1	RAD51C	SYT1
ADAMTS20	CD74	EPHB6	GNAS	MAF	NRAS	RAD51D	TAF1
AFF1	CD79A	ERBB2	GPR124	MAFB	NSD1	RAF1	TAF1L
AFF3	CD79B	ERBB3	GPS2	MAGEA1	NTRK1	RALGDS	TAL1
AKAP9	CDC73	ERBB4	GRIN2A	MAGI1	NTRK2	RARA	TBX22
AKT1	CDH1	ERCC1	GRM8	MALT1	NTRK3	RB1	TCF12
AKT2	CDH11	ERCC2	GSK3B	MAML2	NUMA1	RBM15	TCF3
AKT3	CDH2	ERCC3	GUCY1A2	MAP2K1	NUP214	RECQL4	TCF7L1
ALK	CDH20	ERCC4	HCAR1	MAP2K2	NUP93	REL	TCF7L2
AMER1	CDH23	ERCC5	HGF	MAP2K4	NUP98	RET	TCL1A
ANKRD24	CDH5	ERG	HIF1A	MAP3K1	PAK3	RHOH	TERT
APC	CDK12	ESR1	HIST1H1E	MAP3K7	PALB2	RICTOR	TET1
AR	CDK4	ETS1	HLF	MAPK1	PARP1	RNASEL	TET2
ARAF	CDK6	ETV1	HNF1A	MAPK8	PAX3	RNF2	TFE3
ARFGAP3	CDK8	ETV4	HNRNPK	MARK1	PAX5	RNF213	TGFB1
ARFRP1	CDKN1B	ETV5	HOOK3	MARK4	PAX7	RNF43	TGFBR2
ARID1A	CDKN2A	ETV6	HOXB13	MBD1	PAX8	ROS1	TGM7
ARID2	CDKN2B	EWSR1	HRAS	MCL1	PBRM1	RPL22	THBS1
ARNT	CDKN2C	EXT1	HSP90AA1	MDM2	PBX1	RPN1	TIMP3
ASPSCR1	CEBPA	EXT2	HSP90AB1	MDM4	PCDHAC2	RPS6KA2	TLR2
ASXL1	CHEK1	EZH2	ICK	MECOM	PDE4DIP	RPTOR	TLR4
ATF1	CHEK2	EZR	ID3	MED12	PDGFB	RRM1	TLX1
ATM	CHIC2	FAM175A	IDH1	MEF2B	PDGFRA	RUNX1	TMEM216
ATR	CIC	FAM46C	IDH2	MEN1	PDGFRB	RUNX1T1	TMPRSS2
ATRX	CKS1B	FAM5C	IGF1R	MET	PDK1	SAMD9	TNFAIP3
AURKA	CMPK1	FANCA	IGF2	MITF	PER1	SBDS	TNFRSF14
AURKB	COL1A1	FANCC	IGF2R	MKL1	PGAP3	SDHA	TNK2
AURKC	CRBN	FANCD2	IKBKB	MLF1	PHF6	SDHB	TOP1
AXL	CREB1	FANCE	IKBKE	MLH1	PHLPP2	SDHC	TP53
B2M	CREB3L2	FANCF	IKZF1	MLH3	PHOX2B	SDHD	TPM3
BAI3	CREBBP	FANCG	IL2	MLLT1	PIK3C2B	SEPT9	TPR
BAP1	CRKL	FANCL	IL21R	MLLT10	PIK3C3	SETBP1	TRAF3
BARD1	CRLF2	FAS	IL3	MLLT3	PIK3CA	SETD2	TRIM24
BCL10	CRTC1	FBXW7	IL6ST	MLLT4	PIK3CB	SF3B1	TRIM33
BCL11A	CSF1R	FGF10	IL7R	MMP2	PIK3CD	SGK1	TRIP11
BCL11B	CSF3R	FGF14	ING4	MN1	PIK3CG	SH2B3	TRRAP
BCL2	CSMD3	FGF19	INHBA	MNX1	PIK3R1	SH2D1A	TSC1
BCL2L1	CSNK2B	FGF23	INPP4B	MPL	PIK3R2	SMAD2	TSC2

BCL2L2	CTCF	FGF3	IRF4	MRE11A	PIM1	SMAD4	TSHR
BCL3	CTDNEP1	FGF4	IRF8	MSH2	PKD1L2	SMARCA4	TYK2
BCL6	CTNNA1	FGF6	IRS2	MSH6	PKHD1	SMARCB1	U2AF1
BCL9	CTNNB1	FGFR1	ITGA10	MTOR	PLAG1	SMC1A	UBR5
BCOR	CUL3	FGFR2	ITGA9	MTR	PLCG1	SMC3	UGT1A1
BCORL1	CYLD	FGFR3	ITGB2	MTRR	PLCG2	SMO	UMODL1
BCR	CYP2C19	FGFR4	ITGB3	MUC1	PLEKHG5	SMUG1	USP9X
BIRC2	CYP2D6	FH	JAK1	MUTYH	PML	SNX31	VHL
BIRC3	DAXX	FIP1L1	JAK2	MYB	PMS1	SOCS1	WAS
BIRC5	DCC	FLCN	JAK3	MYC	PMS2	SOCS3	WHSC1
BLM	DDB2	FLI1	JUN	MYCL	POT1	SOX10	WISP3
BLNK	DDIT3	FLT1	KAT6A	MYCN	POU5F1	SOX11	WRN
BMPR1A	DDR2	FLT3	KAT6B	MYD88	PPARG	SOX2	WT1
BOD1L1	DDX3X	FLT4	KDM5A	MYH11	PPP2R1A	SP140	XPA
BRAF	DEK	FN1	KDM5C	MYH9	PPP6C	SPEN	XPC
BRCA1	DICER1	FOXA1	KDM6A	NBN	PRCC	SPI1	XPO1
BRCA2	DIS3	FOXL2	KDR	NCOA1	PRDM1	SPOP	XRCC2
BRD3	DNAH9	FOXO1	KEAP1	NCOA2	PRDM16	SRC	ZMYM2
BRIP1	DNMT3A	FOXO3	KIT	NCOA4	PREX2	SRSF2	ZNF217
BTK	DOT1L	FOXP1	KLF6	NCOR2	PRKAR1A	SS18L1	ZNF384
BUB1B	DPYD	FOXP4	KLHL6	NF1	PRKDC	SSX1	ZNF521
C11orf30	DST	FUS	KMT2A	NF2	PSIP1	SSX2	ZNF703
CACNA1E	EGFR	FZR1	KMT2C	NFE2L2	PTCH1	SSX4	ZRSR2
CALR	EGR1	G6PD	KMT2D	NFKB1	PTEN	STAG2	ZSWIM4
CARD11	EML4	GATA1	KRAS	NFKB2	PTGS2	STAT3	
CASC5	EP300	GATA2	LAMP1	NFKBIA	PTPN11	STAT4	
CASP8	EP400	GATA3	LCK	NIN	PTPRD	STK11	
CBFB	EPCAM	GDNF	LIFR	NKX2-1	PTPRT	STK36	
CBL	EPHA3	GID4	LPHN3	NLRP1	RAC1	SUFU	

Translocation genes (78)

ABL1	CCND1	ETV6	IL3	MLLT3	PBX1	ROS1	TFE3
AFF1	CD74	EWSR1	MAF	MLLT4	PDGFB	RPN1	TMPRSS2
ALK	CHIC2	EZR	MALT1	MNX1	PDGFRA	RUNX1	TPM3
ASPSCR1	COL1A1	FGFR1	MAML2	MYC	PDGFRB	RUNX1T1	WT1
ATF1	CREB3L2	FGFR3	MECOM	MYH11	PML	SS18L1	ZMYM2
BCL2	CRTC1	FIP1L1	MKL1	NPM1	PPARG	SSX1	IGL
BCL6	DDIT3	FLI1	MLF1	NUP214	PRCC	SSX2	IGK
BCR	DEK	FOXO1	MLL	PAX3	PRDM16	SSX4	IGH
BIRC3	EML4	FUS	MLLT1	PAX7	RARA	SYT1	
CBFB	ERG	HLF	MLLT10	PAX8	RBM15	TCF3	

APPENDIX F TABLE OF DRUGS WITH A KNOWN RISK OF QT PROLONGATION/ TORSADES DE POINTES

Amiodarone
Anagrelide
Arsenic trioxide
Astemizole
Azithromycin
Bepridil
Chloroquine
Chlorpromazine
Cilostazol
Ciprofloxacin
Cisapride
Citalopram
Clarithromycin
Cocaine
Disopyramide
Dofetilide
Domperidone
Donepezil
Dronedarone
Droperidol
Erythromycin
Escitalopram
Flecainide
Fluconazole
Gatifloxacin
Grepafloxacin
Halofantrine
Haloperidol
Ibogaine
Ibutilide
Levofloxacin
Levomepromazine
Levomethadyl acetate
Levosulpiride
Mesoridazine
Methadone
Moxifloxacin
Ondansetron
Oxaliplatin
Papaverine HCl (Intra-coronary)
Pentamidine
Pimozide
Probucol
Procainamide
Propofol
Quinidine
Roxithromycin
Sevoflurane
Sotalol
Sparfloxacin
Sulpiride
Sultopride
Terfenadine
Terlipressin
Terodiline
Thioridazine
Vandetanib

NOTE: The table above may not be exhaustive, and investigators should refer to a frequently updated medical reference for the most current information. This list was obtained from www.crediblemeds.org and accessed on 09Jun2017.

APPENDIX G DOSIMETRIC PARAMETERS FOR RADIOTHERAPY POST END OF TREATMENT FOR PATIENTS WHO HAD BRACHYTHERAPY AND EBRT PELVIC BOOST

Instructions: If patient completed more than 4 fractions of brachytherapy, print multiple pages as necessary. Once radiotherapy is completed, send a copy of the form to Central Office Coordinator.

Radiation Treatment Summary

	Total Dose	# of Fractions	Start Date	End Date
Whole Pelvis EBRT				
Brachytherapy				
EBRT Pelvic Boost				

Whole Pelvic EBRT & EBRT Pelvic Boost (if applicable) Dosimetric Parameters

Whole Pelvis EBRT	Percentage ≥50%	Percentage ≥90%	Absolute value ≥50%	Absolute value ≥90%
Rectum				
Bladder				
Sigmoid				
Small Bowel				

EBRT Pelvic Boost	Percentage ≥50%	Percentage ≥90%	Absolute value ≥50%	Absolute value ≥90%
Rectum				
Bladder				
Sigmoid				
Small Bowel				

Brachytherapy (if applicable) Dosimetric Parameters

	Rectum D2cc	Bladder D2cc	Sigmoid D2cc	Small Bowel D2cc
Fraction 1				
Fraction 2				
Fraction 3				
Fraction 4				

Investigator Signature: _____