October 18, 2016

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #3 to EA2131, *A Phase I and Randomized Phase II Study of Nab-Paclitaxel/Gemcitabine with or without AZD1775 for Treatment of Metastatic Adenocarcinoma of the Pancreas.* This amendment is in response to CTEP's Request for Rapid Amendment on September 23, 2016 from Dr. Naoko Takebe.

The following revisions to EA2131 protocol have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated Version Date
2.	Section 5.1	Replaced CAEPR with updated Version 2.4 dated August 3, 2016

The following revisions to EA2131 Informed Consent Document have been made in this addendum:

	Section	**Change**
1.	Phase I Cover Page	Updated Version Date
2.	Phase I Risk Section	Updated Risk List based on new CAEPR Version 2.4 dated August 3, 2016
3.	Phase II Cover Page	Updated Version Date
4.	Phase II Risk Section	Updated Risk List based on new CAEPR Version 2.4 dated August 3, 2016

If you have any questions regarding this addendum, please contact spiers.madeline@jimmy.harvard.edu or 857-504-2900

We request review and approval of this addendum to EA2131 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Protocol Development Manager

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Enclosure

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA2131

A Phase I and Randomized Phase II Study of Nab-Paclitaxel/Gemcitabine with or without AZD1775 for Treatment of Metastatic Adenocarcinoma of the Pancreas

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Version Date: October 18, 2016
NCI Update Date: June 26, 2014

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Phase II – US Sites only
FDG Imaging Studies –ACRIN Qualified Institutions
(See Section 10)
FLT Imaging Studies – Limited Institutions:
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ACTIVATION DATE
June 26, 2014
Update #1 – Incorporated Prior to Activation
Addendum #1 – 7/14
Addendum #2 – 4/16
Addendum #3 – 11/16

Agents	NSC#	Supply
Gemcitabine	NSC#613327	Commercially Available
Nab-Paclitaxel	NSC#736631	Commercially Available
AZD1775	NSC#751084	NCI-Supplied
18F-FLT	NSC#743144	Commercially Available
18F-FDG	NSC#723398	Commercially Available

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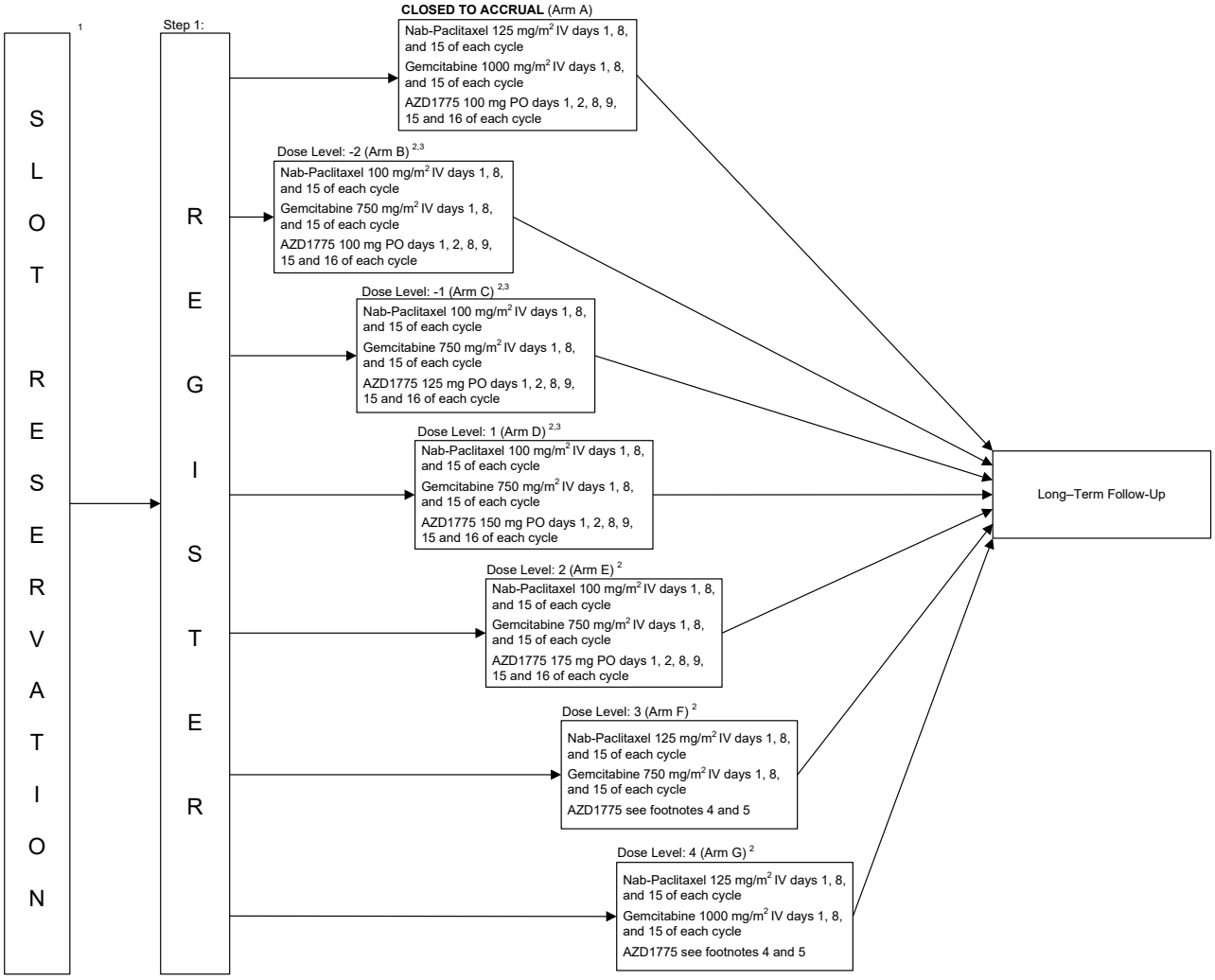
Phase I Schema

Phase I will follow a traditional 3+3 design.



Phase I Accrual Goal = Maximum of 50 patients
IV doses are based on actual weight.
Cycle = 4 weeks (28 days)

1. Slot registration is required prior to beginning eligibility verification. Only after a slot has been reserved should the patient be worked up for the study. Slots will automatically EXPIRE after 10 days. If the patient is found to be ineligible, the site must withdraw the slot.
2. Patients will be evaluated during each cycle for toxicity. Treatment will continue until progression or unacceptable toxicity. See Section 5.6.
3. If no dose limiting toxicity (DLT) is encountered on the first 3-6 patients enrolled, then 3 more patients will be treated with the combination at the next higher Phase I AZD1775 dose. If there is 1 DLT among the first 3 patients, then 3 more patients will be enrolled at that same dose. See Section 9.3.1.
4. If AZD1775 150 mg is the highest achievable dose – Arm D – (DLTs observed in Arm E), proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using the highest tolerated AZD1775 dose.
5. If AZD1775 175 mg is achievable in Arm E, proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using AZD1775 175 mg. If unacceptable toxicity is observed with AZD1775 175 mg in either Arm F or Arm G, each/either of these dose levels may be reassessed (Arm F 150, Arm G 150) using AZD1775 150 mg.

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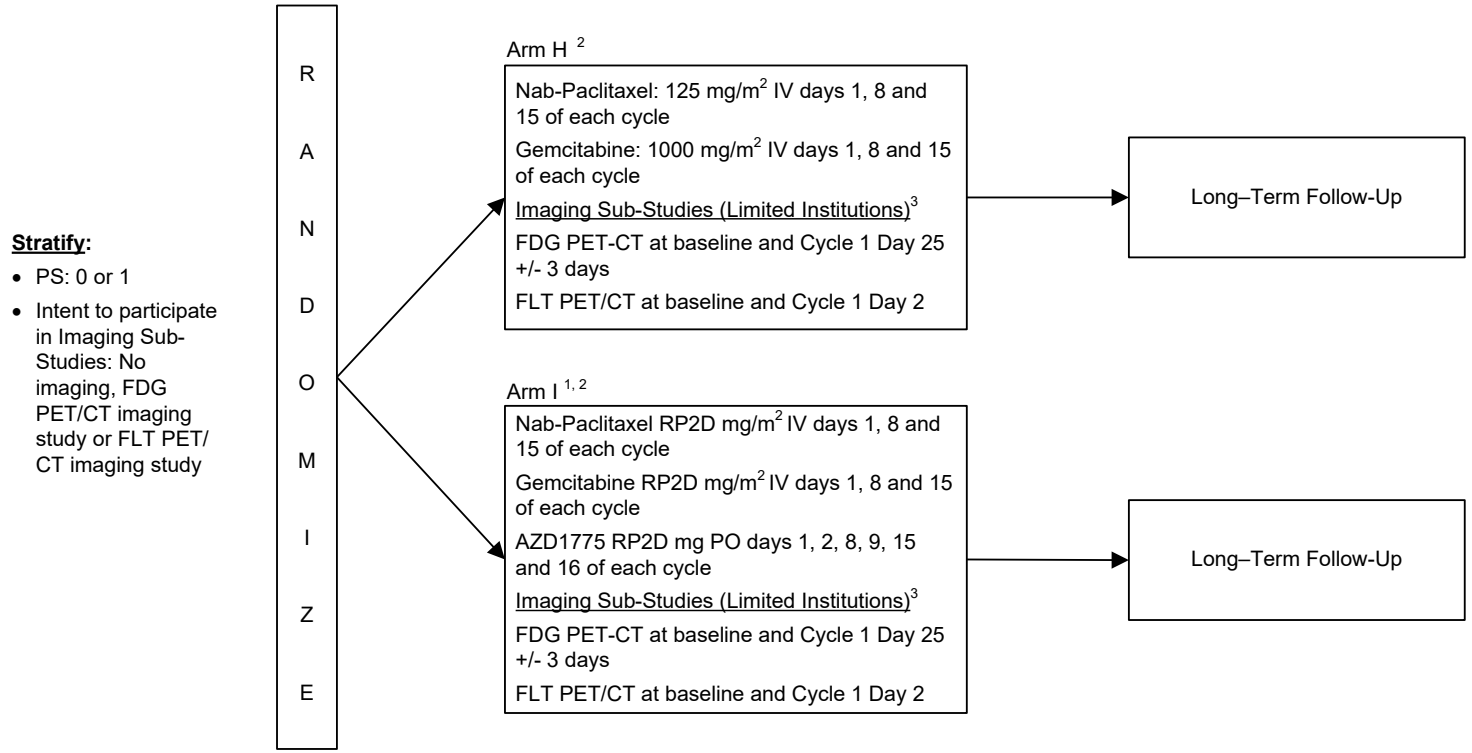
Phase II Schema



Phase II Accrual Goal = 84 patients
Phase II Imaging Sub-Study Accrual Goals:
FDG PET/CT = 60 patients (30 in each Arm)
FLT PET/CT = 10 patients (5 in each Arm)
Cycle = 4 weeks (28 days)
IV doses are based on actual weight.

1. Nab-Paclitaxel, Gemcitabine, and AZD1775 dose for patients on Arm I of the Phase II to be determined in the Phase I portion of the study.
2. Treatment will continue until progression or unacceptable toxicity. See Section 5.6.
3. FDG PET/CT open to ACRIN qualified institutions. FLT PET/CT open to limited institutions. FLT PET/CT at Cycle 1 Day 2 must be performed 20-24 hours after Cycle 1 initiation. FDG PET/CT at Cycle 1 Day 25 may be performed +/- 3 days, but must be before Cycle 2 initiation. Patients may not participate in both the FDG PET/CT and FLT PET/CT imaging studies. See Section 10 for more information.

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1. Introduction

1.1 Adenocarcinoma of the Pancreas

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer mortality in the United States with approximately 45,220 new cases and 38,460 deaths in 2013.[1] PDAC is rarely curable and patients with advanced disease have an overall survival rate of < 1% at 5-years, with most patients dying within 1 year. Therefore, there is a strong need for more effective systemic therapy in this devastating disease.

1.2 Systemic Therapy in Metastatic Pancreatic Ductal Adenocarcinoma

Gemcitabine is the only approved single agent in treatment of metastatic PDAC, with a median survival of 5.7 months and 20% 1-year survival.[2] It is a pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase and is cell cycle-specific for the S-phase of the cycle (also blocks cellular progression at G1/S phase). A recent meta-analysis of randomized trials showed a general survival benefit for gemcitabine-based chemotherapies for patients with good performance status.[3] Unfortunately, the current standard gemcitabine and gemcitabine-based regimens only have moderate activity.

Recently, results of the MPACT study, a randomized phase III study of Nab-Paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic PDAC, showed significant overall survival benefit with Nab-Paclitaxel and gemcitabine over gemcitabine alone (8.5 months vs. 6.7 months, HR 0.72, p=0.000015).[5] The combination treatment was well-tolerated and has become a new standard of care option for first-line treatment of metastatic PDAC. The selection of Nab-Paclitaxel, a 130-nm albumin-bound formulation of paclitaxel particles (Abraxane, Celgene, Summit, NJ), in combination with the standard gemcitabine was based on a molecular profiling of PDAC tumor samples,[5] in which secreted protein acidic and rich in cysteine (SPARC), an albumin-binding protein, was noted to be overexpressed.[7] Nab-Paclitaxel has shown antitumor activity in various advanced cancer types that overexpress SPARC[8-10] including breast,[11-13] lung[4,14] and melanoma.[15]

1.3 The Cell Cycle, DNA Damage Checkpoints, and Wee1 Signaling

Treatment efficacy of DNA damaging agents is determined not only by the amount of therapy-induced DNA damage but also by the capacity of tumor cells to repair the damaged DNA. When cells are treated with DNA damaging agents, multiple checkpoints in the cell cycle are activated, including G1, intra-S, and G2/M, leading to cell cycle arrest, thus providing time for the cell to repair the damage and to evade apoptosis before resuming the cell cycle. Tumor cells can exploit these repair mechanisms in response to DNA damaging agents, rendering tumors resistant to current therapeutic interventions. Therefore, abrogation of checkpoint function may drive tumor cells toward apoptosis and enhance the efficacy of anti-neoplastic agents.

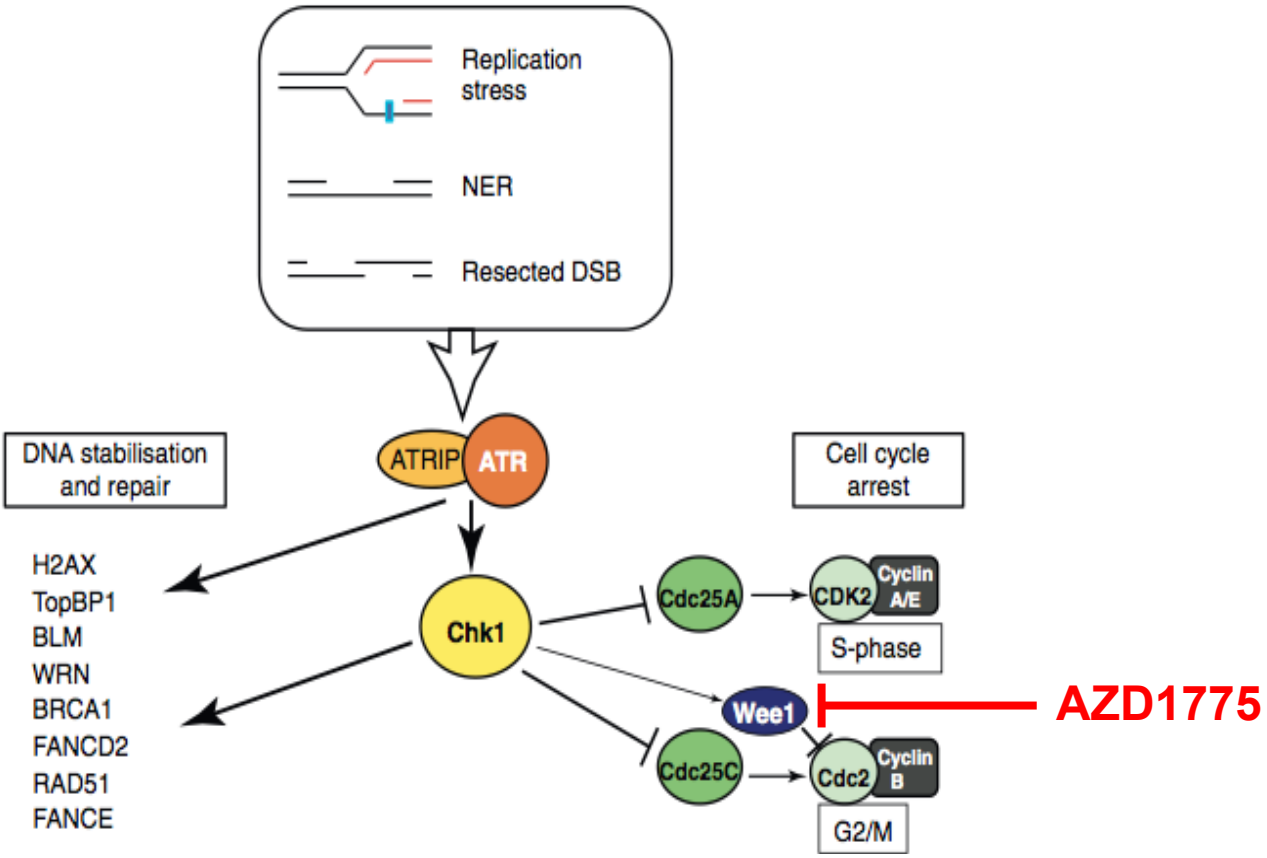
The cell cycle is a series of events that take place in a cell which leads to its division and replication. Checkpoints are biological stoplights which delay cells from transitioning from one cell cycle phase to the next when there is genotoxic

and replicative stress. The three key checkpoints in the cell cycle are: G1, S- and G2/M checkpoints. The G1 checkpoint is regulated by p53. Checkpoint 1 (Chk1) is a serine/threonine kinase which regulates the S- and G2/M checkpoints. Wee1 is an atypical tyrosine kinase which regulates the G2/M checkpoint. Wee1 inactivates Cdc2 through selective phosphorylation of its Tyr15 residue and consequently leads to G2 arrest that gives tumor cells survival advantage by allowing time to repair their damaged DNA.[16] Wee1 has also been shown to be a regulator of genomic stability during S-phase in protection against replication stress-associated DNA breakage.[17] It was shown that Wee1 depletion by siRNA transfection rapidly induces DNA damage in S-phase in replicating areas, which is accompanied by a marked accumulation of ssDNA. Similar to effects of Chk1 inhibition, these deleterious S-phase effects of Wee1 depletion are highly dependent on CDK activity.[18]

1.4 AZD1775 (Wee1 inhibitor)

AZD1775, previously known as MK-1775, is an oral, small molecule inhibitor of the Wee1 kinase with high potency, selectivity and oral bioavailability.[19] It exerts its mechanism of action by inhibiting Wee1 and thus phosphorylation of Cdc2Tyr15.20 (Figure 1)

Figure 1: DNA damage and Wee1 (Adapted from Chen et al.[21])



1.4.1 In Vitro Studies of AZD1775

AZD1775in combination with gemcitabine inhibited phosphorylation of $Cdc2^{Tyr15}$ by 50% at a concentration of 81.87 ± 17.04 nM (EC_{50}; the concentration causing 50% effect), as well as induced the G2 checkpoint escape (EC_{50} of 84.09 ± 9.1 nM) in the p53-deficient human colon adenocarcinoma cell line, WiDr.[19, 22] [redacted]

1.4.2 In Vivo Studies of AZD1775

AZD1775 (10 mg/kg) administered orally (PO) once a week, 24 hours following gemcitabine (5 mg/kg intravenously [IV]) for 3 weeks, significantly enhanced the anti-tumor effect of gemcitabine in the WiDr (p53-deficient human colon adenocarcinoma) tumor nude rat xenograft model (measured 1 week after the third dose). [redacted] Target modulation was assessed by Western blotting and immunohistochemistry. Single agent AZD1775 treatment produced greater than 50% inhibition of tumor growth in 2 xenografts (PANC286, p53 wild-type xenograft and PANC198, p53 mutated xenograft). However, 5 of 9 xenografts treated with gemcitabine and 6 of 9 xenografts treated with gemcitabine plus AZD1775 produced complete tumor growth inhibition and in fact resulted in tumor shrinkage compared to control, suggesting that the combination should be further tested.[23] Combination of gemcitabine and AZD1775 resulted in greater than 50% regression of initial tumor volume in 4 of 6 xenografts (66.66%) with p53-deficient status.[23] All five combinations of AZD1775 (gemcitabine, carboplatin, cisplatin, capecitabine, and 5-FU) were well tolerated at the active dose levels demonstrating minimal weight reduction. Moderate but transient reduction in white blood cells and platelet counts compared to untreated controls were observed after treatment with AZD1775 in combination with gemcitabine, carboplatin, and cisplatin. [redacted]

1.4.3 Pharmacokinetics of AZD1775

AZD1775 (1 µM) was moderately bound to plasma proteins from rat, dog, and human, with the unbound fractions being 23.2, 40.0, and 39.5%, respectively. [redacted] The major metabolic pathway of AZD1775 in human liver preparations was oxidative metabolism. [redacted]

[redacted] All metabolites observed in human liver preparations were also formed in vivo in the rat and dog. Oxidative metabolism of AZD1775 was mediated predominantly by cytochrome P450 3A4 (CYP3A4) and flavin-containing monooxygenase 3 (FMO3). [redacted] In addition, AZD1775 was a time-dependent inhibitor of CYP3A4. [redacted] Pending additional data, moderate and strong inhibitors or inducers of CYP3A4, including aprepitant, are excluded in clinical trials. [redacted]

1.4.4 Pharmacology and Toxicology of AZD1775

[redacted] Only minimal effects on blood pressure (-5%) and heart rate (-5%) were observed at the 10 mg/kg dose. [redacted] AZD1775 partially reversibly inhibited the human ether-a-go-go-related gene (hERG) current with an IC_{50} value of 6.9 μM in whole-cell voltage clamp studies. The maximum plasma concentration (C_{max}) of AZD1775 at 325 mg which likely exceed the combination dose, is less than 1 μM. Taking into account the effect of human plasma protein binding (~60%), this provides a significant margin to anticipated clinical exposures. [redacted]

[redacted] A 15-day PO toxicity study was conducted in rats dosed at 30, 100, or 300 mg/kg, once weekly, on study Days 1, 8, and 15. [redacted] The magnitude of absolute reticulocyte counts and WBC parameters observed after the first dose were generally similar to those after the third dose, indicating that additive toxicity was not seen after 3 weekly intermittent doses. [redacted] Reproductive toxicity studies have not been performed. [redacted]

[redacted]

1.4.5 Clinical Development of AZD1775

[redacted] The monotherapy portion of study PN001 is currently closed, as pre-defined in the protocol. In this portion of the study, a single dose of AZD1775 up to 1300 mg as monotherapy was generally well tolerated without DLTs. [redacted] To date, AZD1775 has been sufficiently well tolerated to permit further evaluations, including evaluations of longer dosing regimens, and evaluations of regimens combining the compound with standard doses of two chemotherapeutic agents.

[redacted]

The single-dose MTD for both the gemcitabine and cisplatin combination therapies is 200 mg of AZD1775.[19, 24] DLTs tended to be hematological in nature in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD for the combination with carboplatin was 325 mg of AZD1775. DLTs in this group were related to serum chemistry.[19, 24]

[redacted] An attenuated QD for 2 days schedule in combination with gemcitabine is currently enrolling. Two DLTs have been observed to date with this regimen, which is being used exclusively in combination with gemcitabine. One patient experienced Grade 3 febrile neutropenia and the other experienced Grade 3 AST/ALT increase. The MTD for combination with cisplatin has been exceeded at the 250 mg dose level, and tolerability of the MTD at 200 mg BID has been confirmed.[19, 24] DLTs observed in the multiple-dose carboplatin combination have been both hematological and constitutional in nature. The multiple-dose MTD in combination with carboplatin is 225 mg BID.[19, 24]

[redacted]

[redacted] No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a weak drug interaction between AZD1775and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was coadministered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. [redacted]

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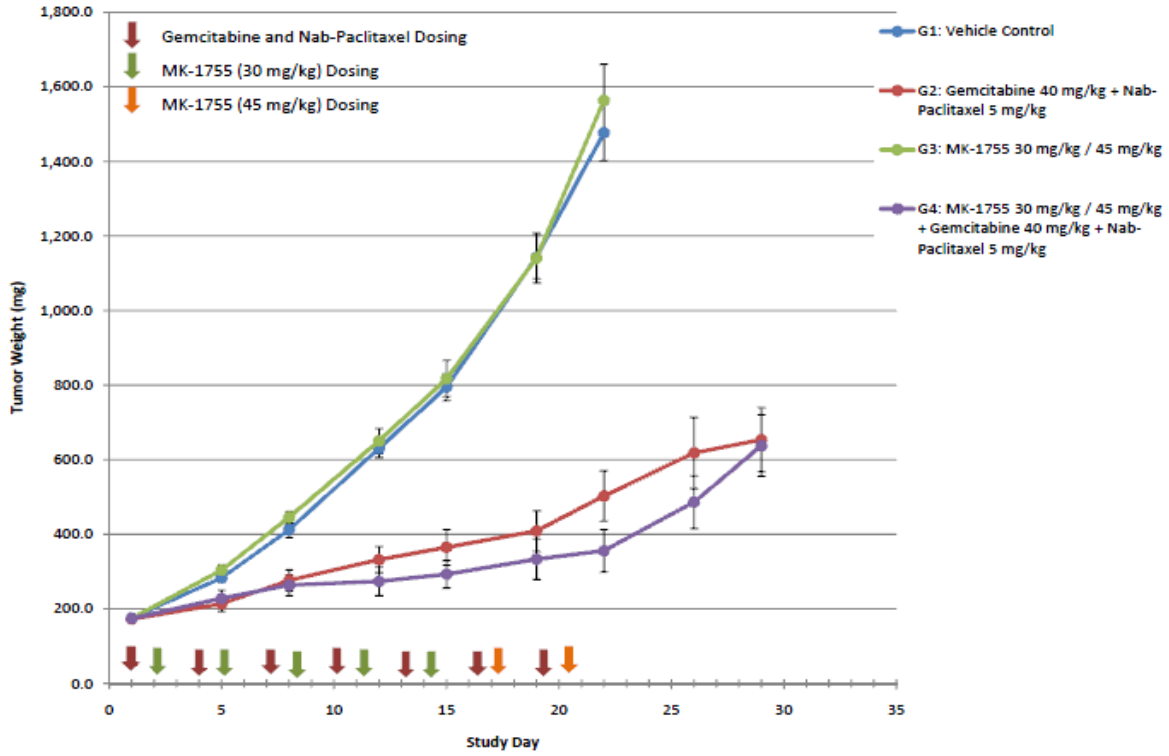
Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction become available. In vitro studies have also suggested that AZD1775 may be a weak inhibitor of CYP2C19, CYP2C8 and CYP2C9, a weak inducer of CYP1A2, substrate and inhibitor of P-glycoprotein (P-gp) and inhibitor of BCRP. [redacted] AZD1775 may inhibit MATE1 and MATE2K renal efflux transporters and may result in a meaningful drug interaction due to inhibition of these transporters.

1.5 Pre-Clinical Study of Nab-Paclitaxel/Gemcitabine/AZD1775

In a KPC mouse model of PDAC (mutant *Kras* and *Trp53* alleles), it has been shown that Nab-Paclitaxel and gemcitabine have synergistic antitumor effects.[25] Nab-Paclitaxel exhibits monotherapeutic antineoplastic effects and simultaneously depresses Cda levels through induction of reactive oxygen species to stabilize gemcitabine and thereby sensitize the PDAC tumor to combination treatment.[25] In the evaluation of AZD1775 in combination with gemcitabine and Nab-Paclitaxel in a p53-mutant Mia-PaCa-2 human pancreas tumor xenograft model, it appeared that AZD1775 did not antagonize the combination of Nab-Paclitaxel and gemcitabine and appeared to have increased efficacy.[26] (Figure 1 – courtesy of Dr. Han, Translational Genomics Research Institute)

Figure 2: Effect of gemcitabine, Nab-Paclitaxel and AZD1775 on tumor weight in a p53-mutant Mia-PaCa-2 human pancreas tumor xenograft model



1.6 Rationale for Clinical Study

Given that p53-deficient cancer cells rely on S- and G2/M-checkpoints in response to DNA damage, a Wee1 inhibitor (regulator of S-phase and inhibitor of G2 checkpoint) will synergize with DNA damaging chemotherapy in enhancing tumor cell death. We therefore hypothesize that therapy with a checkpoint inhibitor plus gemcitabine-based chemotherapy will be more effective than gemcitabine-based chemotherapy alone in patients with metastatic PDAC, a tumor characterized by frequent p53 mutation. Therefore, we have designed a phase I/II randomized study of Nab-Paclitaxel/gemcitabine with or without AZD1775 (Wee1 inhibitor)in patients with treatment-naïve metastatic PDAC. This study uses Nab-Paclitaxel/gemcitabine chemotherapy backbone as it has been shown that this chemotherapy combination is superior to gemcitabine monotherapy and is a new standard of care for treatment of metastatic PDAC in 2013. As there are no phase I studies with Nab-Paclitaxel/gemcitabine/AZD1775, a phase I study has been incorporated to ensure safety of the drug combination.

1.6.1 Correlation Between p53 Status and Tumor Response

p53 status will be assessed as studies have suggested preferential killing of p53-deficient cells with S-/G2-checkpoint inhibitors.[27] However, some studies have also suggested p53-proficient tumors are killed with S-/G2-checkpoint inhibitors.[28-31] Combination of AZD1775 and gemcitabine potentiates the efficacy of gemcitabine in established human pancreatic cancer xenografts.[23] Nine individual patient-derived low passage pancreatic cancer xenografts (3 with

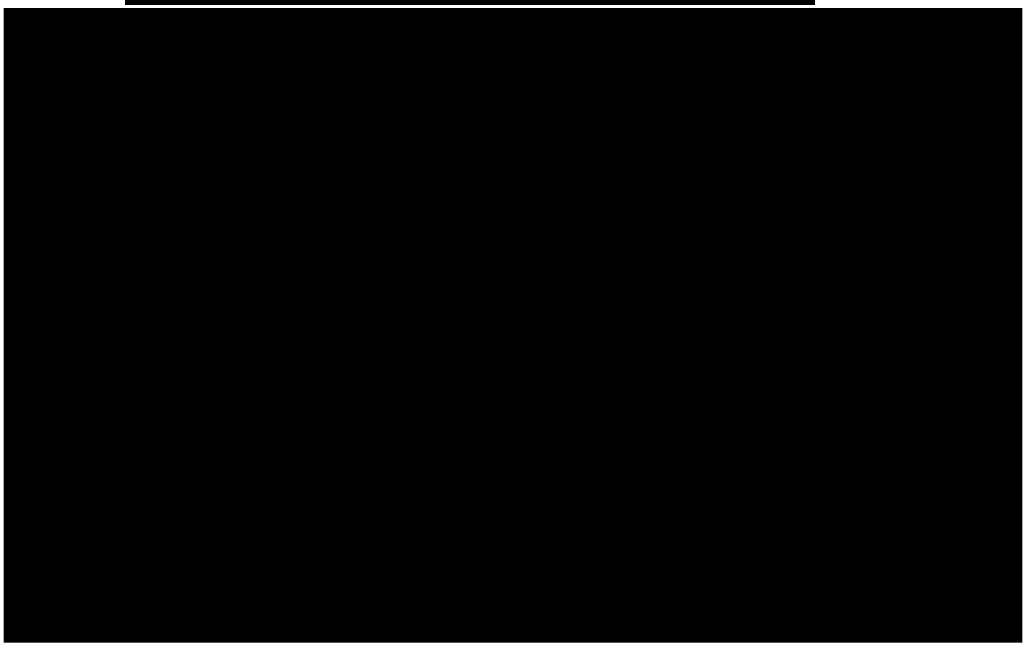
wild-type p53 and 6 with deficient p53 [mutant]) were implanted in athymic mice. Five of 9 xenografts treated with gemcitabine and 6 of 9 xenografts treated with combination of gemcitabine and AZD1775 produced complete tumor growth inhibition resulting in tumor shrinkage.[23] Combination treatment caused greater than 50% regression in tumor size in 4 of 6 xenografts with p53-deficient tumors.[23] The p53 pathway can also be inactivated by genetic or epigenetic events that occur upstream or downstream of p53.[32] Therefore, it is important to assess the integrity of the p53 pathway to determine optimal timing of administration of S-/G2-checkpoint inhibitors and for correlations to be drawn between p53 functional status and tumor response.[32] p53 mutation status will be assessed by DNA sequencing.

1.6.2 Tissue Correlative Studies for AZD1775

Inhibition of $Cdc2^{Tyr15}$ phosphorylation and induction of Histone $H3^{Ser10}$ phosphorylation were observed upon Wee1 inhibition *in vitro*. *In vivo* pharmacodynamic (PD) effects of AZD1775 were evaluated using the WiDr xenograft nude rat model.[19,24] AZD1775 (0.5, 1.0, 3.0 and 7.0 mg/kg/hr) was intravenously infused for 8 hrs, 24 hrs after administration of gemcitabine (50 mg/kg, IV). [19,24] PD marker analyses were performed on tumor tissue isolated immediately after the infusion. Continuous infusion of AZD1775 caused reduction of phospho-$Cdc2^{Tyr15}$ in WiDr xenograft tumor tissue in a dose-dependent manner. The EC_{50} value was 0.28 μM, and about 80% inhibition was achieved at 1.0 mg/kg/hr (0.45 μM at 8hr). Similar dose dependency was observed in the CEA (induction of phospho-Histone $H3^{Ser10}$) in tumor tissue. EC_{50} value was 0.21 μM, and maximal effect was observed at approximately 1.0 mg/kg/hr. [19,24] These data suggest that phospho-$Cdc2^{Tyr15}$ and phospho-Histone $H3^{Ser10}$ could be useful as AZD1775 PD biomarkers in tumors. [19,24] As Wee 1 inactivates Cdc2 through selective phosphorylation of its Tyr15 residue and consequently leads to G2 arrest, measurement of Cyclin B can also be used as a surrogate marker for G2/M-phase entry.[33]

Similar PD marker changes were observed in surrogate tissues, such as skin hair follicle which include proliferating cells in the presence or absence of the DNA damaging agent gemcitabine. [redacted] An almost complete reduction of phospho-Cdc2 signal was achieved at 3.0 mg/kg/hr.[19,22] Therefore, phospho-$Cdc2^{Tyr15}$ inhibition in skin hair follicle is a promising surrogate marker for pharmacodynamics effects in tumor tissue and antitumor effects of AZD1775 treatment.[22]

[redacted]



1.7 Summary of Phase I Toxicity Review

The phase I portion of the study was open to accrual in August 2014 and two patients were enrolled at dose level 1—Nab-Paclitaxel 125 mg/m^2 and Gemcitabine 1000 mg/m^2 on days 1, 8 and 15 as well as AZD1775 100 mg daily on days 1, 2, 8, 9, 15, 16. Given the toxicities observed in these two patients, the trial was suspended and the phase I dose levels redesigned.

Patient 1 received full dose treatment on days 1 and 2. This patient was subsequently admitted to the hospital with grade 3 dehydration and was noted to have liver function abnormalities with a grade 3 bilirubin. The grade 3 dehydration was thought to possibly be related to any of the three treatment agents (AZD1775, gemcitabine, Nab-Paclitaxel) while the grade 3 bilirubin was thought to possibly be related to AZD1775 but unlikely related to either gemcitabine or Nab-Paclitaxel. The patient was treated with supportive care measures with resolution of all issues. Imaging obtained during the hospitalization showed no evidence of biliary obstruction. The patient subsequently went on to receive gemcitabine and Nab-Paclitaxel at a 20% dose reduction (off study), which was well tolerated.

Patient 2 received full dose treatment on days 1 and 2. This patient was admitted to the hospital with grade 3 dehydration as well as difficulty with eating and grade 3 mucositis. Labs during hospitalization revealed a grade 3 AST. All of these grade 3 adverse events were thought to possibly be related to any of the three treatment agents (AZD1775, gemcitabine and/or Nab-Paclitaxel. The patient was treated with supportive care measures and was discharged from the hospital where they went on to receive single agent gemcitabine at a 10% dose reduction, which was poorly tolerated and resulted in additional hospitalizations. This patient transitioned to hospice less than 2 months after her initial evaluation suggesting a rapid clinical decline.

Administration of AZD1775 at doses exceeding the doses proposed in this trial has been successful in both the monotherapy setting and in combination with chemotherapy with acceptable toxicity as outlined above. Previous results show that pCDK1 was decreased at a dose of 125 mg BID and new preliminary data suggests that at least 150 mg daily of AZD1775 is needed to achieve pharmacodynamic effect. By adopting a dose escalation strategy whereby we begin with lower doses of gemcitabine and Nab-Paclitaxel and dose escalate the AZD1775 to an optimal dose, followed then by escalation of gemcitabine and Nab-Paclitaxel (if possible), we believe that administration of AZD1775 at an optimal dose is feasible, particularly if aggressive antiemetic therapy is instituted.

1.8 Rationale for Imaging Research Studies

1.8.1 FDG-PET

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) detects increased glucose metabolism associated with neoplastic lesions. ^{18}F-FDG is transported into cells and phosphorylated by the enzyme hexokinase to ^{18}F-FDG-6-phosphate, which cannot proceed down the glycolytic pathway and therefore is accumulated in the malignant tissue. PET allows accurate quantification of FDG uptake in tissue, and previous studies have demonstrated that standardized uptake values (SUVs) provide highly reproducible parameters of tumor glucose use.[34] The hybrid PET-CT scanners allow functional and anatomic data to be obtained in a single examination, improving lesion localization and resulting in significant diagnostic improvement.[35] FDG-PET is a useful imaging modality to stage and diagnose cancer and studies have shown that its uptake often declines after successful treatment.[36-38] However, the utility of FDG-PET as a reflection of tumor biology and treatment response in pancreatic cancer is unknown. In this study, we intend to evaluate the accuracy of change in SUV_{max} between baseline and week 4 with FDG-PET as a predictor of progression-free survival (PFS), overall survival (OS) and response assessed by RECIST in patients with metastatic PDAC.

1.8.2 FLT-PET

^{18}F-fluoro-3'deoxy-3'-D-fluorothymidine (FLT) (half life = 110 mins) has been developed as a proliferation tracer for PET.[39, 40] FLT is taken up by cells and follows the salvage pathway of DNA synthesis and, like thymidine, undergoes phosphorylation by thymidine kinase 1 (TK1), which leads to intracellular trapping within the cell.[41, 42] FLT is a selective substrate for TK1. In quiescent cells, TK1 activity is virtually absent but in proliferating cells, it is increased about 10-fold, as cells enter the DNA synthetic phase of the cell cycle.[43-45] The uptake of FLT has been found to increase with increasing TK1 activity in human tumor cell lines.[42, 46] As FLT is not incorporated into DNA, FLT uptake has been validated with an independent measure of DNA synthesis in tissue.[47] The protein Ki-67 identified by MIB-1 antibody staining is a histopathologic measure of proliferation, which correlates with the level of FLT uptake measured by PET.[47-49]

As FLT is a PET-tracer with uptake in the S-phase of the cell cycle, its utility as a functional imaging modality in providing information on the molecular and cellular response of checkpoint inhibitors is of interest in this study. FLT has not been studied in pancreatic carcinoma with Wee1 inhibition. The exploratory imaging sub-study associated with this trial is intended to successfully show uptake with FLT. Future study will define whether FLT can be a prognostic imaging biomarker for treatment response, and guide clinical decision making in the future for pancreatic cancer. The opportunity to assess FLT in this study will act as a proof of concept and guide how FLT will be applied in larger studies.

In vitro models of radio-labeled thymidine uptake has been performed in a mouse PDAC cell line from a spontaneous pancreatic cancer mouse model (*Kras*^{G12D}*Pdx1-cre*). When the cells were treated with gemcitabine for 24 hours, cell viability assays indicated that the IC_{50} was 7.3 ng/ml. When the PDAC cell line was treated with gemcitabine for 24 hours and ^{3}[H] Thymidine, uptake of radio-labeled thymidine (measured by the H-3-thymidine assay) was observed. As depicted in Figure 4a, the viable PDAC cells treated with 8 ng/ml and 15 ng/ml of gemcitabine for 24 hours had almost twice the uptake of radio-labeled thymidine compared to control. The increase in uptake of radio-labeled thymidine was not increased when the cells were treated with gemcitabine for 6 hours. This *in vitro* observation is supportive of the "flare" phenomenon observed shortly after treatment with gemcitabine. (Unpublished data courtesy of N. Avril, Case Western Reserve University).

Figure 4a: Thymidine uptake in PDAC cells normalized to viable cell number

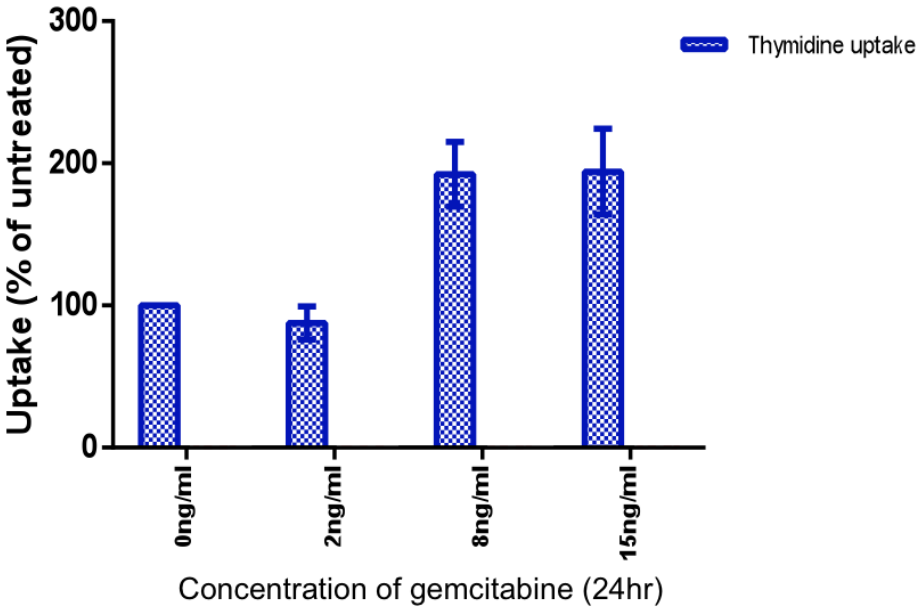
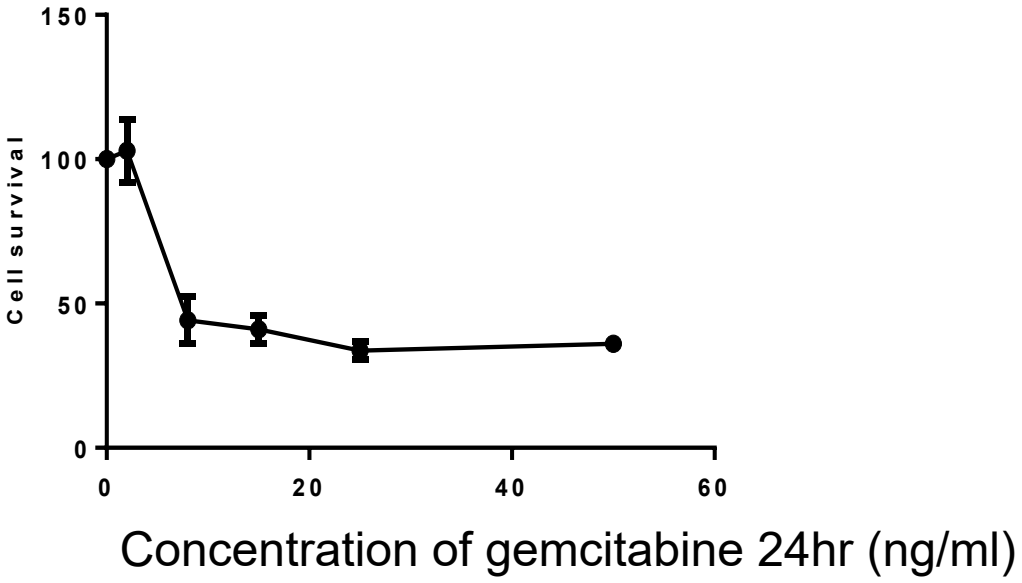


Figure 4b: Cell viability of PDAC cells treated with gemcitabine



Investigators have shown that in PC-3 human prostate cancer xenografts, gemcitabine induced a 8-fold increase in tumoral uptake of FLT at 21 hours that correlated with a 3-fold increase in thymidine kinase activity and S-phase arrest. Treatment with PF-477736 (a Chk1 inhibitor) at 17 hours after gemcitabine abrogated the early FLT-flare at 21 hours by 82% ($p< 0.001$).[50] This was associated with both an increased fraction of cells in mitosis and G1-phase of the cell cycle.[50] Furthermore, the combination of gemcitabine and PF-477736 enhanced DNA damage as measured by γ-H2AX and significantly delayed tumor growth when compared to tumors treated with gemcitabine alone.[50] Therefore, FLT-PET is a promising strategy in monitoring responses to therapeutic agents that target cell cycle checkpoints. A pilot study in humans was performed looking at the flare of FLT-PET imaging after capecitabine. Five patients (2 breast cancer, 2 colon cancer and 1 esophageal cancer) were imaged before and 1 day after the start of capecitabine (after 3 doses) and increased FLT uptake was observed in 3 of the 5 patients. In those 3 patients, SUV_{max} was increased by 26%, 55% and 155%, respectively. (Personal communication with A. Shields, Wayne State University)

There are currently no studies with Wee1 inhibitors and FLT-PET. However, recent studies have shown that Wee1 controls CDK activity to support genome integrity during DNA replication in S-phase.[17] It was also shown that Wee1 depletion by siRNA transfection also rapidly induces DNA damage in S-phase in replicating areas, which is accompanied by a marked accumulation of ssDNA. Similar to effects of Chk1 inhibition, these deleterious S-phase effects of Wee1 depletion are highly dependent on CDK activity.[18] Based on these

findings, it would be reasonable to extrapolate the findings with Chk1 inhibition to Wee1 inhibition using FLT-PET. The current study will be a pilot and feasibility study of FLT-PET in pancreas cancer whereby, we intend to explore the following hypothesis: treatment with gemcitabine-based chemotherapy will induce tumoral uptake of FLT i.e. "flare" and treatment with a Wee1 inhibitor (AZD1775) after gemcitabine-based chemotherapy would abrogate the early FLT-flare indicating therapeutic inhibition of a cell cycle checkpoint. The exploratory FLT findings will be correlated with DNA damage, PFS and response in patients with metastatic pancreatic cancer.

Previous Human FLT Imaging Studies

Several preliminary studies using FLT imaging in human subjects have been performed in Germany and the United States (UCLA, University of Washington in Seattle, Wayne State University). The imaging protocols were pre-approved by their respective regulatory committees and conducted under the RDRC process or under NCI IND, with patients receiving between 1.4 and 13 mCi of FLT. Some of the imaging results have been published (Table 1). The group in Seattle, which has the most experience with this agent in the US, has performed numerous studies in patients with lung cancer as well as a few in patients with primary brain tumors. Their findings demonstrate the feasibility and merit of tumor imaging with FLT. FLT-PET showed increased uptake in tumor lesions outside the liver or bone marrow (standardized uptake value [SUV] 4-7), which were delineated from surrounding tissue (SUV 0.5-2).

Table 1. Summary of published manuscripts reporting [F-18]FLT human imaging studies

Year	Organ System	N	mCi injected	MBq Injected Range (Mean)	Specific Activity	Reference (#)
2008	Brain	12 [a]	4.2 – 5.2	185	> 1.25 Ci/umol	Spence[51]
2008	Bone & Soft Tissue	22		350-425	120 GBq/mmol	Buck[52]
2008	Pancreas	5	5.2 - 7		Not reported	Quon[53]
2008	Lung	55		300-400	Not reported	Tian[54]
2008	Brain	13 [b]		111-370 (322±85)	Not reported	Ullrich[55]
2008	Lung	54 [c]		101-238 (158)	Not reported	Yamamoto[56]
2008	Lung	34 [c]		3.5 /kg	Not reported	Yamamoto[57]
2008	Brain	18	3.5 - 6.4	129-236 (161)	Not reported	Hatakeyama[58]
2007	Sarcoma	10		320-430 (399 med), 120-430 (363 med)	> 10 TBq/mmol	Been[59]
2007	Brain	21 [d]		2.0 /kg	Not reported	Chen[60]
2007	Lymphoma	22		300-370	Not reported	Herrmann[61]
2007	Gastric	45		270-340	Not reported	Herrmann[62]
2007	Lymphoma	48	3.9	148.6	Not reported	Kasper[63]
2007	Breast	15		153-381	15-227 GBq/umol	Kenny[64]

2007	Brain	9 [d]		1.5 kg	Not reported	Schiepers[65]
2007	Head/Neck	10	6.76	250	10 TBq/mmol	Troost[66]
2007	Lung	20 [e]	0.07 /kg	2.59 kg	0.12 -1.6 Ci/umol	Turcotte[67]
2007	Rectal	10	8.1	300	Not reported	Wieder[68]
2007	Lung	18 [c]		145 ± 26	Not reported	Yamamoto[69]
2006	Bone marrow	18	10.8	400	10 TBq/mmol	Agool[70]
2006	Brain	12 [a]	5	185	7.4 GBq/umol	Muzi[71]
2006	Brain	25	10	370	Not reported	Saga[72]
2006	Brain	10	4	104-202	37-222 GBq/umol	Yamamoto[73]
2006	Lymphoma	34	9.3	265-370	Not reported	Buck[74]
2006	Lung & SPN	22	5	185.2	Not reported	Yap[75]
2006	Breast	14	4	150	74 TBq/mmol	Pio[76]
2005	Lung	17	5	2.6/kg; max 185	> 37 GBq/mmol	Muzi[77]
2005	Multiple	33	8.4-9.7	310-360 (350)	> 220 GBq/mmol	Shields[78]
2005	Breast	15	401-10.5	153-380	25-465 GBq/umol	Kenny[79]
2005	Brain	23 [d]	8.6	111-370 (321)	Not reported	Jacobs[80]
2005	Esophageal	10	11.1	340-450 (410)	> 10 TBq/mmol	vanWestreenen[81]
2005	Lung	47 [f]	9.5	265-370	Not reported	Buck[82]
2005	Breast	10		390-420 [3 pts] 60-250 [7 pts]	> 10 TBq/mmol	Been[83]
2005	Brain	25	4.7	141-218 (174)	~74 Bq/mmol	Chen[84]
2005	Brain	26 [d]	10	370	3.2-7.7 Ci/umol	Choi[85]
2004	Lymphoma	7 [g]	4.3 -13.2	159-489 (324)	Not reported	Buchmann[86]
2004	Lung	17	5.7	130-420 (210)	> 10TBq/mmol	Cobben[87]
2004	Lung	28 [h]	9	265-370 (334)	Not reported	Halter[88]
2004	Breast	12	8.1-12.1	300-450	Not reported	Smyczek-Gargya[89]
2004	Colorectal	11 [i]	9.7	360 ± 25	Not reported	Visvikis[90]
2004	HEENT	21	9.2	165-650 (340)	> 10TBq/mmol	Cobben[91]
2004	Soft Tissue	19	10.8	115 -430 (400)	> 10TBq/mmol	Cobben[92]
2003	Lymphoma	11	7.5	280	Not reported	Wagner[93]
2003	Colorectal	10 [i]	9.5	351± 52	Not reported	Francis[94]
2003	Colorectal	17 [i]	9.4	312-412 (360)	Not reported	Francis[95]
2003	Lung	18	5	185 max	37 GBq/umol	Vesselle[96]
2003	Lung	16	5.4 -10.8	200 - 400	Not reported	Dittmann[48]
2003	Melanoma	10	10.8	185-430 (med 400)	> 10TBq/mmol	Cobben[97]

2003	SPN	26 [j]	9	265-370 (334)	Not reported	Buck[49]
2002	SPN	30 [j]	9	265-370 (334)	Not reported	Buck[98]
2002	Lung	10 [k]	5	185 max	37 GBq/umol	Vesselle[47]
Total # Subjects:		1045				

a) There appears to be an overlap of two patients reported in the Muzi 2006[71] and Spence 2008[51] manuscripts.

(b) There appears to be an overlap of two patients reported in the Ullrich 2008[55] and Jacobs 2005[80] manuscripts.

(c) Comparison of the three Yamamoto lung cancer manuscripts[56,57,69] indicates that they represent 72 unique patients.

(d) The Chen 2005[84], Chen 2007[60], and Schiepers[99] manuscripts appear to represent a total of 34 unique patients.

(e) Turcotte[67] appears to include an additional 2 patients who were not reported in the Vesselle 2003[96] manuscript.

(f) Only 13 unique patients can be confirmed against the previous manuscripts from this group.

(g) All 7 patients were previously reported in Wagner 2003.[93]

(h) There appear to be 10 additional unique patients who were not described in the Buck 2002[98] and 2003[49] manuscripts.

(i) It is unclear if the same patients are being described for both of the Francis[94,95] manuscripts and the Visvikis[90] manuscript.

(j) It is unclear if the same patients are being described in the Buck 2002[98] and 2003[49] manuscripts.

(k) It appears that these patients were described in the 2003 Vesselle[96] manuscript.

Due to the possibility that the same patients are being described in some reports, the total number of unique patients represented in the published studies appears to be 827. As evidenced in Table 1, many of the published studies did not report the specific activity of the FLT, so it is not possible to determine the amount of FLT that was actually administered to the patient.

No adverse events have been reported for FLT at the strength to be used for this study. As described above, non-radioactive FLT has been investigated as an anti-AIDS drug, and reversible peripheral neuropathy was observed in subjects exposed to 50 ng-h/mL plasma over a course of 16 weeks (15µg/kg q12h). The FLT dose anticipated for this study will be < 6.1µg for a single injection. Assuming a 70 kg individual, the maximum concentration of FLT would be expected to be equivalent to 0.29 ng-h/mL. The radiation exposure associated with this study is comparable to the dose for other widely used clinical nuclear medicine procedures.

In a 2007 study performed at the University of Washington, Turcotte et al[67] assessed the toxicity of FLT in 20 patients with proven or suspected diagnosis of non-small cell lung cancer. Blood samples from multiple timepoints before and after FLT-PET were assayed for comprehensive metabolic panel, total bilirubin, complete blood and platelet counts. A standard neurological examination was also performed by a qualified physician for each patient before and immediately after FLT-PET. No side effects were reported by patients

or witnessed. No change in the neurological status of patients was observed.

The group in Seattle also recently published the results from safety studies performed in patients with recurrent glioma.[51] Twelve patients were injected with 0.07 mCi/kg (5 mCi maximum) of FLT (specific activity 1.25 Ci/umol) and were closely monitored for three hours afterward. Additional follow-up was performed at 1 day post- and 1 month post-injection. Their findings showed no evidence of toxicity at this dose. Monitoring of vital signs and ECG, review of systems, neurological assessments, and laboratory evaluations revealed no evidence of adverse effects. Notably, no signs or symptoms of peripheral neuropathy were observed in any patient at any time.

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2. Objectives

2.1 Phase I Objectives

2.1.1 Primary Objectives

2.1.1.1 To evaluate the toxicity of combination therapy with Nab-Paclitaxel, gemcitabine and AZD1775 in patients with metastatic adenocarcinoma of the pancreas or locally-advanced adenocarcinoma of the pancreas which is not surgically resectable.

2.1.1.2 To determine the dose of AZD1775 to be used in combination with Nab-Paclitaxel and gemcitabine chemotherapy in the phase II portion of the trial.

2.1.1.3 To determine the pharmacokinetics of AZD1775 in combination with Nab-Paclitaxel and gemcitabine

2.2 Phase II Objectives

2.2.1 Primary Objective

2.2.1.1 To evaluate the progression free survival (PFS) associated with Nab-Paclitaxel/gemcitabine or Nab-Paclitaxel/gemcitabine/AZD1775 in patients with treatment-naïve metastatic adenocarcinoma of the pancreas.

2.2.2 Secondary Objectives

2.2.2.1 To evaluate the overall survival (OS) associated with Nab-Paclitaxel/gemcitabine or Nab-Paclitaxel/gemcitabine/AZD1775 in patients with treatment naïve metastatic adenocarcinoma of the pancreas.

2.2.2.2 To evaluate response rate (CR + PR) associated with Nab-Paclitaxel/gemcitabine or Nab-Paclitaxel/gemcitabine/AZD1775 in patients with treatment naïve metastatic adenocarcinoma of the pancreas.

2.2.2.3 To evaluate disease control rate (CR + PR +SD) associated with Nab-Paclitaxel/gemcitabine or Nab-Paclitaxel/gemcitabine/AZD1775 in patients with metastatic adenocarcinoma of the pancreas.

2.2.3 Laboratory Studies Objectives

2.2.3.1 To evaluate the ability of AZD1775 to inhibit Wee1 and increase DNA damage and tumor cell death when combined with Nab-Paclitaxel/gemcitabine compared to Nab-Paclitaxel/gemcitabine alone.

2.2.3.2 To evaluate if biomarker changes in tumor tissue associated with Wee1 inhibition may also be present in hair follicles.

2.2.4 Advanced Imaging Studies Objectives

2.2.4.1 To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of response using RECIST as the reference standard for response.

2.2.4.2 To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of overall survival.

2.2.4.3 To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of progression-free survival.

2.2.4.4 To compare the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET between the patients from treatment arms H and I. Rev. 4/16

2.2.4.5 To evaluate if an early increase in tumor FLT uptake (FLT-flare) is observed within 24 hours after initiation of treatment with Nab-Paclitaxel/gemcitabine.

2.2.4.6 To evaluate if an early (within 24 h) increase in tumor FLT uptake (FLT-flare) is abrogated after initiation of treatment with Nab-Paclitaxel/gemcitabine/AZD1775.

2.2.4.7 To compare the change in tumor FLT uptake (SUV_{max}) from baseline to 24 hours after initiation of treatment between the patients from treatment arms H and I. Rev. 4/16

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3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 29.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Phase I Study – Arm A (Closed to Accrual), Arms B, C, D, E, F and G

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_____ 3.1.1 Patients must be at least 18 years of age.

_____ 3.1.2 Patients must have histologically or cytologically confirmed metastatic or unresectable locally advanced adenocarcinoma of the pancreas. Prior therapy with a non-gemcitabine based regimen is permitted.

_____ 3.1.3 Previous neo-adjuvant or adjuvant treatment is allowed provided that it was given ≥ 6 months prior to registration.

_____ 3.1.4 Patients must NOT be receiving any other investigational agents concurrently and must not have received any other investigational agents ≤ 4 weeks prior to registration.

Patient is receiving or has received an investigational agent within the last 4 weeks?

_____ (Yes or No) If yes, date treatment discontinued: _____

_____3.1.5 Patients must not have a pre-existing > grade 1 motor or sensory neuropathy.

_____ 3.1.6 Patients must NOT have history of allergic reactions attributed to compounds of similar chemical or biologic composition to Nab-Paclitaxel, gemcitabine or AZD1775.

_____ 3.1.7 Patients must have ECOG performance status of 0 or 1.

_____ 3.1.8 Patients must have a life expectancy of ≥ 12 weeks.

_____ 3.1.9 Patients may have had prior radiotherapy for metastatic disease as long as it was > 4 weeks prior to registration *and* the patient has recovered from adverse events associated with the radiotherapy.

_____ 3.1.10 Patients must NOT have undergone major surgical procedures ≤ 28 days of beginning study treatment, or minor surgical procedures ≤ 7 days. No waiting requried following port-a-cath placement.

_____ 3.1.11 Patient must NOT have any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2:

3.1.11.1 Unstable angina pectoris

3.1.11.2 Congestive heart failure

3.1.11.3 Acute myocardial infarction

3.1.11.4 Conduction abnormality not controlled with pacemaker or medication

3.1.11.5 Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absense of other cardiac abnormalities are eligible.)

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_____ 3.1.13 Patients must NOT have uncontrolled serious medical illness including, but not limited to, ongoing or active infection, cardiac arrhythmia, or psychiatric illness that would limit compliance with study requirements.

_____ 3.1.14 Patients with known human immunodeficiency virus (HIV) are not eligible if CD4 count is ≤ 200 cell/mm^3 or if receiving antiretroviral therapy due to potential unfavorable interactions of the agents with the study treatment.

_____ 3.1.15 Patients must NOT have corrected QT interval QTc > 470 msec (as calculated per institutional standards) at study entry or congenital long QT syndrome).

_____ 3.1.16 Patients must be able to swallow capsules whole.

_____ 3.1.17 Patients must NOT have previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions:

- Non-melanoma skin cancer, in situ cervical cancer, breast cancer in situ, or superficial bladder cancer (noninvasive papillary carcinoma or carcinoma in situ).
- Prior malignancy completely excised or removed and patient has been continuously disease free for >5 years.

Date of last evidence of disease: _____

_____ 3.1.18 Patients must be able to tolerate CT, MRI or PET imaging including contrast agents.

_____ 3.1.19 Women must not be pregnant or breast-feeding as developmental and reproductive toxicity studies of AZD1775 have not been performed;

and the drugs used in this study (Nab-Paclitaxel, gemcitabine and AZD1775) are genotoxic.

Females of childbearing potential must have a blood test or urine study within 5 days prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.20 Women of child-bearing potential and men must agree to use adequate contraception (hormonal and barrier method of birth control; two barrier methods of birth control; abstinence) for the duration of study treatment and for 3 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Should a man impregnate or suspect that he has impregnated a woman while participating in this study, he should inform his treating physician immediately.

_____ 3.1.21 Patients must have normal organ and marrow function as defined below within 14 days of registration:

_____ 3.1.21.1 Leukocytes ≥ 3,000/mcL

Leukocytes_____ Date:_____

_____ 3.1.21.2 Absolute neutrophil count ≥ 1,500/mcL

Neutrophil count:_____ Date:_____

_____ 3.1.21.3 Hemoglobin ≥ 9 g/dL

Hemoglobin:_____ Date:_____

_____ 3.1.21.4 Platelets ≥ 100,000/mcL

Platelets: _____ Date:_____

_____ 3.1.21.5 Total bilirubin ≤ 1.5 institutional upper limit of normal (ULN)

Bilirubin:_____ Date:_____

_____ 3.1.21.6 AST(SGOT)/ALT(SGPT) ≤ 3 X institutional upper limit of normal (ULN) or ≤ 5 X ULN if the patient has liver metastases.

AST:_____ Date:_____

ALT:_____ Date:_____

_____ 3.1.21.7 Creatinine ≤ 1.5 mg/dL or creatinine clearance (Cockcroft-Gault) ≥ 60 mL/min for patients with creatinine levels above institutional upper limit of normal (ULN).

Creatinine:_____ Date:_____

Creatinine clearance (Cockcroft-Gault) :_____

Date:_____

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3.2 Randomized Phase II Study – Arms H and I

_____ 3.2.1 Patients must be at least 18 years of age.

_____ 3.2.2 Patients must have histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas with no prior systemic therapy for metastatic disease.

_____ 3.2.3 Patients must NOT have locally advanced disease.

_____ 3.2.4 Patients must have measurable disease outside of the primary tumor (pancreas) by RECIST 1.1 criteria as defined in Section 6.1.2. Baseline measurements and evaluations of all sites of disease must be obtained ≤ 4 weeks prior to randomization.

_____ 3.2.5 Previous neo-adjuvant or adjuvant treatment is allowed provided that there was no evidence of recurrent disease for at least 6 months after completion of neo-adjuvant/adjuvant treatment.

_____ 3.2.6 Patients must NOT have undergone major surgical procedures ≤ 28 days prior to beginning study treatment, or minor surgical procedures ≤ 7 days. No waiting requried following port-a-cath placement.

_____ 3.2.7 Patient must NOT have any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2:

3.2.7.1 Unstable angina pectoris

3.2.7.2 Congestive heart failure

3.2.7.3 Acute myocardial infarction

3.2.7.4 Conduction abnormality not controlled with pacemaker or medication

3.2.7.5 Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absense of other cardiac abnormalities are eligible.)

_____ 3.2.8 Patients may have had prior radiotherapy for metastatic disease as long as it was > 4 weeks prior to randomization *and* the patient has recovered from adverse events associated with the radiotherapy.

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_____ [redacted]

_____ 3.2.10 Patients must NOT have received prior Wee1 inhibitors or AZD1775.

_____ 3.2.11 Patients must NOT have corrected QT interval QTc > 470 msec (as calculated per institutional standards) at study entry or congenital long QT syndrome).

_____ 3.2.12 Patients must NOT have received gemcitabine or Nab-Paclitaxel in a metastatic setting.

_____ 3.2.13 Patients must NOT be receiving any other investigational agents concurrently and must not have received any other investigational agents ≤ 4 weeks prior to randomization.

Patient is receiving or has received an investigational agent within the last 4 weeks?

_____ (Yes or No) If yes, date treatment discontinued: _____

_____ 3.2.14 Patients must not have a pre-existing > grade 1 motor or sensory neuropathy.

_____ 3.2.15 Patients must NOT have history of allergic reactions attributed to compounds of similar chemical or biologic composition to Nab-Paclitaxel, gemcitabine or AZD1775.

_____ 3.2.16 Patients must have ECOG performance status of 0 or 1.

_____ 3.2.17 Patients must have a life expectancy of ≥ 12 weeks.

_____ 3.2.18 Patients must NOT have uncontrolled serious medical illness including, but not limited to, ongoing or active infection, cardiac arrhythmia, or psychiatric illness that would limit compliance with study requirements.

_____ 3.2.19 Patients must be able to swallow capsules whole.

_____ 3.2.20 Patients with bilary stents are allowed.

_____ 3.2.21 Patients must NOT have previous or concurrent malignancy. Exceptions are made for patients who meet any of the following conditions:

- Non-melanoma skin cancer, in situ cervical cancer, breast cancer in situ, or superficial bladder cancer (noninvasive papillary carcinoma or carcinoma in situ).
- Prior malignancy completely excised or removed and patient has been continuously disease free for > 5 years.

Date of last evidence of disease: _____

_____ 3.2.22 Patients must be able to tolerate CT, MRI or PET imaging including contrast agents.

_____ 3.2.23 Women must not be pregnant or breast-feeding as developmental and reproductive toxicity studies of AZD1775 have not been performed; and the drugs used in this study (Nab-Paclitaxel, gemcitabine and AZD1775) are genotoxic.

Females of childbearing potential must have a blood test or urine study within 5 days prior to randomization to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.2.24 Women of child-bearing potential and men must agree to use adequate contraception (hormonal and barrier method of birth control; two barrier methods of birth control; abstinence) for the duration of study treatment and for 3 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Should a man impregnate or suspect that he has impregnated a woman while participating in this study, he should inform his treating physician immediately.

_____ 3.2.25 Patients must have normal organ and marrow function as defined below within 14 days of randomization:

_____ 3.2.25.1 Leukocytes ≥ 3,000/mcL

Leukocytes_____ Date:_____

_____ 3.2.25.2 Absolute neutrophil count ≥ 1,500/mcL

Neutrophil count:_____ Date:_____

_____ 3.2.25.3 Hemoglobin ≥ 9 g/dL

Hemoglobin:_____ Date:_____

_____ 3.2.25.4 Platelets ≥ 100,000/mcL

Platelets: _____ Date:_____

_____ 3.2.25.5 Total bilirubin ≤ 1.5 institutional upper limit of normal (ULN)

Bilirubin:_____ Date:_____

_____ 3.2.25.6 AST(SGOT)/ALT(SGPT) ≤ 3 X institutional upper limit of normal (ULN) or ≤ 5 X ULN if the patient has liver metastases.

AST: _____ Date:_____

ALT: _____ Date:_____

_____ 3.2.25.7 Creatinine ≤ 1.5 mg/dL or creatinine clearance (Cockcroft-Gault) ≥ 60 mL/min for patients with creatinine levels above institutional upper limit of normal (ULN).

Creatinine:_____ Date:_____

Creatinine clearance (Cockcroft-Gault) :_____

Date:_____

_____ 3.2.26 For participation in the Imaging Research Studies outlined in Section 10, patients must meet the additional following critiera:

_____ 3.2.26.1 The patient is participating in the trial at an institution which has agreed to perform the imaging research studies, completed the ACRIN defined scanner qulification procedures and received ACRIN approval as outlined in Section 10.

_____ 3.2.26.2 The patient has consented in writing to participate in one of the *imaging research studies.*

_____ 3.2.26.3 The patient meets the criteria required for the imaging study in which the site is participating:

NOTE: Eligibility for participating in either imaging sub-study will depend on the availability of the imaging sub-study at a particular institution.

_____ 3.2.26.3.1 For participation in the FDG-PET sub-study:

- Patients must NOT have poorly controlled diabetes (defined as fasting glucose level ≥ 200 mg/dL) despite efforts to improve glucose control by fasting duration and adjustment of medications.
- Patient must NOT weigh more than the maximum weight limit for the PET table.
- Patients must have an evaluable lesion of > 20 mm in size on standard practice imaging study as assessed by site (either primary pancreas mass or metastasis).

Eligible for FDG-PET? _____ (Yes or No)

Date: _____

_____ 3.2.26.3.2 For participation in the FLT-PET substudy:

- Patients must be able to lie still for a 1.5 hour PET scan.
- Patient must NOT have a history of allergic reaction attributable to compounds of similar chemical or biologic composition to ^{18}F-fluorothymidine.
- Patient must NOT weigh more than the maximum weight limit for the PET table.
- Patients must have an evaluable lesion in the pancreas > 20 mm in size on standard practice imaging study as assessed by site (lesion must be likely primary adenocarcinoma of the pancreas that is not primarily fibrotic or mucinous in nature).

Eligible for FLT-PET? _____ (Yes or No)

Date: _____

Physician Signature _____ Date _____

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration and Randomization Procedures

Submitting Regulatory Documents

Before an ECOG-ACRIN Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**

   Or

   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).

   Or

   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - **Indicate all sites approved for the protocol under an assurance number.**
   - **OHRP assurance number of reviewing IRB**
   - **Full protocol title and number**
   - **Version Date**
   - **Type of review (full board vs. expedited)**
   - **Date of review.**
   - **Signature of IRB official**

The CTSU encourages you to go to the following CTSU RSS webpage so that more information on RSS2.0 as well as the submission forms can be accessed. Log in to http://www.ctsu.org and click on the Regulatory tab to access the RSS webpage. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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4.1 Phase I Registration Procedures (Phase I Arms)

Phase I registration will be a two step process: Slot reservation followed by Step 1 treatment registration.

Patients must not start protocol treatment prior to registration to Step 1.

4.1.1 Slot Reservation

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Please note that a slot must be reserved prior to starting eligibility verification. Slots will automatically EXPIRE after 10 days. Only after a slot has been reserved should the patient be worked up for the study. If the patient is found to be ineligible, the site must withdraw the slot via the OPEN Registration System. The expired slot will then be made available for reassignment.

The following information will be requested for Phase I:

4.1.1.1 Protocol Number

4.1.1.2 Investigator Identification

4.1.1.2.1 Institution name (Institution CTEP ID)

4.1.1.2.2 Site contact information

4.1.1.3 Patient Identification

4.1.1.3.1 Patient's initials

4.1.1.3.2 Patient demographics

4.1.1.3.2.1 Gender

4.1.1.3.2.2 Birth date

4.1.1.3.2.3 Nine-digit ZIP code

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4.1.2 Registration to Step 1 - All Phase I Arms

Patients must not start protocol treatment prior to registration Step 1.

Treatment must start within 10 working days after registration.

The following information will be requested at the time of registration to Step 1:

4.1.2.1 Protocol Number

4.1.2.2 Investigator Identification

4.1.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2.2 Investigator's name (NCI number)

4.1.2.2.3 Cooperative Group Credit

4.1.2.2.4 Credit Investigator

4.1.2.2.5 Protocol specific contact information

4.1.2.3 Patient Identification

4.1.2.3.1 Patient's initials (first and last)

4.1.2.3.2 Patient's Hospital ID and/or Social Security number

4.1.2.3.3 Patient demographics

4.1.2.3.3.1 Gender

4.1.2.3.3.2 Birth date

4.1.2.3.3.3 Race

4.1.2.3.3.4 Ethnicity

4.1.2.3.3.5 Nine-digit ZIP code

4.1.2.3.3.6 Method of payment

4.1.2.3.3.7 Country of residence

4.1.3 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.1.

4.1.4 Additional Requirements

4.1.4.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.1.4.2 Plasma samples for pharmacokinetic studies must be collected and submitted as outlined in Section 11.

4.1.4.3 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 in RSS after IRB approval is obtained. To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent 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 listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts 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 website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

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4.1.5 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient registers to Step 1 and does not start therapy, the reason the patient did not start protocol therapy will be collected; no additional data will be collected.

If the above scenario occurs, please notify the EA2131 study team at the ECOG-ACRIN Operations Office – Boston and Study Chair so that an additional patient may be accrued to that cohort to replace the patient who did not receive treatment. If a patient does start therapy and leaves the study prior to completion of 1 cycle of treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the EA2131 Forms Completion Guidelines.

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4.2 Phase II Randomization Procedures (Arms H and I)

Patients must not start protocol treatment prior to randomization.

Treatment must start within 10 working days after registration.

Please note that when a patient has been successfully randomized, the confirmation of registration will indicate that the patient is on either arm H or I.

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The following information will be requested:

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

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4.2.5 Stratification Factors

Patients will be stratified according to the following factors for purposes of balancing arms:

4.2.5.1 ECOG Performance Status

4.2.5.1.1 ECOG PS 0 or 1: Randomized to Arm H or Arm I

4.2.5.2 Imaging sub-studies – Intent to Participate

4.2.5.2.1 No imaging, FDG-PET imaging study, or FLT-PET imaging study: Randomized to Arm H or Arm I

4.2.6 Additional Requirements

4.2.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

4.2.6.2 Biological samples to be submitted for laboratory research studies as outlined in Section 12.

4.2.6.3 This study has two optional imaging sub-studies. Availability of the imaging sub-studies will vary depending on the status of accrual and whether a given site is participating. Before asking patients to consent, the registrar should determine which studies are available. If the FLT study is available, patients should be offered participation in this study first. If the FLT study is not available or the patient declines to participate and the FDG study is available, the patient should be offered the FDG study. If neither study is available or the patient declines, the patient will be stratified into the "no optional imaging study" group.

Imaging studies are to be submitted from participating patients as outlined in Section 10.

4.2.6.4 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 in RSS after IRB approval is obtained. To access iMedidata/Rave the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA, Read-Only, Site Investigator) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling

site may assign the appropriate roles from the Site Roles tab on the CTSU website.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent 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 listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts 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 website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.2.7 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the EA2131 Forms Completion Guidelines.

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5. Treatment Plan

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5.1 Phase I (Arms B, C, D, E, F and G)

5.1.1 Treatment Design – Phase I

Phase I treatment will employ a standard 3 + 3 dose escalation schema. Patients will therefore be treated in cohorts of 3 patients starting with Arm B, first with escalating doses of AZD1775, followed then by escalation of Nab-Paclitaxel and gemcitabine chemotherapy. Gemcitabine and Nab-Paclitaxel will be administered on Days 1, 8 and 15 with AZD1775 being given by mouth daily on days 1, 2, 8, 9, 15 and 16. Escalation will continue through all of the armsuntil the MTD has been determined. The dose escalation strategy is as follows:

Arm	Gemcitabine (mg/m^2) days 1, 8 and 15	Nab-Paclitaxel (mg/m^2) days 1, 8 and 15	AZD1775 (mg) days 1, 2, 8, 9, 15 and 16
Arm A (CLOSED TO ACCRUAL)			
Arm B	750	100	100
Arm C	750	100	125
Arm D	750	100	150
Arm E	750	100	175
Arm F	750	125	*see footnote
Arm G	1000	125	*see footnote

*If AZD1775 150 mg is the highest achievable dose—Arm D—(DLTs observed in Arm E), proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using the highest tolerated AZD1775 dose.

*If AZD1775 175 mg is achievable in Arm E, proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using AZD1775 175 mg. If unacceptable toxicity is observed with AZD1775 175 mg in either Arm F or Arm G, each/either of these dose levels may be reassessed (Arm F_{150}, Arm G_{150}) using AZD1775 150 mg.

If no dose limiting toxicity (DLT) (see Section 5.1.5) is observed amongst 3 patients enrolled on Arm B, or if 1 DLT is seen amongst 6 patients enrolled on Arm B, 3 more patients will be treated at the next dose level. Each patient is monitored for DLTs for four weeks (cycle 1).

If 2 DLTs occur on Arm B, accrual will be suspended and the trial will be re-evaluated.

If 1 DLT is seen across 3 patients at a particular dose level during the first 4 weeks after the start of treatment, 3 additional patients will be treated at that dose level.

With the exception of table footnotes outlined above, if at any time 2 or more DLTs are seen in 3 or 6 patients at any given dose level, the

preceeding dose level will be declared the MTD (Maximum Tolerable Dose). MTD is defined as the highest dose level at which < 33% of 6 patients experience a DLT. If 1 DLT is seen out of 6 patients at a given dose level, that dose level will be declared the MTD. Dose escalation of AZD1775 beyond 175 mg is not permitted.

If a patient received less than 66.7% of the planned doses of any study agent, for reasons at least possibly related to side effects or toxicity from the study treatment, during their first cycle on the phase I study, the patient will be considered as having had a DLT. Furthermore, as the primary safety concern related to potential exacerbation of the expected hematologic toxicity of the Nab-Paclitaxel/gemcitabine regimen with the addition of AZD1775, any observed hematologic toxicity except lymphopenia will be considered a DLT if it results in treatment delay of more than 14 days. If Arm B exceeds the MTD definition, then the study will be suspended and additional arms will be considered and discussed with CTEP.

Arms B, C, D, E and F

Number of Observed DLTs	Action
0/3	Escalate next 3 patients to next dose level
1/3	Add 3 more patients to current dose level
≤ 1/6	Escalate next 3 patients to next dose level
≥ 2/3	Suspend accrual and re-evaluate trial
≥ 2/6	Suspend accrual and re-evaluate trial

*If AZD1775 150 mg is the highest achievable dose—Arm D—(DLTs observed in Arm E), proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using the highest tolerated AZD1775 dose.

*If AZD1775 175 mg is achievable in Arm E, proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using AZD1775 175 mg. If unacceptable toxicity is observed with AZD1775 175 mg in either Arm F or Arm G, each/either of these dose levels may be reassessed (Arm F_{150}, Arm G_{150}) using AZD1775 150 mg.

Arm G

Number of Observed DLTs	Action
≤ 1/3	Add 3 more patients to current dose level Arm G
> 1/3	Arm F is MTD if max of 1/6 DLT on Arm F*
≤ 1/6	Arm G declared as MTD
≥ 2/6	Arm F is MTD if max of 1/6 DLT on Arm F*

*If only 3 patients were enrolled on Arm F prior to escalation to Arm G, another 3 patients will need to be enrolled on Arm F.

The recommended phase II dose (RP2D) is the highest dose of each of the three agents (AZD1775, Nab-Paclitaxel and gemcitabine) that

can be administered as a combination regimen as determined by the phase I dose escalation. A minimum of 6 patients will be treated at the RP2D on the Phase I portion of the study to obtain sufficient toxicity data prior to proceeding to the comparative phase II evaluation of this regimen.

5.1.2 Treatment Administration

1 Cycle = 4 weeks (28 days)

NOTE: Doses associated with the Nab-Paclitaxel and gemcitabine regimen will be based on actual body weight. Change the dose of Nab-Paclitaxel and gemcitabine if the calculated dose changes by > 10%. BSA should be calculated using the Mosteller formula.

- AZD1775 will be supplied as both 100 mg and 25 mg capsules, depending on the dose level.
- AZD1775 must be administered orally one hour prior to or two hours after a meal.
- AZD1775 capsules should be swallowed whole and they cannot be crushed.
- A missed or vomited dose of AZD1775 should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time.

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5.1.3 Administration Schedule – Phase I (Arms B, C, D, E, F and G)

1 Cycle = 4 weeks (28 days)

Treatment will continue until development of progressive disease (as defined by Section 6.1.4) or unacceptable toxicity.

5.1.3.1 Arm A (CLOSED TO ACCRUAL)

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5.1.3.2 Arm B

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration.

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

AZD1775 100 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 100 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 750 mg/m^2 IV over 30 minutes

On days 2, 9, and 16.

AZD1775 100 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

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5.1.3.3 Arm C

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

AZD1775 125 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 100 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 750 mg/m^2 IV over 30 minutes

On days 2, 9, and 16.

AZD1775 125 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: For drug-drug interaction, see Appendix VI for list of medications.

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5.1.3.4 Arm D

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

AZD1775 150 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 100 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 750 mg/m^2 IV over 30 minutes.

On Days 2, 9 and 16:

AZD1775 150 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

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5.1.3.5 Arm E

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

AZD1775 175 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 100 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 750 mg/m^2 IV over 30 minutes.

On Days 2, 9 and 16:

AZD1775 175 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

5.1.3.6 Arm F

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

If 175 mg of AZD1775 was tolerated in Arm E:

AZD1775 175 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 125 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 750 mg/m^2 IV over 30 minutes.

On Days 2, 9 and 16:

AZD1775 175 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

5.1.3.7 Arm G

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

If 175 mg of AZD1775 was tolerated in Arm E

AZD1775 175 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 125 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 1000 mg/m^2 IV over 30 minutes.

On Days 2, 9 and 16:

AZD1775 175 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

If 175 mg of AZD1775 was NOT tolerated in Arm E

AZD1775 150 mg PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel 125 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 1000 mg/m^2 IV over 30 minutes.

On Days 2, 9 and 16:

AZD1775 150 mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted]

5.1.4 Evaluation for Adverse Events – Phase I

Patients must be evaluated for adverse events on a weekly basis during the first cycle of treatment (4 weeks).

Any patient who receives any study agent will be evaluable for adverse events.

Any patient who experiences a dose-limiting toxicity (DLT) during Cycle 1 observation is considered fully evaluable for adverse events.

Assessment of AZD1775 requires 3 patients at a time per cohort, and a total of 6 patients per cohort are required to confirm the MTD for AZD1775 when given in combination with Nab-Paclitaxel and gemcitabine.

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5.1.5 Dose-Limiting Toxicity (DLT) – Phase I

A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.4) possibly, probably, or definitely related to study drug(s) within first cycle (28 days).

- Grade 4 neutropenia for more than 7 days
- Grade 3-4 febrile neutropenia of any duration
- Grade 4 anemia of any duration
- Grade 3 thrombocytopenia in the presence of bleeding of any duration
- Grade 4 thrombocytopenia of any duration
- Rev. 4/16 Any observed hematologic adverse event (of any grade) if it results in treatment delay of more than 14 days, *except* lymphopenia
- Grade 4 nausea, vomiting or diarrhea of any duration
- Rev. 4/16 Grade 3-4 GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin of any duration
- Grade 4 creatinine of any duration
- Grade 3 creatinine lasting longer than 72 hours despite hydration
- Grade 4 hyperglycemia lasting longer than 24 hours despite active management or any duration with life-threatening consequence
- Grade 3-4 hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia lasting longer than 72 hours despite active replacement
- Grade 4 hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia of any duration with life-threatening consequence
- ≥ Grade 3 non-hematological toxicity of any duration, ***except***:
  - Grade 3 nausea, vomiting or diarrhea will be considered a DLT only if it occurs for more than 72 hours despite optimal medical management
  - Alopecia (any grade)
  - Reversible laboratory abnormalities with no clinical sequelae and/or no clinical significance in the opinion of Investigator
- Receipt of less than 66.7% of the planned dose of any study agent for reasons related to side effects or toxicity from study treatment.

NOTE: If patient experiences DLT during Cycle 1, treatment must be discontinued.

NOTE: As the primary safety concern relates to potential exacerbation of the expected hematologic toxicity of the Nab-Paclitaxel/gemcitabine regimen with the addition of AZD1775, any observed hematologic toxicity except lymphopenia will be considered a DLT if it results in treatment delay of more than 14 days.

NOTE: Growth factor support is allowed on cycle 1. See Sections 5.6.1.2.1 and 5.7.2 for further information.

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5.2 Phase II (Arms H and I)

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5.2.1 Treatment – Phase II (Arms H and I)

1 Cycle = 4 weeks (28 days)

NOTE: Doses associated with the Nab-Paclitaxel and gemcitabine regimen will be based on actual body weight. Change the dose of Nab-Paclitaxel and gemcitabine if the calculated dose changes by > 10%.

5.2.2 Administration Schedule – Phase II (Arm H)

1 Cycle = 4 weeks (28 days)

Treatment will continue until development of progressive disease (as defined by Section 6.1.4) or unacceptable toxicity

5.2.2.1 Arm H

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

Nab-Paclitaxel 125 mg/m^2 IV given first over 30 minutes followed by

Gemcitabine 1000 mg/m^2 IV over 30 minutes

5.2.3 Administration Schedule – Phase II (Arm I)

1 Cycle = 4 weeks (28 days)

Treatment will continue until development of progressive disease (as defined by Section 6.1.4) or unacceptable toxicity.

- AZD1775 will be supplied as both 100 mg and 25 mg capsules.
- AZD1775 must be administered orally one hour prior to or two hours after a meal.
- AZD1775 capsules should be swallowed whole and they cannot be crushed.
- A missed or vomited dose of AZD1775 should not be replaced. The patient should be instructed to take the next scheduled dose at the regularly scheduled time.

5.2.3.1 Arm I

On days 1, 8 and 15:

CBC and platelet count to be checked prior to drug administration

Palenosetron 0.25 mg IV/Dexamethasone 16 mg IV over 15 minutes and premedications (see Section 5.7) will be given followed by

AZD1775 RP2D PO per day. AZD1775 should be administered concomitantly or just prior to the start of chemotherapy.

Nab-Paclitaxel RP2D IV given first over 30 minutes followed by

Gemcitabine RP2D IV over 30 minutes

On days 2, 9, and 16.

AZD1775 RP2D mg PO per day should be taken approximately 24 hours after the last dose.

NOTE: Anti-emetics such as neurokinin-1 (NK-1) receptor inhibitor (e.g., aprepitant or fosaprepitant) are **not allowed** due to drug-drug interactions with AZD1775. See Supportive Care (Section 5.7) for anti-emetic recommendations.

NOTE: [redacted] Appendix VI

5.3 Adverse Event Reporting Requirements

5.3.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.3.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans (or with FLT or FDG imaging agents administered in the EA2131 imaging sub-studies), whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Dose Limiting Toxicity (DLT):** The appearance of side effects during the first cycle of treatment that are possibly severe enough to prevent further increase in dosage or strength of treatment agent, or to prevent continuation of treatment at any dosage level. Any adverse event that meets the EA2131 definition of DLT must be reported via CTEP-AERS.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.

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- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.3.3 Reporting procedure

This study requires that expedited adverse event reporting use the CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.3.4 Determination of reporting requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event

- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol EA2131 and outline the specific expedited adverse event reporting requirements for study EA2131.

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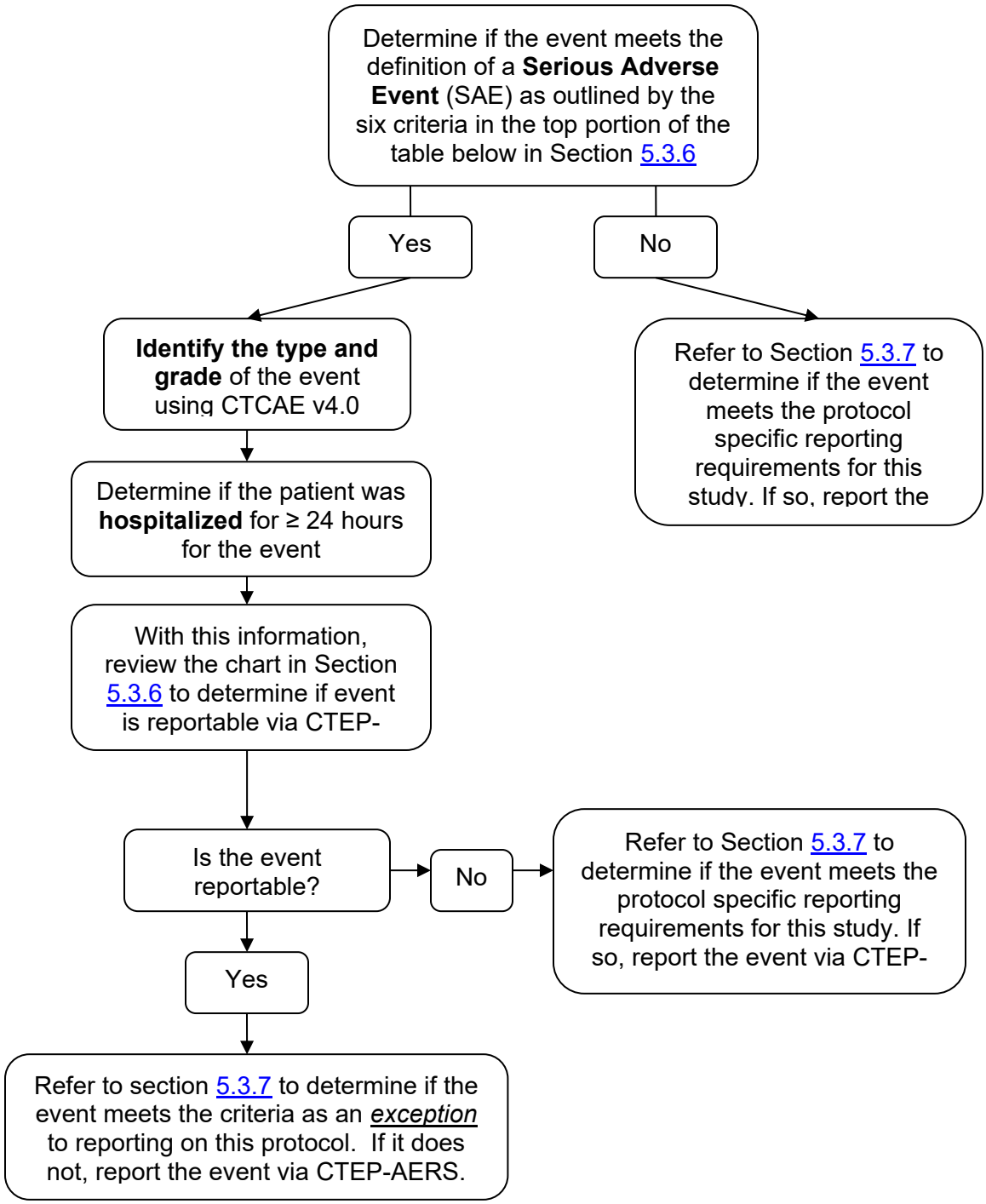
5.3.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arms A (CLOSED), B, C, D, E, F, G, H and I

5.3.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.3.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.3.6, AND has an attribution of possible, probably or definite, the following events 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

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

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5.3.6 Expedited Reporting Requirements for Arms A (CLOSED), B, C, D, E, F, G, H and I on protocol EA2131

Investigational Agents: AZD1775

Commercial Agents: Nab-Paclitaxel, Gemcitabine

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Phase 1 and Early Phase 2 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention* [1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	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

Effective Date: May 5, 2011

5.3.7 Additional instructions, requirements and exceptions for protocol EA2131

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EA2131 specific expedited reporting requirements:

- **Dose Limiting Toxicities (DLTs) – Phase I (All Arms):** The following events require expedited reporting via CTEP-AERS.

  NOTE: In order to avoid unnecessary queries and delays in meeting reporting deadlines, please be sure to state that you are reporting a DLT and include all relevant details in the 'Description of Event' and/or 'Abnormal or Relevant Normal Lab values' sections of the CTEP-AERS report so that the ECOG-ACRIN Operations Office - Boston can document that the adverse event meets the definitions of DLT below (i.e.: duration, grade, relevant lab values, etc).

  A DLT is defined by the occurrence of any of the following toxicities (CTCAE v.4) possibly, probably, or definitely related to study drug(s) within first cycle (28 days):

  - Grade 4 neutropenia for more than 7 days
  - Grade 3-4 febrile neutropenia of any duration
  - Grade 4 anemia of any duration
  - Grade 3 thrombocytopenia in the presence of bleeding of any duration
  - Grade 4 thrombocytopenia of any duration
  - Any observed hematologic adverse event (of any grade) if it results in treatment delay of more than 14 days, *except* lymphopenia
  - Grade 4 nausea, vomiting or diarrhea of any duration
  - Grade 3-4 GGT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin of any duration
  - Grade 4 creatinine of any duration
  - Grade 3 creatinine lasting longer than 72 hours despite hydration

- Grade 4 hyperglycemia lasting longer than 24 hours despite active management or any duration with life-threatening consequence
- Grade 3-4 hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia lasting longer than 72 hours despite active replacement
- Grade 4 hypokalemia, hypomagnesemia, hyponatremia or hypophosphatemia of any duration with life-threatening consequence
- ≥ Grade 3 non-hematological toxicity of any duration, *except*:
  - Grade 3 nausea, or vomiting or diarrhea will be considered a DLT only if it occurs for more than 72 hours despite optimal medical management
  - Alopecia (any grade)
  - Reversible laboratory abnormalities with no clinical sequelae and/or no clinical significance in the opinion of Investigator.
- Receipt of less than 66.7% of the planned dose of any study agent for reasons related to side effects or toxicity from study treatment.

- **FLT-PET Imaging Adverse Events (Arm H and I only):**
  No adverse events have been attributed to Positron-Emission Tomography (PET) imaging/diagnostic administration of [3'-deoxy-3'-[F-18]fluorothymidine (FLT) at the levels described in the Investigators Brochure. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of FLT for typical PET imaging applications. However, AE evaluation must be performed (in person or by phone) at 24 hours (± 4 hours) after each FDG-PET/CT and FLT-PET/CT imaging scan and any event that meets the criteria in Section 5.3.6 must be reported as an adverse event via CTEP-AERS.
- **Pregnancy**
  Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on AZD1775, or within 28 days of the subject's last dose of AZD1775, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix XIII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.**

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EA2131 specific expedited reporting exceptions:

For study arms H and I (phase II only), the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.3.8 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.3.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave.

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     - *Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy*

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form

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

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, 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 via CTEP-AERS (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. [redacted]

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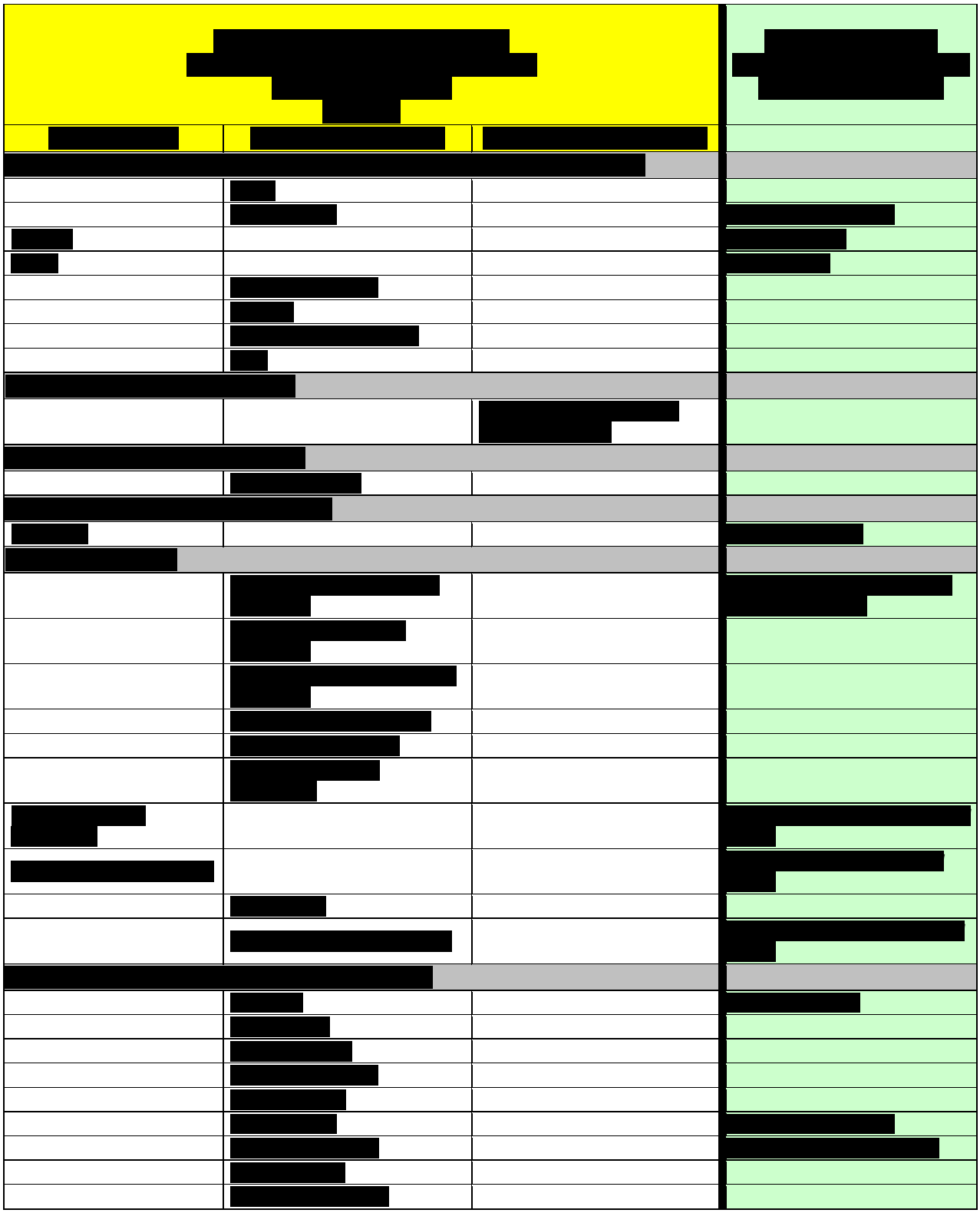
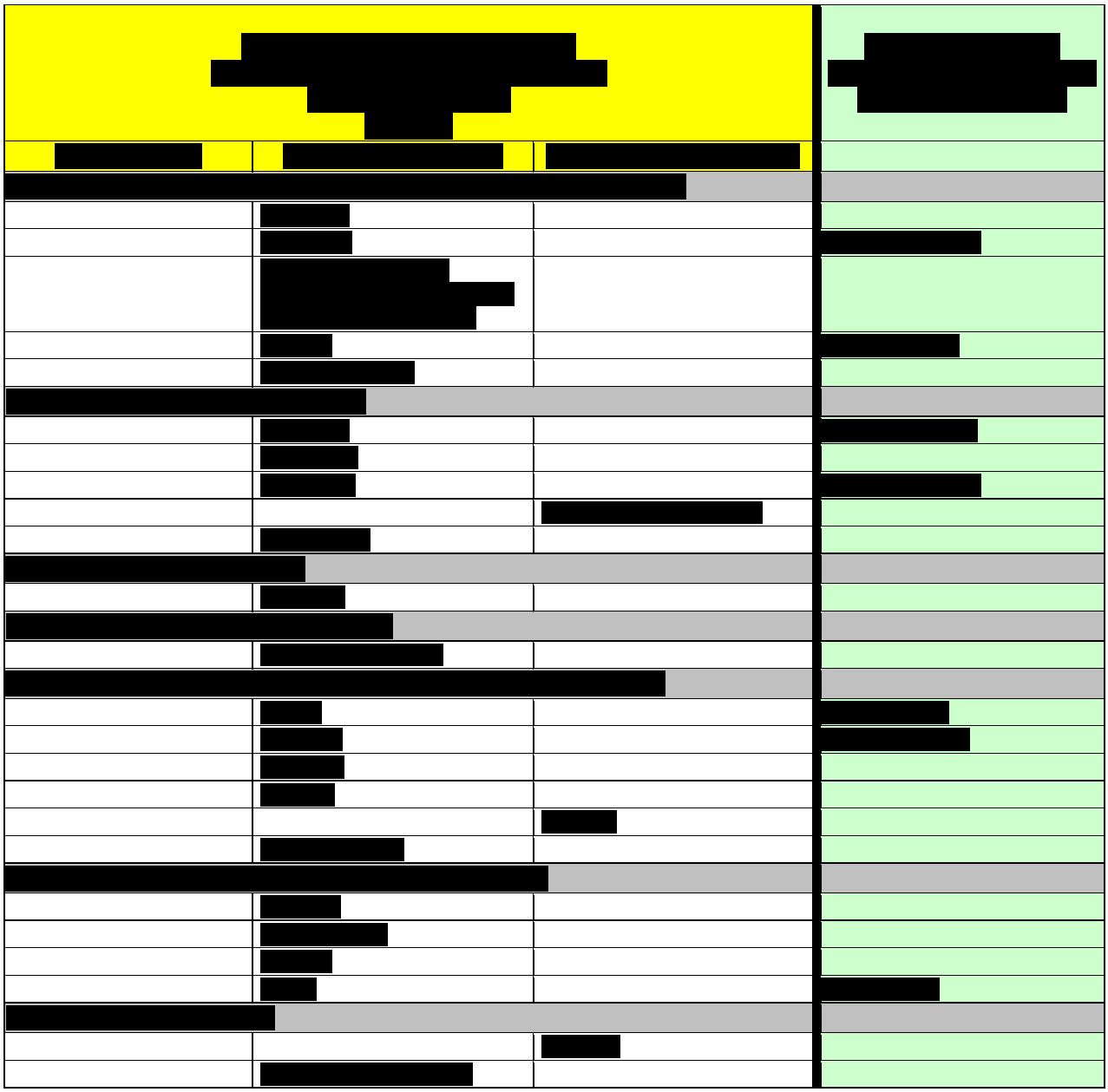
NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

NOTE: The SPEER should **ONLY** be used for the Phase II portion of this study.

Version 2.4, August 3, 2016[1]

[redacted]





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

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

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

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

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (thrombocytosis); Leukocytosis

CARDIAC DISORDERS - Acute coronary syndrome; Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia

EAR AND LABYRINTH DISORDERS - Ear pain

EYE DISORDERS - Blurred vision; Cataract; Conjunctivitis; Eye disorders - Other (eye swelling); Eye disorders - Other (visual impairment); Eye pain; Keratitis; Photophobia; Scleral disorder; Watering eyes

GASTROINTESTINAL DISORDERS - Anal pain; Ascites; Bloating; Cheilitis; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Gastric ulcer; Gastritis; Gastrointestinal disorders - Other (duodenitis); Gastrointestinal disorders - Other (eructation); Hemorrhoids; Lower gastrointestinal hemorrhage; Rectal pain; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Gait disturbance; General disorders and administration site conditions - Other (catheter site pain); Infusion site extravasation

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (ligament sprain)

INVESTIGATIONS - Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (blood urea increased); Lymphocyte count increased

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperkalemia; Hyperuricemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Flank pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (groin pain); Neck pain

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 - Cognitive disturbance; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (hemiparesis); Peripheral neuropathy[5]; Presyncope; Somnolence; Syncope

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression

RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Female genital tract fistula; Genital edema

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Bronchopulmonary hemorrhage; Nasal congestion; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (diaphragmalgia); Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Purpura; Rash acneiform; Skin ulceration; Urticaria

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension

NOTE: AZD1775 (MK-1775) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.5 Comprehensive Adverse Events & Potential Risks Lists (CAEPRs) for 3'-deoxy-3'-[F-18]fluorothymidine (NSC 743144)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, 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 via CTEP-AERS (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. *The CAEPR does not provide frequency data; refer to the Investigator's Brochure for that information.*

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Version 1.0, July 1, 2010 [1]

Category (Body System)	Adverse Events[2] with Possible Relationship to 3'-deoxy-3'-[F-18]fluorothymidine (CTCAE v4.0 Term)	EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
	No AEs reported in human studies[2,3].	

[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] No adverse events have been attributed to Positron-Emission Tomography (PET) imaging/diagnostic administration of[3'-deoxy-3'-[F-18]fluorothymidine at the levels described in the Investigators Brochure. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of 3'-deoxy-3'-[F-18]fluorothymidine for typical PET imaging applications.

[3] As with many intravenously administered agents, 3'-deoxy-3'-[F-18]fluorothymidine could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions should be taken, consistent with normal radiologic and clinical facility practice. The patient should be monitored until the PET procedure is completed, and trained personnel and emergency equipment should be available per facility standards.

For purposes of informed consent regarding reasonably foreseeable risks to subjects in trials utilizing 3'-deoxy-3'-[F-18]fluorothymidine, the following potential adverse events are considered extremely rare:

- **Injection-related risks that may include infection, or accidental extravasation of the dose that may lead to discomfort, localized pain, or infection.**
- **Risks related to allergic reaction/anaphylaxis that may be life threatening.**

NOTE: As with all PET imaging agents, 3'-deoxy-3'-[F-18]fluorothymidine is a radiopharmaceutical that decays with positron emission. As such, it poses an intrinsic radiation exposure risk. However, when administered in accordance with the Investigator's Brochure as a PET imaging agent, this risk is felt to be extremely small. The organ and total body doses associated with FLT PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures.

NOTE: 3'-deoxy-3'-[F-18]fluorothymidine 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.

5.6 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

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5.6.1 Phase I (Arms B, C, D, E, F and G) Dose Modification

The following general rules apply:

- For individual subjects, dose modifications will be based on hematologic or non-hematologic toxicity, laboratory test results, and clinical assessment on the day of treatment and during the previous cycle.
- CBC with differential and platelet count must be drawn on Day 1, Day 8, and Day 15, and results known prior to treatment administration on Day 1, Day 8, and Day 15, respectively.
- If more than one toxicity requiring dose reduction occurs, use lowest dose level required.
- If multiple toxicities are seen, the dose administered in subsequent cycle should be based on the most severe toxicity experienced in the current cycle.
- When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment unless otherwise specified in the Dose Modification for Hematologic Toxicity tables below.
- If patient experiences study drug-related toxicity that requires a delay in scheduled gemcitabine dosing for >14 days, the patient must discontinue all protocol therapy.
- Patients who require discontinuation of both Nab-Paclitaxel and gemcitabine for toxicity will discontinue all protocol therapy.
- Patients who discontinue Nab-Paclitaxel may continue to receive gemcitabine and AZD1775. This is expected to be common since the cumulative neurotoxicity of Nab-Paclitaxel often requires its cessation after 4-6 months.
- Patients experiencing peripheral neuropathy that requires a delay in scheduled Nab-Paclitaxel dosing for ≥ 14 days will discontinue all protocol therapy.
- If AZD1775 is held or discontinued for toxicities solely related to AZD1775, Nab-Paclitaxel and gemcitabine therapy should be continued.
- Please refer to the respective tables for dose modifications related to protocol treatment.
- The study chair or study chair liaison should be contacted for dose delays and modifications for all other toxicities not listed in this section.

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Dose levels for Nab-Paclitaxel, gemcitabine and AZD1775:

Arm A

Closed to Accrual

Arm B

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	100	750	[redacted]
-1	75	600	[redacted]
-2[b]	50	500	[redacted]

Arm C

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	100	750	[redacted]
-1	75	600	[redacted]
-2[b]	50	500	[redacted]

Arm D

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	100	750	[redacted]
-1	75	600	[redacted]
-2[b]	50	500	[redacted]

Arm E

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	100	750	[redacted]
-1	75	600	[redacted]
-2[b]	50	500	[redacted]

Arm F

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	125	750	[redacted]
-1	100	600	[redacted]
-2[b]	75	500	[redacted]

[redacted]

Arm G

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	[redacted]
Starting dose	125	1000	[redacted]
-1	100	750	[redacted]
-2[b]	75	600	[redacted]

[redacted]

a. Dose reductions may or may not be concomitant. Please refer to Section 5.6.1.1 for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity. Please refer to Section 5.6.1.2 for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.

b. A maximum of 2 dose level reductions are allowed.

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5.6.1.1 Phase I (Arms B, C, D, E, F and G) Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of Nab-Paclitaxel, gemcitabine and AZD1775 may be adjusted as detailed below:

Phase I Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

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Phase I (Arms B, C, D, E, F and G): Treatment day counts and toxicity			
ANC		**Platelets**	**Timing**
≥ 1,500/mm^3	And	≥ 100,000/mm^3	Treat on time
< 1,500/mm^3	Or	< 100,000/mm^3	Delay by 1 week intervals until recovery and decrease Nab-Paclitaxel, gemcitabine, and AZD1775 by one dose level.

Abbreviation: ANC = Absolute neutrophil count.

Phase I Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Category	Grade	Nab-Paclitaxel	Gemcitabine	AZD1775
Tinnitus	1	No dose modification	No dose modification	No dose modification
	2	No dose modification	No dose modification	Hold until ≤ grade 1, then reduce by one dose level
	3	No dose modification	No dose modification	Hold until ≤ grade 1, then reduce by one dose level
Fatigue (lethargy, malaise, asthenia)	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Peripheral sensory neuropathy[a]	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then reduce by one dose level	No dose modification	No dose modification
	3-4	Discontinue	May continue. No dose modification.	May continue. No dose modification.
Cutaneous toxicity	1-2	No dose modification	No dose modification	No dose modification
	3	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
	4	Discontinue	Discontinue	Discontinue
Diarrhea	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Mucositis oral	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level
Vomiting (All patients should receive prophylaxis)	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics
	3	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics
	4	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics
AST and/or ALT Bilirubin	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level
Hepatic failure	3-4	Discontinue	Discontinue	Discontinue

Category	Grade	Nab-Paclitaxel	Gemcitabine	AZD1775
All Other Non-Hematologic Toxicities[b, c]	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level

[a]Nab-Paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine and AZD1775 administration can continue during this period. Nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled Nab-Paclitaxel dosing for ≥ 14 days will discontinue study treatment. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

[b]Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement. Asymptomatic or clinically mild pulmonary embolism can be treated with standard anti-coagulation (see Section 5.7.3) without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

[c]Dose reduce if investigator deems appropriate and clinically necessary

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5.6.1.2 Phase I (Arms B, C, D, E, F and G) Dose Modifications within a Treatment Cycle

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up.

Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Section 5.6.1.2.1. Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Section 5.6.1.2.2.

5.6.1.2.1 Phase I Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-Paclitaxel	Day 8 Gemcitabine	Day 8, 9 AZD1775	Day 15 Blood Counts	Day 15 Nab-Paclitaxel	Day 15 Gemcitabine	Day 15, 16 AZD1775	Any Day Nab-Paclitaxel	Any Day Gemcitabine	Any Day AZD1775
ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3	100%	100%	100%	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3**	100%	100%	100%			
				ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Full Dose (treat on time) + G-CSF[a]	Full Dose (treat on time) + G-CSF[a]	Full Dose (treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			
ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time	Decrease dose by 1 level (treat on time)	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3**	Return to Previous Dose level (treat on time) + G CSF[a]	Return to Previous Dose level (treat on time) + G CSF[a]	Return to Previous Dose level (treat on time) + G-CSF[a]			
				ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Same Dose (as Day 8, treat on time) + G-CSF[a]	Same Dose (as Day 8, treat on time) + G-CSF[a]	Same Dose (as Day 8, treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			

Day 8 Blood Counts	Day 8 Nab-Paclitaxel	Day 8 Gemcitabine	Day 8, 9 AZD1775	Day 15 Blood Counts	Day 15 Nab-Paclitaxel	Day 15 Gemcitabine	Day 15, 16 AZD1775	Any Day Nab-Paclitaxel	Any Day Gemcitabine	Any Day AZD1775
ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold	Hold	Hold	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3**	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]			
				ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			
Febrile Neutropenia (Grade 3 or 4)								Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)[b]								Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Decrease to next lower dose level and do not re-escalate throughout the rest of treatment

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.

a G-CSF is optional if descent only affects platelets. .For the prevention of neutropenia or febrile neutropenia, granulocyte colony stimulating factors (G-CSF) may be administered throughout the study, including during cycle 1, in order to maintain adequate blood counts. If G-CSF is

used for the prevention of neutropenia or febrile neutropenia, it may be administered from days 10-13 (total of 4 days) and/or days 17-20 (total of 4 days) after the most recent systemic therapy. G-CSF is not permitted within 48 hours prior to or following any systemic therapy. Pegfilgrastim (Neulasta) is not permitted in this study. G-CSF may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia. Patients not experiencing resolution of neutropenia within 14 days, despite uninterrupted G-CSF treatment, will discontinue study treatment. The use of G-CSF and the associated dose and scheduling is entirely per the discretion of the treating physician.

b If patients do not experience resolution of neutropenia within 14 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

c Patients with grade 4 fever (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 2 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

5.6.1.2.2 Phase I Dose Modifications for Non-Hematologic Toxicity Within a Cycle

Category	Grade	Nab-Paclitaxel	Gemcitabine	AZD1775
Tinnitus	1	No dose modification	No dose modification	No dose modification
	2	No dose modification	No dose modification	Hold until ≤ grade 1, then reduce by one dose level
	3	No dose modification	No dose modification	Hold until ≤ grade 1, then reduce by one dose level
Fatigue (lethargy, malaise, asthenia)	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Peripheral sensory neuropathy[a]	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then reduce by one dose level	No dose modification	No dose modification
	3-4	Discontinue	May continue. No dose modification.	May continue. No dose modification.
Cutaneous toxicity	1-2	No dose modification	No dose modification	No dose modification
	3	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
	4	Discontinue	Discontinue	Discontinue
Diarrhea	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Mucositis oral	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level
Vomiting (All patients should receive prophylaxis)	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics
	3	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics
	4	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics
AST and/or ALT Bilirubin	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level

Category	Grade	Nab-Paclitaxel	Gemcitabine	AZD1775
Hepatic failure	3-4	Discontinue	Discontinue	Discontinue
All Other Non-Hematologic Toxicities[b, c]	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level

[a]Nab-Paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine and AZD1775 administration can continue during this period. Nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled Nab-Paclitaxel dosing for ≥ 14 days will discontinue study treatment. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

[b]Pulmonary embolism if mild or asymptomatic, will be exempt from this requirement. Asymptomatic or clinically mild pulmonary embolism can be treated with standard anti-coagulation (see Section 5.7.3) without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

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5.6.2 Phase II (Arms H and I) Dose Modifications

The following general rules apply:

- For individual subjects, dose modifications will be based on hematologic or non-hematologic toxicity, laboratory test results, and clinical assessment on the day of treatment and during the previous cycle.
- Laboratory tests must be performed within 3 working days prior to treatment administration Day 1 of each cycle. CBC with differential and platelet count must be drawn on Day 1, Day 8, and Day 15, and results known prior to treatment administration on Day 1, Day 8, and Day 15, respectively.
- If patient experiences study drug-related toxicities that require a delay in scheduled gemcitabine dosing for > 14 days, the patient must discontinue all protocol treatment.
- When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment unless otherwise specified in the Dose Modification for Hematologic Toxicity tables below.
- If more than one toxicity requiring dose reduction occurs, use lowest dose level required.
- If multiple toxicities are seen, the dose administered in subsequent cycle should be based on the most severe toxicity experienced in the current cycle.
- Patients who require discontinuation of both Nab-Paclitaxel and gemcitabine for toxicity will discontinue all protocol therapy.
- Patients who discontinue Nab-Paclitaxel may continue to receive gemcitabine and AZD1775. This is expected to be common since the cumulative neurotoxicity of Nab-Paclitaxel often requires its cessation after 4-6 months.

- Patients experiencing peripheral neuropathy that requires a delay in scheduled Nab-Paclitaxel dosing for ≥ 14 days will discontinue all protocol therapy.
- If AZD1775 is held or discontinued for toxicities solely related to AZD1775, Nab-Paclitaxel and gemcitabine therapy should be continued.
- Please refer to the respective tables for dose modifications related to protocol treatment.
- The study chair or study chair liaison should be contacted for dose delays and modifications for all other toxicities not listed in this section.

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Dose levels for Nab-Paclitaxel, gemcitabine & AZD1775:

Dose Level	Nab-Paclitaxel (mg/m^2)[a]	Gemcitabine (mg/m^2)[a]	AZD1775(mg)
0	RP2D	RP2D	RP2D
-1	TBD	TBD	TBD
-2[b]	TBD	TBD	TBD

a. Dose reductions may or may not be concomitant. Please refer to Section 5.6.2.1 for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to Section 5.6.2.2 for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.

b. A maximum of 2 dose level reductions are allowed.

5.6.2.1 Phase II Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of Nab-Paclitaxel, gemcitabine and AZD1775 may be adjusted as detailed below:

5.6.2.1.1 Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

Hematologic nadir (complicated or otherwise) anytime in the cycle should be used to decide on dose reduction for the next cycle.

Phase II Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1,500/mm^3	And	≥ 100,000/mm^3	Treat on time
< 1,500/mm^3	Or	< 100,000/mm^3	Delay by 1 week intervals until recovery

Key: ANC = Absolute neutrophil count.

5.6.2.1.2 Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

If more than one grade 4 non-hematologic toxicity is seen concurrently as a result of therapy patients should be taken off study, unless continuation is approved by the study chair.

Phase II Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Toxicity/dose held	Nab-Paclitaxel+Gemcitabine+AZD1775 dose this cycle
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle
Grade 3 toxicity	Decrease Nab-Paclitaxel, gemcitabine and AZD1775 to next lower dose level[a]
Grade 4 toxicity[a, b]	Off protocol treatment[b]

a. If the toxicity only affects neuropathy, then only Nab-Paclitaxel should be reduced.

b. Pulmonary embolism, if mild or asymptomatic, will be exempt from this requirement.

5.6.2.2 Phase II Dose Modifications within a Treatment Cycle

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up.

Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Section 5.6.2.2.1. Dose modifications due to non-hematologic toxicity within a treatment cycle should be adjusted as outlined in Section 5.6.2.2.2.

5.6.2.2.1 Phase II Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-Paclitaxel	Day 8 Gemcitabine	Day 8, 9 AZD1775	Day 15 Blood Counts	Day 15 Nab-Paclitaxel	Day 15 Gemcitabine	Day 15, 16 AZD1775	Any Day Nab-Paclitaxel	Any Day Gemcitabine	Any Day AZD1775
ANC ≥ 1000/mm^3 and Platelets ≥75,000/mm^3	100%	100%	100%	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3**	100%	100%	100%			
				ANC 500-999 or Platelets 50,000-74,999	Full Dose (treat on time) + G-CSF[a]	Full Dose (treat on time) + G-CSF[a]	Full Dose (treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			
ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000**	Return to Previous Dose level (treat on time) + G-CSF[a]	Return to Previous Dose level (treat on time) + G-CSF[a]	Return to Previous Dose level (treat on time) + G-CSF[a]			
				ANC 500-999/mm^3 or Platelets 50,000-74,999/mm^3	Same Dose (as Day 8, treat on time) + G-CSF[a]	Same Dose (as Day 8, treat on time) + G-CSF[a]	Same Dose (as Day 8, treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			

Day 8 Blood Counts	Day 8 Nab-Paclitaxel	Day 8 Gemcitabine	Day 8, 9 AZD1775	Day 15 Blood Counts	Day 15 Nab-Paclitaxel	Day 15 Gemcitabine	Day 15, 16 AZD1775	Any Day Nab-Paclitaxel	Any Day Gemcitabine	Any Day AZD1775
ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold	Hold	Hold	**ANC ≥ 1000/mm^3 and Platelets ≥ 75,000/mm^3**	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]			
				500-999/mm^3 or Platelets 50,000-74,999/mm^3	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[a]			
				ANC < 500/mm^3 or Platelets < 50,000/mm^3	Hold + G-CSF[a]	Hold + G-CSF[a]	Hold + G-CSF[a]			
Febrile Neutropenia (Grade 3 or 4)								Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)[b]								Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Decrease to next lower dose level and do not re-escalate throughout the rest of treatment

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.

a G-CSF is optional if descent only affects platelets. For the prevention of neutropenia or febrile neutropenia, granulocyte colony stimulating factors (G-CSF) may be administered throughout the study, in order to maintain adequate blood counts. If G-CSF is used for the prevention of neutropenia or febrile neutropenia, it may be administered from days 10-13 (total of 4 days) and/or days 17-20 (total of 4 days) after the most

recent systemic therapy. G-CSF is not permitted within 48 hours prior to or following any systemic therapy. Pegfilgrastim (Neulasta) is not permitted in this study. G-CSF may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia. Patients not experiencing resolution of neutropenia within 14 days, despite uninterrupted G-CSF treatment, will discontinue study treatment. The use of G-CSF and the associated dose and schduleing is entirely per the discretion of the treating physican.

b If patients do not experience resolution of neutropenia within 14 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

c Patients with Grade 4 fever (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

5.6.2.2.2 Dose Modification for Non-Hematologic Toxicity Within a Cycle

Category	Grade	Nab-Paclitaxel	Gemcitabine	AZD1775
Tinnitus	1	No dose modification	No dose modification	No dose modification
	2-3	No dose modification	No dose modification	Hold until ≤ grade 1, then reduce by one dose level
Fatigue (lethargy, malaise, asthenia)	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Peripheral sensory neuropathy[a]	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then reduce by one dose level	No dose modification	No dose modification
	3-4	Discontinue	May continue. No dose modification.	May continue. No dose modification.
Cutaneous toxicity	1-2	No dose modification	No dose modification	No dose modification
	3	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
	4	Discontinue	Discontinue	Discontinue
Diarrhea	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level	Hold until ≤ grade 2, then reduce by one dose level
Mucositis oral	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level
Vomiting (All patients should receive prophylaxis)	1	No dose modification	No dose modification	No dose modification
	2	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics	Hold until ≤ grade 1, then maintain dose level and intensify anti-emetics
	3	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 1, then reduce by one dose level and intensify anti-emetics
	4	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics	Hold until ≤ grade 2, then reduce by one dose level and intensify anti-emetics
AST and/or ALT Bilirubin	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level
Hepatic failure	3-4	Discontinue	Discontinue	Discontinue
All Other Non-Hematologic Toxicities[b, c]	1-2	No dose modification	No dose modification	No dose modification
	3-4	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level	Hold until ≤ grade 1, then reduce by one dose level

[a] Nab-Paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine and AZD1775 administration can continue during this period. Nab-Paclitaxel treatment may be

resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled Nab-Paclitaxel dosing for ≥ 14 days will discontinue study treatment. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

[b] Pulmonary embolism , if mild or asymptomatic, will be exempt from this requirement. Asymptomatic or clinically mild pulmonary embolism can be treated with standard anti-coagulation (see Section 5.7.3) without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Information on possible interactions with other agents for patients and their caregivers and non-study health care team is provided in Appendix VIII.

Anxiolytics and analgesics may be provided at treating physician's discretion.

5.7.1 Anti-emetics:

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- Patients must be premedicated for nausea with palenosetron 0.25 mg/Dexamethasone 16 mg IV over 15 minutes. The anti-emetic regimen may substitute ondansetron for palenosetron per the treating physician's discretion.
- Coadministration with administration with NK-1 antagonists (e.g. aprepitant or fosaprepitant) must be avoided due to possible drug-drug interaction with AZD1775.

5.7.2 Growth Factors

- For low white blood cell counts, G-CSF (filgrastim, Neupogen) may be used, however, routine prophylactic use of G-CSF is not recommended. Due to the treatment schedule, G-CSF (filgrastim, Neupogen) is preferred (see dose modification guidelines, Section 5.6) Pegfilgrastim (Neulasta) is not permitted in this study. ASCO guidelines should be followed. Therapeutic G-CSF use in patients with serious neutropenic complications such as tissue infections, sepsis syndrome, fungal infection, etc., may be given at the investigator's discretion and should follow ASCO Guidelines for G-CSF use. The use of G-CSF and the associated dose and scheduling is entirely per the discretion of the treating physician.
- Erythropoietin Stimulating Agents (ESA): Please follow ASCO guidelines for the use of ESA in patients diagnosed with cancer.

5.7.3 Anticoagulant Use

- Prophylactic anticoagulation will be allowed during therapy provided the activity of the agent used is reflected in either INR or PPT and that those parameters remain as follows: INR < 1.5 or PTT within normal limits
- Anticoagulation for therapeutic use of treatment of DVT or PE is allowed.

5.7.4 Prohibited Treatments

- NK-1 antagonists (e.g. aprepitant or fosaprepitant)

- Any concurrent anticancer therapy including but not limited to chemotherapy, radiotherapy, hormonal therapy (except megestrol acetate as supportive care), immunotherapy, locoregional therapy, other investigational agents, or immunosuppressive therapies.
- Medications that may cause QTc prolongation are prohibited. See Appendix VII.

[redacted]

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

5.8 Duration of Therapy – Phase I and Phase II

Patients will receive protocol treatment unless:

5.8.1 Patient has disease progression per Section 6.1.4.

5.8.2 Patient experiences unacceptable toxicity or DLT.

5.8.3 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.

5.8.4 Patient withdraws consent.

5.8.5 Patient receives any non-protocol therapies.

5.9 Duration of Follow-up – Phase I and Phase II

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated and for survival for 2 years from the date of registration/randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients must be re-evaluated for response every 8 weeks.

Response and progression will be evaluated in this study using the 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 RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.
2. All measurements should be recorded in metric notation by use of a ruler or calipers.
3. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

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

Evaluable Non-Target Disease Response

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

6.1.2 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, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

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

Target Lesions

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the 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 or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of 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 registration.

The same method of assessment and the same technique must 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 in 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 must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

Tumor Markers

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

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.

6.1.4 Response Criteria

6.1.4.1 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 progression, See Section 6.1.4.3).

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. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesion(s).

Progressive Disease (PD)

Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions (see Section 6.1.4.3). *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

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

Table 6.1: Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 8 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease (Section 6.1.4.2) for further explanation.

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.

Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks

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7. Study Parameters

7.1 Phase I Therapeutic Parameters

1. To be completed within **5 days** before registration:
   - Pregnancy test
2. To be completed within **14 days** before registration:
   - Pre-study labs including CBC (with differential and platelet count) and chemistries, unless otherwise specified
3. To be completed within **28 days** before registration:
   - CT of chest
   - CT and/or MRI of abdomen and pelvis

	Baseline requirements[1]	Day 1 of each cycle	Days 8 and 15 of each cycle	Every 2 cycles (every 8 weeks)	Post Treatment[8]
Tests & Observations					
History & Progress Notes[2]	X	X			X
Physical Examination[2]	X	X			X
Pulse, Blood Pressure[2]	X	X			
Height	X				
Weight/BSA[2]	X	X			
Performance Status[2]	X	X			
Tumor Measurements[2]	X			X	X
Adverse Events Assessment[2]		X	X[10]		X[11]
Capsule Diary		X			
EKG[9]	X			X	X
Laboratory Studies					
CBC with Differential, Platelets[3]	X	X[3]	X[3]		
Serum Electrolytes[2,4]	X	X			
Other Serum Chemistry[2,5]	X	X			
CA 19-9[2]	X			X	
Serum or Urine Pregnancy Test [7]	X				

Radiographic Studies[2,6]	X			X	X

1. Baseline requirements must be assessed prior to registration as outlined in Section 3. Blood tests must be performed ≤ 2 weeks prior to registration. CT and/or MRI must be performed ≤ 4 weeks prior to registration.
2. After Cycle 2, the following assessments may be scheduled with a +/- 3 day leeway. History and Progress Notes, including Physical Examination; Pulse, Blood Pressure; Weight/BSA; Performance Status; Adverse Events Assessment, Serum Electrolytes; Other Serum Chemistry, CA-19-9; Radiographic Studies; and Tumor Measurements.
3. CBC with differential and platelet count required prior to each dose of gemcitabine (days 1, 8, and 15) and should be checked on the day of study treatment. For cycle 1 only: CBC with differential and platelet count should be checked on days 1, 8, 15 and 22.
4. Serum electrolytes: Glucose, Na+, K+, bicarbonate, BUN, Cl, creatinine – every cycle
5. Other serum chemistries: Albumin, total protein, alkaline phosphatase, SGOT(AST), SGPT(ALT), total bilirubin; Ca++, Mg++, phosphorus - every cycle.
6. CT of chest, abdomen and pelvis. If only MRI of the abdomen and/or pelvis is available, this can be substituted, for CT of abdomen and/or pelvis, but CT of chest should still be obtained. Contrast agents should be administered.
7. For women of childbearing potential. Must be done ≤ 5 days prior to registration.
8. After completion of protocol treatment, monitor for survival, adverse events, and scans every 3 months until patient is 2 years from registration. Follow-up is no longer required after patient is more than 2 years from registration. Once the patient progresses, adverse event assessments and scans no longer need to be performed.

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9. EKG to be performed at baseline for phase I study (Arm B, C, D, E, F and G) only. Additional EKGs will be collected prior to and approximately 2 hours after study drug AZD1775 (matching PK time points) on Cylce 1 Day 1 and Cycle 1 Day 16. Starting with Cycle 3, EKGs will be collected every 2 cycles prior to treatment and at end of protocol treatment. All EKGs should be performed in triplicate.
10. Cycle 1 only. Patients must be evaluated for adverse events on a weekly basis during the first cycle of treatment (4 weeks total). See Section 5.1.3.6.
11. Adverse Events Assessment is required 30 days after last dose of protocol therapy.

7.1.1 Phase I Biospecimen Submissions

The collection and submission of pharmacokinetic blood samples is MANDATORY. Guidelines for sample submissions are outlined in Section 11.

All samples must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS). All times are relative to time of administration of AZD1775.

	Time pt abbreviation	Time point of draw 3 mL EDTA vacutainer Process and submit **PLASMA**
Visit: Cycle 1 Day 1		
1	C1D1-0h	Cycle 1, Day 1, Prior to AZD1775 administration
2	C1D1-1h	Cycle 1, Day 1, 1 hour
3	C1D1-2h	Cycle 1, Day 1, 2 hours
4	C1D1-4h	Cycle 1, Day 1, 4 hours
5	C1D1-6h	Cycle 1, Day 1, 6 hours
6	C1D1-8h	Cycle 1, Day 1, 8 hours
7	C1D1-24h	Cycle 1, Day 2, 24 hours after Day 1 AZD1775 administration (prior to day 2 administration of AZD1775)
Visit: Cycle 1 Day 16		
8	C1D16-0h	Cycle 1, Day 16, Prior to AZD1775 administration
9	C1D16-1h	Cycle 1, Day 16, 1 hour
10	C1D16-2h	Cycle 1, Day 16, 2 hours
11	C1D16-4h	Cycle 1, Day 16, 4 hours
12	C1D16-6h	Cycle 1, Day 16, 6 hours
13	C1D16-8h	Cycle 1, Day 16, 8 hours
14	C1D16-24h	Cycle 1, Day 17 (24 hours after Day 16 AZD1775 administration) – strongly encouraged but not required

7.2 Phase II Therapeutic Parameters

1. To be completed within **5 days** before randomization:
   - Pregnancy test
2. To be completed within **14 days** before randomization:
   - Prestudy labs including CBC (with differential and platelet count) and chemistries, unless otherwise specified.
3. To be completed within **28 days** before randomization:
   - CT of chest
   - CT or MRI of abdomen and pelvis

	Baseline[1]	Day 1 of each cycle	Days 8 and 15 of each cycle	Every 2 cycles (every 8 weeks)	Post Treatment[8]
Tests & Observations					
History & Progress Notes[2]	X	X			X
Physical Examination[2]	X	X			X
Pulse, Blood Pressure[2]	X	X			
Height	X				
Weight/BSA[2]	X	X			
Performance Status[2]	X	X			
Tumor Measurements[2]	X			X	X
Adverse Events Assessment[2]		X			X[9]
Capsule Diary		X			
Laboratory Studies					
CBC with Differential, Platelets	X	X[3]	X		
Serum Electrolytes[2,4]	X	X			
Other Serum Chemistry[2,5]	X	X			
CA 19-9[2]	X			X	
Serum or Urine Pregnancy Test [7]	X				
Radiographic Studies[2,6]	X			X	X

1. Baseline requirements must be assessed prior to randomization as outlined in Section 3. Blood tests must be performed ≤ 2 weeks prior to randomization. CT and/or MRI must be performed ≤ 4 weeks prior to randomization.
2. After Cycle 1, the following assessments may be scheduled with a +/- 3 day leeway. History and Progress Notes, including Physical Examination; Pulse, Blood Pressure; Weight/BSA; Performance Status; Adverse Events Assessment, Serum Electrolytes; Other Serum Chemistry, CA-19-9; Radiographic Studies; and Tumor Measurements.
3. CBC with differential and platelet count required prior to each dose of gemcitabine (days 1, 8, and 15) and should be checked on the day of study treatment.
4. Serum electrolytes: Glucose, Na+, K+, bicarbonate, BUN, Cl, creatinine – every cycle
5. Other serum chemistries: Albumin, total protein, alkaline phosphatase, SGOT(AST), SGPT(ALT), total bilirubin; Ca++, Mg++, phosphorus - every cycle.
6. CT of chest, abdomen and pelvis. If only MRI of the abdomen and/or pelvis is available, this can be substituted, for CT of abdomen and/or pelvis, but CT of chest should still be obtained. Contrast agents should be administered.
7. For women of childbearing potential. Must be done within 5 days prior to randomization.
8. After completion of protocol treatment, monitor for survival, adverse events, and scans every 3 months until patient is 2 years from registration. Follow-up is no longer required after patient is more than 2 years from registration. Once the patient progresses, adverse event assessments and scans no longer need to be performed..
9. Adverse Events Assessment is required 30 days after last dose of protocol therapy.

7.2.1 Phase II Submissions for Central Review and Ancillary Studies

Imaging studies guidelines are provided in Section 10.

Specimens are to be submitted as outlined in Section 12. All samples submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

	Baseline	Cycle 1 day 2	Cycle 1, day 25 ± 3 days (prior to start of Cycle 2 Treatment)	Submit to:
Specimen submissions (Section 12): Submit from patients who answer "Yes" to "*I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above*."				
Tumor Tissue – FFPE[2]	X			**CBPF**
Hair follicles in NBF[1]	X	X		
Imaging Studies - Limited Institution: Patients from ACRIN-qualified participating sites who are participating in either or both imaging studies. Patients may participate in only one of the imaging substudies, and to do so must consent to participate in the relevant imaging study and must meet the appropriate eligibility criteria as outlined in Section 3.2.26. Patients participating in an imaging study must have laboratory values and adverse events monitored as outlined in Section 10.4, including Table 10.1 and related footnotes.				
FLT-PET[3,5]	X	X		**ACRIN**
FDG-PET[4,5]	X		X	

1. Time of specimen collection AND time of administration of treatment (if applicable) must be reported with the sample submission.
2. Representative tumor tissue block from previous biopsy or surgery. Pathology reports and completed ECOG-ACRIN Generic Specimen Submission Form (#2981)must accompany all tissue submissions.
3. FLT-PET to be performed pre-treatment (within 2 weeks prior to randomization), and again at day 2 (20-24 hours) after initiation of cycle 1. A limited number of sites will perform the FLT-PET studies. FLT-PET study consent language will be included in local IRB reviews and approvals only at qualified participating sites.
4. FDG-PET to be performed pre-treatment (within 2 weeks prior to randomization) and again at day 25 ± 3 days after initiation of cycle 1 only (prior to the start of cycle 2). FDG-PET sub-study qualification through the ACR Imaging Core Laboratory will be open to all ECOG-ACRIN membership sites for participation. Similarly, FDG-PET study consent language will be included in local IRB reviews and approvals only at qualified participating sites.
5. Patients on FDG-PET study will not be enrolled in the FLT-PET study and vice versa.

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8. Drug Formulation and Procurement

Availability

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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.

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: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

NCI Supplied Agents – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: Only undispensed drug supplies (no partial bottles) should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at (240) 276-6575. These forms will be reviewed for accuracy and completeness during NCI cooperative group quality assurance audits.

8.1 Nab-Paclitaxel

8.1.1 Other Names

ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension

8.1.2 Classification

Antimicrotubular, Taxane Derivative

8.1.3 Mode of Action

Nab-Paclitaxel is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium (Desai et al, 2004). A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane (Desai et al, 2004). Nab-Paclitaxel is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

8.1.4 Storage and Stability

Storage: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.

Stability: Unopened vials of Nab-Paclitaxel are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted Nab-Paclitaxel should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8 hours.

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8.1.5 Dose Specifics

100-125 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of each cycle as outlined in Administration Schedule (Sections 5.1.3 and 5.2.2). The use of an in-line filter is not recommended.

8.1.6 Reconstitution and use of Nab-Paclitaxel

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by > 10% by using the Mosteller formula.
2. Calculate the total dose (in mg) to be administered by:
   - **Total Dose (mg) = BSA x (study dose mg/m^2)**
3. Calculate the total number of vials required by:

   $$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each Nab-Paclitaxel vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted Nab-Paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.

10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Nab-Paclitaxel suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted Nab-Paclitaxel suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

8.1.7 Route of Administration

IV infusion

8.1.8 Availability

Nab-Paclitaxel is commercially available.

8.1.9 Side Effects

Hematologic Effects

Neutropenia was dose dependent and reversible. Among patients with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm^3 (Grade 4) in 9% of the patients treated with a dose of 260 mg/m^2 compared to 22% in patients receiving paclitaxel injection at a dose of 175 mg/m^2. Pancytopenia has been observed in clinical trials.

Infections

Infectious episodes were reported in 24% of the patients treated with Nab-Paclitaxel. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications.

Hypersensitivity Reactions (HSRs)

Grade 1 or 2 HSRs occurred on the day of Nab-Paclitaxel administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all < 1%). The use of Nab-Paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of patients. Bradycardia, during the 30-minute infusion, occurred in < 1% of patients. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation. Severe cardiovascular events possibly related to single-agent Nab-Paclitaxel occurred in approximately 3% of patients. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported. Electrocardiogram (ECG) abnormalities were common

among patients at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of patients. Among patients with a normal ECG prior to study entry, 35% of all patients developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory

Dyspnea (12%), cough (7%), and pneumothorax (< 1%) were reported after treatment with Nab-Paclitaxel.

Neurologic

The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of Nab-Paclitaxel discontinuation in 7/229 (3%) patients. Twenty-four patients (10%) treated with Nab-Paclitaxel developed Grade 3 peripheral neuropathy; of these patients, 14 had documented improvement after a median of 22 days; 10 patients resumed treatment at a reduced dose of Nab-Paclitaxel and 2 discontinued due to peripheral neuropathy. Of the 10 patients without documented improvement, 4 discontinued the study due to peripheral neuropathy. No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders

Ocular/visual disturbances occurred in 13% of all patients (n=366) treated with Nab-Paclitaxel and 1% were severe. The severe cases (keratitis and blurred vision) were reported in patients who received higher doses than those recommended (300 or 375 mg/m^2). These effects generally have been reversible.

Arthralgia/Myalgia

The symptoms were usually transient, occurred two or three days after Nab-Paclitaxel administration, and resolved within a few days.

Hepatic

Grade 3 or 4 elevations in GGT were reported for 14% of patients treated with Nab-Paclitaxel and 10% of patients treated with paclitaxel injection in the randomized trial.

Renal

Overall 11% of patients experienced creatinine elevation, 1% severe. No discontinuations, dose reductions, or dose delays were caused by renal toxicities.

Other Clinical Events

Nail changes (changes in pigmentation or discoloration of nail bed) have been reported. Edema occurred in 10% of patients; no patients had severe edema. Dehydration and pyrexia were also reported.

8.1.10 Nursing/Patient Implications

Nab-Paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended.

8.1.11 References

FDA approved package insert.

8.2 Gemcitabine

8.2.1 Other Names

2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

8.2.2 Classification

Antimetabolite (nucleoside pyrimidine analogue)

8.2.3 Mode of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell

8.2.4 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature (15ºC to 30ºC, 59ºF to 86ºF). Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; as crystallization may occur. The unused portion should be discarded.

8.2.5 Dose Specifics

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750-1000 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of each cycle as outlined in Administration Schedule (Sections 5.1.3 and **Error! Reference source not found.**).

8.2.6 Preparation

Gemcitabine may be further diluted with normal saline as per institutional standards.

8.2.7 Route of Administration

IV infusion.

8.2.8 Availability

Gemcitabine is commercially available in 200 mg and 1 gm vials

8.2.9 Side Effects

8.2.9.1 Hematologic: Neutropenia, anemia, thrombocytopenia, and leukopenia are reported.

8.2.9.2 Dermatologic: A rash is seen in about 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is usually minimal. Injection-site reactions.

8.2.9.3 Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely dose limiting, and is easily manageable with standard antiemetics. Diarrhea, constipation, mucositis.

8.2.9.4 Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, non-progressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.

8.2.9.5 Pulmonary: Bronchospasm and/or dyspnea within a few hours of infusion of the drug, cough, rhinitis, pneumonitis.

8.2.9.6 Neurologic: Somnolence, insomnia, paresthesia, pain.

8.2.9.7 Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmias have been reported. Peripheral edema is reported in about 30% of patients.

Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose-limiting, sometimes painful, and reversible after stopping gemcitabine treatment.

8.2.9.8 Other: Flu-like symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are reported.

8.2.10 Nursing/Patient Implications

If the patient reports burning at the injection site, slow down rate to allow the dose to run in over 1 hour.

Rash can be treated with topical therapy or the administration of diphenhydramine prior to administration.

Flu-like symptoms can be treated with acetaminophen.

8.2.11 Reference

FDA-approved package insert.

8.3 AZD1775 (NSC 751084)

8.3.1 Chemical Name

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

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8.3.2 Other Names

MK-1775

8.3.3 Molecular Formula

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

8.3.4 Description

AZD1775 is a crystalline, non-hygroscopic, monohydrate of the neutral drug. It dehydrates upon heating leading to formation of a crystalline anhydrate.

8.3.5 Classification

Highly selective, adenosine-triphosphate (ATP) competitive, small molecule inhibitor of Wee1 kinase.

8.3.6 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.

8.3.7 Storage and Stability

Store bottles at controlled room temperature, not to exceed 30° C. Shelf life studies of AZD1775 are on-going.

8.3.8 Dose Specifics

100-175 mg

8.3.9 Route of Administration

Oral administration on days 1, 2, 8, 9, 15, and 16 of each cycle. Take AZD1775 one hour prior to or two hours after a meal.

8.3.10 Availability

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

8.3.11 Side Effects

See Section 5.4 for side effects.

8.3.12 Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), 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.

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 (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.3.13 Agent Inventory Records

Agent Accountability:

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received by the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. A separate NCI Drug Accountability Record Form must be maintained for each patient ID number (e.g., "088-xxx") on this protocol. The combination Julian date / order number in the upper right hand corner of the patient-specific bottle label (e.g., 12365-9999) should be recorded as the lot number.

Agent Returns:

Only undispensed drug supplies (no partial bottles) should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Agent Transfers:

Bottles may NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the registering investigator for a given patient changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov).

For questions about drug orders, transfers, returns, or accountability, call 240-276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.3.14 Nursing/Patient Implications

Do not open capsules. Wash the exposed area with soap and water immediately after direct contact with the drug.

Patients will be required to record dose of capsules in diary and return capsules, bottles and diary with each cycle.

8.3.14.1 [redacted]

8.3.14.2 **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 and men participating in clinical studies of AZD1775 must use appropriate contraception throughout the study including abstinence and double barrier methods throughout treatment. Contraception use must continue for 3 months after the last dose of study treatment.

8.3.15 References

AZD1775 Investigator Brochure

8.4 3'-deoxy-3'-[F-18]fluorothymidine (FLT)-PET

For complete information, please refer to the Investigator's Brochure:

"3'-deoxy-3'-[F-18]fluorothymidine: [F-18]FLT, An Investigational Positron Emission Tomography (PET) Radiopharmaceutical for Injection and intended for use as an in vivo diagnostic for imaging active cellular proliferation of malignant tumors", Edition Number 7, Edition date 2009.

8.4.1 Pharmacology and Toxicology

The pharmacology of FLT is based on its action as an inhibitor of DNA synthesis.[36-38] Intracellular metabolism of FLT produces nucleotides that inhibit endogenous DNA polymerases because they lack a 3'-hydroxyl substituent. This results in premature chain termination of DNA synthesis.[39, 40] These biochemical properties can account for FLT's prominent hematological and liver toxicity.[40-42] The pharmacology of FLT closely parallels that of the widely used prescription HIV-antiviral drug azidothymidine (AZT).[43, 44] Both FLT and AZT are 3'-deoxythymidine analogs that act as inhibitors of DNA synthesis and are cleared from the body in the same way. However, FLT is significantly more cytotoxic than AZT in test cell lines.[42] Cellular uptake of FLT and thymidine is greater than that of AZT. Transport of FLT and thymidine across cell membranes occurs by active transport and passive diffusion.[44]

8.4.2 Toxicity of FLT in Humans

FLT was investigated as an anti-AIDS drug in humans.[41] Toxic effects and death were reported for some subjects who received FLT during randomized concentration-controlled trials during a 16-week treatment of oral multi-dosing. Doses of 0.125 mg/kg every 12h produced a mean cumulated drug exposure (AUC12: area under curve) of 417 ng-h/mL. At this level, serious (grade 3) hematologic toxicity occurred in 6 of 10 subjects. At 300 ng-h/mL, grade 2 or greater (fall in hemoglobin to < 9.4 g/dL) developed within 4 weeks in 9 of 12 subjects. At 200 ng-h/mL almost no clinically significant anemia developed, but dose-limiting granulocytopenia (< 750 granulocytes/mm^3) occurred in 5 of 15 subjects. Mild peripheral

neuropathy occurred in 2 of 10 subjects at 50 ng-h/mL, but was not dose- limiting. FLT drug trials were terminated after the unexpected death of 2 subjects of hepatic failure. One patient assigned to 200 ng-h/mL developed progressive liver failure and died after 12 weeks of FLT therapy. A second subject, who received a fixed dose of 10 mg/day, developed progressive liver failure and died at about the same time. All surviving subjects were followed closely for 4 weeks after stopping FLT and none had evidence of clinically significant liver disease or other adverse effects. Overall, 25 of the 44 subjects receiving at least two doses of FLT completed the 16 week study without clinically significant adverse effects.

FLT (Alovudine) was withdrawn from development for several years, and then reinvestigated for multi-drug resistant HIV infection. Fifteen patients with multi-drug resistance HIV received 7.5 mg each day for 28 days along with their ongoing therapy.[72] No serious adverse events were observed. In a randomized, double-blind, placebo-controlled study by the same group, 51 patients received 0.5 mg, 1.0 mg, or 2.0 mg daily for 28 days in addition to their routine therapy; 21 patients received placebo.[73] No unexpected adverse events were observed, and no serious AEs were attributed to the study drug.

8.4.3 Dosimetry

The dose of FLT to be administered in this imaging trial is 1400-fold lower than the dose that led to serious toxicity in the studies described above. A summary of the relevant human dosimetry for 2 different voiding scenarios from the investigator's brochure.

Table 8.1. Human dosimetry estimates

Organ of Interest	Men mGy/MBq (mrad/mCi)			Women mGy/MBq (mrad/mCi)		
Total Body Dose	Scenario 1	1.23E-02	(46)	Scenario 1	1.56E-02	(58)
	Scenario 2	1.26 E-02	(47)	Scenario 2	1.59 E-02	(59)
Bladder	Scenario 1	1.79E-01	(662)	Scenario 1	1.74E-01	(646)
	Scenario 2	7.91E-02	(293)	Scenario 2	7.76E-02	(287)
Liver	Scenario 1	4.51E-02	(167)	Scenario 1	6.42E-02	(238)
	Scenario 2	4.54 E-02	(168)	Scenario 2	6.45 E-02	(239)

Scenario 1: Single bladder voiding at 6 h after FLT administration with a 10% post-voiding bladder residual decayed to infinity. This scenario assumed no urine reaccumulation after 6 h.

Scenario 2: First bladder voiding at 2 h after FLT administration with a 10% post-voiding residual; urine reaccumulation between 2 and 6 h at a rate determined by the bladder curve fit; second bladder voiding at 6 h with a 10% post-voiding residual decayed to infinity. This scenario assumed no urine reaccumulation after 6 h. The first scenario is conservative, whereas the second has a more realistic voiding scheme.

8.4.4 FLT Administered Dose

The administered dose will be 0.07 mCi/kg with a maximum of 5 mCi. A ± 20% allowance for dose modification is allowable at the discretion of the site PI. The drug solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours. The injectable dose of FLT for most studies will be ≤ 0.07 mCi/kg of fluorine 18, not to exceed 5 mCi with a specific activity greater than 200 Ci/mmol at the time of injection. In the dose of FLT, only a small fraction of the FLT molecules are radioactive. The amount of injected drug is ≤ 6.1 µg (≤ 25 nmol per dose) of FLT. FLT is administered to subjects by intravenous injection of ≤ 10 mL. There is no evidence that nonradioactive and radioactive FLT molecules display different biochemical behavior.

8.4.5 Quality Assurance, Quality Control, and Storage

In accordance with regulations, the radioisotope vendor conducts several quality control tests on the FLT product prior to release for human administration. Once delivered to the participating institution, doses will be stored in the appropriate storage area in the nuclear medicine facility until they are administered to the patient.

8.4.6 Supplier of FLT

Drug Ordering: FLT will be purchased from a commercial vendor of radioisotopes in most cases. The vendor must be authorized within the NCI IND. The investigator or the investigator-designee will order patient doses of FLT; orders must be made a minimum of 2 calendar days prior to the scheduled FLT-PET/CT imaging study. The investigative radiopharmaceutical FLT solution will be shipped to the site the same day the participant is to be injected.

The investigational pharmacist or qualified nuclear medicine technologist at the participating institution will be the responsible party designated by the investigator.

FLT can only be synthesized on site if the chemistry manufacturing and control procedures are filed within the NCI IND.

Drug Returns: If for any reason the study imaging is unable to be completed, sites will allow the radioactivity of the [^{18}F]FLT solution to decay and then discard it appropriately per site's policies and procedures. A copy of the policy should be available upon request.

Drug Accountability: The investigator or the investigator-designee must maintain a detailed record of receipt, disposition, and destruction dates of FLT solution, using the Drug Accountability Record form available on the ACRIN web site.

[^{18}F]FLT will be synthesized according to the standard operating procedures provided by the NCI. A summary of the synthesis procedure and associated quality control can be found in the investigator's brochure.

[^{18}F]FLT will be administered in the PET imaging suite under physician supervision. The imaging technologist or nurse will administer the [^{18}F]FLT by intravenous infusion over one minute, followed by a saline flush. A fully equipped emergency cart and ACLS certified personnel will be available. Reported adverse events and potential risks are described in Section 5.5. The infusion and imaging procedure will be terminated in any patient who exhibits anaphylaxis, chest pain, dyspnea, or grand mal seizure.

8.4.7 FLT Imaging IND Agent Estimated Effective Dose from Isotope and Scans

Table 8.2 Estimated Effective Dose from Isotope and Scans

(Sponsor: Cancer Imaging program, NCI, NIH)

Scans	Eligible Patients	PET Agent Dose	ED for maximum dose of isotope (mSv)	Equipment Type	PET/CT Image Acquisition	Attenuation (Transmission) Scan	ED from CT scan (mSv) (mean)	ED from CT scan (mSv) (Max)	ED from transmission scan (mSv) (max)	Total ED (mSv) (likely)	Total ED (mSv) (max)	ED (mSv) with transmission scan
FLT-1 prior to therapy (baseline, Day 1, Cycle 1)	All	2.6 MBq/kg (0.07 mCi/kg) maximum 185 MBq (5 mCi)	4.8	PET/CT or PET	Torso Scan 60 minutes dynamic post injection	low-dose CT scan or transmission	6.4	8.6	0.2	11.2	13.4	5
FLT-2 (early-treatment, ~Day 4, Cycle 1)	All	2.6 MBq/kg (0.07 mCi/kg) maximum 185 MBq (5 mCi)	4.8	PET/CT or PET	Torso Scan 60 minutes dynamic post injection	low-dose CT scan or transmission	6.4	8.6	0.2	11.2	13.4	5
2 FLT Scans	Arms H and I	≤ 10 mCi	9.6				12.8	17.2	0.4	22.4	26.8	10

ED = Estimated Effective Dose in mSv

Likely dose = radionuclide + mean from CT scan

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9. Statistical Considerations

9.1 Endpoints

The definitions of primary and secondary endpoints are described in Sections 2 and 9.2.

Phase I (Open-label study)

Maximum tolerated-dose (MTD)

Phase II (Randomized study)

Primary endpoint: Progression free survival (PFS)

Secondary endpoints: Overall survival (OS), response rate (CR+PR), and disease control rate (CR+PR+SD)

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9.2 Sample Size With Power Justification

A maximum total of 109 patients will be needed for the entire trial that consists of Phase I and Phase II.

9.2.1 Phase I

Assuming a roughly 5% dropout rate, a maximum of 50 patients will be needed to accrue a maximum of 48 eligible patients in the 3+3 dose escalation design described in Section 9.3.

9.2.2 Phase II

A total of 84 patients will be in Phase II. The study seeks to establish an improvement in the primary endpoint, which is defined as a 66.6% increase in median progression free survival (PFS) from 6 months in the control arm (Arm H) to 10 months in the experimental arm (Arm I) assuming exponential failure. The study is designed to have 85% power for a hazard ratio of 0.6 with 69 PFS events (as total information) which are expected to occur with 14 months of accrual at 6 patients per month and 13 additional months of follow-up, using a log-rank test at a one–sided significance level of 0.15. The sample size was computed using seqopr6 (part of the study design library at the ECOG-ACRIN Statistical Office).

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9.3 Analysis Plan Including Plans for Formal Interim Analysis

9.3.1 Phase I

The MTD of all three agents, gemcitabine, Nab-Paclitaxel and AZD1775 when given as a combination will be determined using a 3+3 dose escalation design with escalating doses of gemcitabine, Nab-Paclitaxel and AZD1775 and six patients treated at the proposed MTD. The dose escalation strategy is as follows:

Arm	Gemcitabine (mg/m^2) days 1, 8 and 15	Nab-Paclitaxel (mg/m^2) days 1, 8 and 15	AZD1775 (mg) days 1, 2, 8, 9, 15 and 16
Arm A (CLOSED TO ACCRUAL)			
Arm B	750	100	100
Arm C	750	100	125
Arm D	750	100	150
Arm E	750	100	175
Arm F	750	125	*see footnote
Arm G	1000	125	*see footnote

*If AZD1775 150 mg is the highest achievable dose—Arm D—(DLTs observed in Arm E), proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using the highest tolerated AZD1775 dose.

*If AZD1775 175 mg is achievable in Arm E, proceed to Arm F and continue with dose escalation of gemcitabine and Nab-Paclitaxel using AZD1775 175 mg. If unacceptable toxicity is observed with AZD1775 175 mg in either Arm F or Arm G, each/either of these dose levels may be reassessed (Arm F_{150}, Arm G_{150}) using AZD1775 150 mg.

Enrollment to the phase I component will be within limited participating institutions. In the dose escalation design, 3 patients will be initially treated at the lowest dose level. If more than one patient experience DLT at this dose, accrual will stop and the regimen will be reconsidered as the MTD will have been exceeded. If no DLT occurs in the first 3 patients, accrual to the next dose level will begin, again with 3 patients. If at either dose one DLT occurs in the first 3 patients, 3 additional patients will be treated at that dose level and the dose either escalated or deemed the MTD if none of the additional 3 patients experiences DLT. If one or more of the additional 3 patients experiences DLT, the MTD will have been exceeded and the MTD will be defined to be the lower dose. If at any time 2 or more patients experience DLT at a dose level, the MTD will have been exceeded. With the escalation strategy, the table below gives the probability of escalation as a function of the true underlying DLT rate for a variety of true rates. The definition of DLT is given in Section 5.1.5. There will be 6 patients treated at the MTD before moving to the phase II component of the study. That is, if the second dose is deemed too toxic and only 3 patients had been treated at the first dose, a second cohort of 3 patients will be treated at the first dose. If the dose escalates and three patients are treated at the second dose with no DLTs, a second cohort of 3 patients will be treated at the second dose in order to study a total of 6 patients at the proposed MTD and further define the adverse event profile.

In addition, we have also stipulated that if a patient receives less than 66.7% of the planned doses of any study agent for reasons at least possibly related to side effects or toxicity from the study treatment during their first cycle on the phase I study, the patient will be counted as having had a DLT. Information about the dose intensity (or percent

of planned dose received) and any toxicity experienced will be reviewed and reported for each patient on the Phase I portion of the study. The dose intensity and toxicity information will be reviewed at each decision point in the Phase I dose escalation study and will be included in the evaluation of the recommended Phase II dose.

True rate of DLT	10%	20%	30%	40%	50%	60%	70%
Probability of escalation	.91	.71	.49	.31	.17	.08	.03

9.3.2 Phase II

Once the MTD of gemcitabine, Nab-Paclitaxel and AZD1775 has been determined, the study will move to Phase II defined as a randomized, Phase II study in patients with PS 0-1 and metastatic adenocarcinoma of the pancreas who are equally randomized between gemcitabine/Nab-Paclitaxel (Arm H) or gemcitabine/Nab-Paclitaxel/AZD1775 (Arm I). Stratification factors on randomization are ECOG PS and intent to participate in an imaging study (see Section 4.2.5) and these factors will not be used in analysis. The primary analysis set will be an intent-to-treat (ITT) set that includes all randomized patients.

A total of 84 patients will be randomized in the Phase II component of the study. The study seeks to establish an improvement in the primary endpoint, progression free survival (PFS), which is defined as a 66.6% increase in median PFS from 6 months in the control arm (Arm H) to 10 months in the experimental arm (Arm I), a hazard ratio of 0.60. Progression free survival (PFS) is defined as time from randomization to documented progression or death without progression. Disease progression will be evaluated using evaluation criteria defined in Section 6. Patients without documented progression or death reported will be censored at the time of the last documented disease evaluation. The study is designed to have 85% power for the target hazard ratio of 0.60 with 84 patients and 69 PFS events at full information, which are expected to occur at 27 months post activation (assuming 14 months of accrual at 6 patients per month and 13 additional months of follow-up). The primary analysis will be via a stratified log rank test at a one-sided significance level of 0.15.

The study will be monitored for potential efficacy stopping using an early look at PFS after approximately 50% of the planned full information (35 PFS events) has been observed. A one-sided stratified log rank test for PFS will be performed for the monitoring analysis. To preserve the overall type I error at 0.15, a critical value at the interim analysis will be determined using the O'Brien-Fleming boundary. Under the planned accrual schedule with six patients per month, the monitoring analysis is projected to occur at 13 months following the start of accrual, a time point that should be close to the end of accrual. If the true control median PFS is 6 months and the true experimental median PFS is 10 months, there will be 41% probability of crossing the upper efficacy boundary (1.72).

This study will also be monitored for futility using a rule that the study will be stopped early for lack of benefit if the estimated hazard ratio for experimental/control ≥ 1 at 50% of the planned full information.

Overall survival, overall objective response, disease control rate and toxicity will be important secondary endpoints of this phase II trial. Overall survival is defined as time from randomization to death from any cause, censoring cases who are alive at the date of last contact. PFS and OS by arm will be compared using one-sided log-rank tests. Cox's proportional hazards models will be used to estimate hazard ratios. Response rate (complete response or partial response) and disease control rate (complete response, partial response, or stable disease) are also secondary endpoints which will be analyzed using Fisher's exact tests at a one–sided significance level of 0.15. Furthermore, we will perform subset analyses within baseline p53 status (wild type and mutated prior to cycle 1) for each endpoint in an exploratory fashion. The ratio of p53 wild type to p53 mutation is expected to be 50:50. Patient demographics and disease characteristics will be compared using two-sample t-tests or Fisher's exact tests as appropriate.

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Expedited reporting of certain adverse events is required. With 42 patients per arm, phase II will have sufficient precision to provide 90% confidence interval on toxicity that will be no wider than 27.1%. For rare toxicities with 3% true probability, there will be at least 72% probability of observing one or more toxicities in either arm. For rare toxicities with 4% true probability, there will be at least 82% probability of observing one or more toxicities on either treatment arm. Formal comparison of toxicity rates between the arms is not a goal in phase II of this trial and the sample size will provide sufficient power for detecting only relatively large differences in adverse events. With the limited sample size, comparisons of overall survival will also be limited in statistical nature.

9.4 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

9.5 Gender and Ethnicity

The sample size for the phase I component is unknown as it is based on the dose escalation rules; therefore the accrual projection table below is based on the phase II component sample size of 84 patients. Based on previous data from past pancreas trials, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	1	3
Not Hispanic or Latino	35	46	81
Ethnic Category: Total of all subjects	37	47	84
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	3	3	6
Native Hawaiian or other Pacific Islander	0	0	0
White	33	43	76
Racial Category: Total of all subjects	37	47	84

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

9.6 Statistical Analysis for Advanced Imaging Studies

9.6.1

To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of response using RECIST as the reference standard for response in patients with metastatic pancreatic cancer.

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A total of 60 patients (30 patients each from Arm H and I) will undergo FDG-PET imaging and provide data for the FDG-PET imaging analysis. This sample size provides 86.9% power for a two-sided test to determine whether the area under the ROC curve (AUC) for the prediction of RECIST response is above 0.7, assuming that the actual area is 0.9 and 1/3 of the patients (20 out of 60) will have complete or partial response as assessed by RECIST at 8 weeks.

SUV_{max} is defined as the highest single-pixel SUV in a volume of interest (VOI). In the primary analysis for this objective we will estimate the AUC of the change in SUV_{max} (treated as a continuous variable) with a binary RECIST assessment of response at 8 weeks as the reference standard. The RECIST response status will be categorized as “positive” if response is classified as complete or partial and “negative” otherwise. The analysis will be carried out using the pooled data across both arms of the trial. In an elaboration of this analysis we will consider regression modeling with indicators of treatment arm as covariates.[37] In a secondary exploratory analysis we

will dichotomize the SUV_{max} response using a 25% threshold (< -25% versus ≥ -25%) discussed in the literature[38] and compute the sensitivity and specificity of the dichotomized variable with RECIST response defining the reference standard.

9.6.2 To evaluate the accuracy of change in tumor FDG update (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of overall survival in patients with metastatic pancreatic cancer.

Overall survival (OS) is defined as time from randomization to documented death. Patients without documented death will be censored at the time of the last documented disease evaluation.

In the primary analysis for this objective, we will use time-dependent ROC methodology to assess the ability of SUV_{max} change to predict OS[39]. This type of ROC analysis in needed in order to account for the censoring in the OS variable defining the reference standard information. We will derive time-specific estimates of the ROC curve and its area at clinically relevant time-points (e.g. 1 year). We will also estimate the time-averaged AUC as a measure of overall accuracy. In secondary analyses we will examine the performance of SUV_{max} as an independent predicator of OS using Cox-regression modeling.

9.6.3 To evaluate the accuracy of change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of progression-free survival in patients with metastatic pancreatic cancer.

Progression-free survival (PFS) is defined as time from randomization to documented progression or death without progression. Patients without documented progression or reported death will be censored at the time of the last documented disease evaluation.

In the primary analysis for this objective, we will use time-dependent ROC methodology to assess the ability of SUV_{max} change to predict PFS.[39] This type of ROC analysis is needed in order to account for the censoring in the PFS variable defining the reference standard information. We will derive time-specific estimates of the ROC curve and its area at clinically relevant time-points (e.g. 6 months) and we will also estimate the time-averaged AUC as a measure of overall accuracy. In secondary analyses we will examine the performance of SUV_{max} as an independent predictor of PFS using Cox-regression modeling.

9.6.4 To compare the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET between the patients from treatment arms F and G.

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The change in SUV_{max} will be compared between Arm H vs. I only as a continuous variable using Wilcoxon test and as binary variable (defined as summed SUV_{max} change from baseline < -25% versus ≥ -25%) using Fisher's exact tests.

9.6.5 To evaluate if an early increase in tumor FLT uptake (FLT-flare) is observed within 24 hours after initiation of treatment with Nab-Paclitaxel/gemcitabine.

9.6.6 To evaluate if an early (within 24 h) increase in tumor FLT uptake (FLT-flare) is abrogated after initiation of treatment with Nab-Paclitaxel/gemcitabine/AZD1775.

9.6.7 To compare the change in tumor FLT uptake (SUV_{max}) from baseline to 24 hours after initiation of treatment between the patients from treatment arms H and I.

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The analysis for the FLT-PET imaging is exploratory and will be based on data collected on a total of 10 patients (5 patients from Arm H and I, respectively). We will tabulate descriptive statistics on summed SUV_{max} change of the 5 hottest lesions from baseline to Day 2 post-treatment by arm. The change in SUV_{max} will be compared between Arm H vs. I only as a continuous variable using Wilcoxon test and as binary variable (defined as summed SUV_{max} change from baseline < -25% versus ≥ -25%) using Fisher's exact tests.

9.7 Statistical analysis of laboratory biomarkers

9.7.1 Correlational analyses

patients in the Phase II portion of this study. Treating both the changes in biomarker expression from baseline to 24-hours post-treatment in cycle 1 and tumor response at 8 weeks defined by RECIST (complete response, partial response, stable, and progression of disease) as cross-sectional predictors for progression-free endpoint, their correlations will be determined using Spearman correlation coefficients (ρ). We will apply Evan's decision criteria for ρ: 0.19=very weak correlation, 0.20-0.39=weak correlation, 0.40-0.59=moderate correlation, 0.60-0.79=strong correlation, >0.80=very strong correlation in each arm. Assuming that 10% of 42 patients per arm in Phase II of the study will not have laboratory samples, there will be at least 80% power to distinguish between the null hypothesis correlation of 0.59 and the alternative hypothesis correlation of 0.80 using a one-sided Fisher's Z-test with a significance level of 0.15.

9.7.2 Analyses of p53

For analyses of p53 as a prognostic marker, there is at least 80% power to detect a PFS hazard ratio of at least 1.66 using a one-sided 0.05 level log rank test, using the assumptions above that roughly 90% of the patients will have usable biologic samples (n=108) and that roughly half of patients will be mutated. Power for p53 as a predictive marker will be more limited. There will be at least 80% power for an interaction effect (ratio of hazard ratios) of 2.9 in a Cox proportional hazards model with a one-sided 0.05 significance level using a partial likelihood test. Hence power is fairly limited in this phase II study for looking at p53 as a predictive marker but the calculations here are fairly conservative. Power may be higher if a larger number of samples are available. Power is also computed under the assumption of 16 months of follow-up to coincide with the

statistical considerations of the clinical endpoints; if more follow-up is possible due to the timing of completing the laboratory analyses interaction effects smaller than 2.9 may be detectable.

Analyses of pharmacodynamic biomarkers

The biomarkers described in Section 12.2 (Phospho-Cdc2Tyr15, Cyclin A2, etc; 5 primary biomarkers total listed in Section 12.1) can be considered quantitative as they result from assays providing percent of cells or averages of scored components. This section will therefore focus on power for two-sample equal variances t-tests comparing pharmacodynamic biomarker values between the treatment arms for either individual markers measured at pre-treatment (tumor measurements) or change in biomarkers post-treatment minus pre-treatment (hair follicle measurements) and again assuming that 90% of patients will provide data for these analyses (n=76) total or 38 patients per arm). Power will be expressed in terms of detectable effect size since preliminary measures of variability of each marker are not available. For each biomarker, testing will be done strictly at a significance level of 0.05 two-sided but no other type I error control will be used to maximize power for these largely exploratory analyses. If raw distributions or log-transformed values are in violation of normality assumptions, non-parametric Wilcoxon tests will be used. In those cases, power may be somewhat lower than that quoted here. For each marker, a two-sided t-test will have at least 80% power to detect an effect size of 0.67 assuming equal variances. If the variance ratio is large (>/= 4), there is 80% power for an effect size of 1.08 using an unequal variances t-test (using the smaller variance to compute the effect size, and assuming that the larger variance occurs in the group with the higher mean, which is typically the case).

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10. Imaging Studies

The background for the research imaging studies is outlined in Section 1.7. A limited number of ECOG-ACRIN membership institutions will participate in the ACRIN imaging sub-studies. These institutions will need to complete ACRIN qualification requirements prior to consenting and enrolling participants to the ACRIN imaging sub-studies. Once the site is ACRIN-qualified, all imaging-eligible patients enrolling to the EA2131 parent therapeutic trial **must be asked to participate** in the optional imaging sub-study. Qualification procedures are provided in the EA2131 Imaging Manual, posted on the ACRIN web site at www.acrin.org/EA2131_imagingmaterials.aspx.

The target patient populations are:

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a. FDG-PET cohort: 60 patients total, recruited from phase II Arms H and I
b. FLT-PET cohort: 10 patients total, recruited from phase II Arms H and I

** Patients in the FDG-PET cohort may not enroll in the FLT-PET sub-study and vice versa.**

10.1 Research Objectives:

10.1.1 To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of response using RECIST as the reference standard for response.

10.1.2 To evaluate the change in tumor FDG update (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of overall survival.

10.1.3 To evaluate the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET as a predictor of progression-free survival.

10.1.4 To compare the change in tumor FDG uptake (SUV_{max}) between baseline FDG-PET and week 4 FDG-PET between the patients from treatment arms H and I.

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10.1.5 To evaluate if an early increase in tumor FLT uptake (FLT-flare) is observed within 24 hours after initiation of treatment with Nab-Paclitaxel/gemcitabine.

10.1.6 To evaluate if an early (within 24 h) increase in tumor FLT uptake (FLT-flare) is abrogated after initiation of treatment with Nab-Paclitaxel/gemcitabine/AZD1775

10.1.7 To compare the change in tumor FLT uptake (SUV_{max}) from baseline to 24 hours after initiation of treatment between the patients from treatment arms H and I.

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10.2 Imaging Sub-Study Site Review and Qualification

ECOG-ACRIN member institutions interested in participating in the FLT-PET and/or FDG-PET ACRIN imaging sub-studies must meet site review and qualification procedures prior to enrolling patients onto either of the imaging sub-studies:

- For sites participating in the FLT-PET imaging sub-study, a radiologist site PI must be identified and provide the FDA Form 1572 to ACRIN for delivery to the NCI Cancer Imaging Program (CIP);
- The site must complete an ACRIN protocol-specific application (PSA), which will be posted to the ACRIN web site (www.acrin.org), that requires: logistical plan for identifying and consenting patients to the ACRIN imaging sub-study and logistical plan for tracking receipt, storage, and use of the IND FLT imaging agent;
- A copy of the IRB approval letter and the IRB-approved, institutional study-specific informed consent must be delivered to the ACRIN trial monitor to review and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance Department);

Parameters for the FDG-PET and FLT-PET imaging protocols are available in the EA2131 Imaging Manual (www.acrin.org/EA2131_imagingmaterials.aspx). The imaging manual should be printed and made available to imaging technologists at participating, ACRIN-qualified sites to ensure adherence to the research imaging protocols, including quality control procedures as outlined by the manufacturer and ACRIN for PET (see www.acrin.org/CORELABS/PETCORELABORATORY/PETQUALIFICATION/tabid/485/Default.aspx). Sites will be informed when the imaging manual is updated; the most-current version will be made available online.

Qualification at sites comprises: completion of an application including information about local QC procedures; uniform phantom imaging that verifies both quantification (SUV) and uniformity (Normalization); two test cases to validate scanner functionality and image quality and to verify images are properly formatted. Annual renewal with phantom assessment of research machine(s) will follow.

A dedicated PET scan unit or hybrid PET/CT scanner is mandatory. The PET scanner must be capable of performing both emission and transmission images in order to allow for attenuation-corrected PET scan images. The ability to calculate standardized uptake values (SUVs) also is mandatory. All sequential imaging sessions will be performed on an identical or technically equivalent PET/CT scanner.

10.3 ACRIN Regulatory Oversight

The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. Site investigators will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s). The ACRIN Biostatistics and Data Management Committee (BDMC) and the ACRIN Steering Committee will regularly review the sub-study accrual and may request information about the sub-study's accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

10.4 Imaging Sub-Study Time Points and Procedures: FDG and FLT Cohorts

Site Quality Control: A daily quality control (QC) check must be performed at the beginning of the day prior to scheduled imaging, including PET scanner and dose calibrator, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

Participants must be scanned on ACRIN-qualified scanners that are quality controlled per instructions provided in the EA2131 Imaging Manual: www.acrin.org/EA2131_imagingmaterials.aspx

10.4.1 FDG Cohort Procedures

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The FDG Cohort will comprise a total of 60 participants, from study Arms F and G, undergoing FDG-PET/CT at limited institutions that have been ACRIN-qualified for participation in the ACRIN imaging sub-study. Patients enrolled in the EA2131 trial must be eligible for the FDG cohort, including a post-consent evaluation of standard imaging to identify evaluable lesion (either primary pancreas mass or metastasis) of > 2 cm in size. AE-reporting requirements, including those for the imaging sub-studies, are outlined in Sections 5.3- 5.5.

FDG-PET scans will be obtained at two (2) time points:

1. Pre-treatment FDG-1 (at baseline, defined as after consent and standard imaging assessment for eligibility, but before treatment initiation on Day 1 of Cycle 1); and
2. Pre-Cycle 2 FDG-2 (at Day 25 [± 3 days] after Cycle 1 initiation/before Cycle 2 initiation).

Blood Glucose and FDG Administration: The participant's blood glucose level must be checked before FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of FDG administration. If the blood glucose level is greater than 200 mg/dL, the FDG-PET scan should be rescheduled for within 7 working days after the first attempt. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the trial. Insulin administration immediately before the FDG-PET study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should not be administered near the FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the FDG injection. Patients with diabetes who are on oral diabetic medication should take their medication 4 to 5 hours prior to the FDG-PET.

10.4.1.1 VISIT 1: Eligibility/Registration

- Determine patient's eligibility to participate in the imaging sub-study.
- Obtain a signed informed consent form for the imaging sub-study prior to performing any sub-study procedures. For sites which will be performing both

FDG- and FLT-PET scans, allow the participant to choose the cohort to join if eligible for either.

- Schedule the baseline imaging scan for VISIT 2, FDG-1.

10.4.1.2 VISIT 2 FDG-1: Baseline FDG-PET/CT Imaging Scan

The baseline FDG PET/CT (FDG-1) scan will take place prior to chemotherapy on Day 1 of Cycle 1.

- Assess pregnancy status for all women of childbearing potential, per the institution's general practice and standard of care prior to performing any imaging scans using contrast.
- Check glucose level prior to administration of FDG (must be less than 200 mg/dL; see additional instructions above).
- Specific image acquisition and reconstruction protocols can be found on the ACRIN web site at www.acrin.org/EA2131_imagingmaterials.aspx.
- An adverse event evaluation will be performed at 24 hours (+/- 4 hours) after the imaging study is completed.

10.4.1.3 VISIT 3 FDG-2: Pre-Cycle 2 FDG-PET/CT Imaging Scan

The pre-cycle 2 FDG PET/CT (FDG-2) scan will take place prior to chemotherapy on Day 25 (± 3 days) of Cycle 1/prior to initiation of Cycle 2.

- Assess pregnancy status for all women of childbearing potential, per the institution's general practice and standard of care prior to performing any imaging scans using contrast.
- Check glucose level prior to administration of FDG (must be less than 200 mg/dL; see additional instructions above).
- Specific image acquisition and reconstruction protocols can be found on the ACRIN web site at www.acrin.org/EA2131_imagingmaterials.aspx.
- An adverse event evaluation will be performed at 24 hours (+/- 4 hours) after the imaging study is completed.

10.4.2 FLT Cohort Procedures

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The FLT Cohort will comprise a total of 10 participants, 5 each from Arms H and I, undergoing FLT-PET/CT at limited institutions that have been ACRIN-qualified for participation in the ACRIN imaging sub-study. Patients enrolled in the EA2131 trial must be eligible for FLT cohort, including a post-consent evaluation of standard imaging to identify evaluable lesion in the pancreas (likely to have primary adenocarcinoma of the pancreas) > 2 cm in size that is not primarily

fibrotic or mucinous in nature. AE-reporting requirements, including those for the imaging sub-studies, are outlined in Section 5.3. The CAEPR for FLT and radiation exposure associated with the imaging sub-studies are available in Section 5.5.

The FLT agent will need to be ordered a minimum of 2 calendar days prior to the scheduled FLT-PET/CT study.

FLT-PET/CT scans will be obtained at two (2) time points:

1. Pre-treatment FLT-1 (baseline, defined as after consent and standard imaging assessment for eligibility, but before treatment initiation on Day 1 of Cycle 1);
2. Early-Cycle 1 FLT-2 (defined as Day 2 [20 to 24 hours] after Cycle 1 initiation)

See Section 8.4 for FLT IND Administration Information.

10.4.2.1 VISIT 1: Eligibility/Registration

- Determine patient's eligibility to participate in the imaging sub-study.
- Obtain a signed informed consent form for the imaging sub-study prior to performing any sub-study procedures. For sites which will be performing both FDG- and FLT-PET scans, allow the participant to choose the cohort to join if eligible for either.
- Schedule the baseline imaging scan for VISIT 2, FLT-1.

10.4.2.2 VISIT 2 FLT-1: Baseline FLT-PET/CT Imaging Scan

The baseline FLT PET/CT (FLT-1) scan will take place prior to chemotherapy on Day 1 of Cycle 1.

- Assess pregnancy status for all women of childbearing potential, per the institution's general practice and standard of care prior to performing any imaging scans using contrast.
- Specific image acquisition and reconstruction protocols can be found on the ACRIN web site at www.acrin.org/EA2131_imagingmaterials.aspx.
- An adverse event evaluation will be performed at 24 hours (+/- 4 hours) after the imaging study is completed.

10.4.2.3 VISIT 3 FLT-2: Early-Cycle 1 FLT-PET/CT Imaging Scan

The early-cycle 1 FLT PET/CT (FLT-2) scan will take place after chemotherapy on Day 2 (20 to 24 hours after cycle 1 initiation and at least 2 hours after AZD1775 is administered on day 2) of Cycle 1.

- Assess pregnancy status for all women of childbearing potential, per the institution's general practice and

standard of care prior to performing any imaging scans using contrast.

- Specific image acquisition and reconstruction protocols can be found on the ACRIN web site at www.acrin.org/EA2131_imagingmaterials.aspx.
- An adverse event evaluation will be performed at 24 hours (+/- 4 hours) after the imaging study is completed.

Table 10.1: Time points for FDG- and FLT-PET/CT Scans

	Baseline[1] (Day 1, Cycle 1, Prior to Chemotherapy Administration)	**Early-Cycle 1** (Day 2, Cycle 1)	**Pre-Cycle 2** (Day 25 ± 3 Days, Cycle 1/Before Cycle 2 Initiation)
FDG-PET/CT[2]	X[3]	–	X[3]
FLT-PET/CT	X	X	
AE evaluation[4]	X	X	X

1. Must be scheduled for the same day as/prior to chemotherapy initiation.
2. Insulin administration immediately before the FDG-PET/CT study to reduce the glucose levels is not allowed. Patients with diabetes should continue to adhere to their oral agents or insulin routines. These medications should not be administered near the FDG injection time. In insulin-dependent patients, insulin should be administered at least 5 hours prior to the FDG injection. Patients with diabetes who are on oral diabetic medication should take their medication 4 to 5 hours prior to the FDG-PET/CT.
3. Blood glucose level should be checked before FDG injection. Blood sugar (measured by glucometer) must be less than 200 mg/dL at the time of the FDG-PET study. If the blood glucose level is greater than 200 mg/dL, the FDG-PET imaging should be rescheduled. If the blood glucose level still exceeds 200 mg/dL on the following scheduled day for PET scanning, the patient will not be included in the trial.
4. AE evaluation must be performed (in person or by phone) at 24 hours (± 4 hours) after each FDG-PET/CT and FLT-PET/CT imaging scan. See Sections 5.3 and 5.5 for AE reporting requirements of the imaging sub-studies.

10.4.3 FDG-PET/CT Analysis Description

Analysis will determine the degree of change in summed SUV_{max}, and its correlation with tumor response by standard RECIST criteria and PFS. The percentage change in the sum of SUV_{max} of the 5 hottest lesions at baseline will be determined. The same lesions will be measured pre- and post-treatment. The change in SUV_{max} will be used in the primary analysis as a continuous variable. In secondary analysis, the change will be categorized into 2 groups – summed SUV_{max} change from baseline ≥ -25% vs. summed SUV_{max} change from baseline < -25%. We hypothesize that the larger SUV_{max} change will predict better tumor response with standard imaging at 8 weeks and have improved outcomes as assessed by PFS. The change in SUV_{max} between Arms H and I will also be compared.

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10.4.4 FLT-PET/CT Analysis Overview and Release of Results

The percentage change in the sum of SUV_{max} of the 5 hottest lesions at baseline will be determined. The same lesions will be measured

pre- and post-treatment. We hypothesize the early-FLT flare will be induced by gemcitabine-based chemotherapy and that early-FLT flare will be abrogated by the addition of AZD1775 to gemcitabine-based chemotherapy. The final results of the FLT-PET study will be shared with the participating centers at the completion of the entire study. With agreement between the patient and the treating physician, and at the discretion of the participating center, the treating physician may share the experimental results of the FLT imaging scans with the participant. The sharing of the informal results should be done with caution, as the FLT-PET is still experimental and the significance of these results is unknown. The results from the FLT-PET scans should not be part of the patient's medical record and should not be used to direct or change therapy. We emphasize that sharing of imaging results with patients remains optional and at the discretion of the participating center, the patient and the treating physician.

10.4.5 Off-Imaging Criteria

Participants who do not complete baseline FDG-PET or FLT-PET imaging scans will not continue on-study for the imaging sub-studies to complete the second protocol-defined imaging study. Additional participants will be recruited until target accrual is reached, as long as study funds and overall trial recruitment timelines allow.

10.5 Imaging Submissions for Quality Control and Central Reader Study

10.5.1 Imaging Submission Instructions

For TRIAD Submission: The preferred image transfer method is via TRIAD, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD software; Internet access is also required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

For more information, contact: TRIAD-support@phila.acr.org or call 215-940-8820.

An Image Transmittal Worksheet (ITW) must accompany all media submissions and should be delivered via email or fax (to: imagearchive@acr.org or 215-923-1737).

Images may be mailed to:

American College of Radiology Imaging Network
ACR Imaging Core Laboratory
Attn: ECOG-ACRIN EA2131
1818 Market Street 16th floor
Philadelphia, PA 19103

10.5.2 Quality Control (QC) Review

First imaging studies from each site must be submitted within 48 hours after acquisition for a review of adherence to study protocol. Local review of imaging studies for completeness, DICOM content, and dose correction, for example, is encouraged prior to submission to the core lab. QC review will be performed on all FDG-PET/CT and FLT-PET/CT image submissions to the ACR Imaging Core Lab. ACRIN's imaging specialists will provide feedback to participating sites, especially during early submissions, in response to QC assessments.

10.5.3 Central Reader Study

A central review and analysis of all FDG-PET and FLT-PET scans will be performed by ACRIN at the ACR Imaging Core Laboratory. The centralized imaging analysis will be used for secondary endpoint analysis.

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11. Phase I Biospecimen Submissions and Research Studies

Plasma specimens for pharmacokinetics studies are REQUIRED from all patients enrolled on the Phase I aspect of the trial.

Kits are requested from and samples submitted to Covance Laboratories, Inc. for assessment of the AZD1775 pharmacokinetics.

11.1 Sample submissions

Submission of plasma samples are MANDATORY. All times are relative to the administration of AZD1775 administration.

Collection and shipping kit request form is in Appendix XI. Each kit will contain the materials (vacutainers, cryovials, labels, and shippers) for the collection and submission of samples for a single patient for all required time points. Two kits may be requested by the Phase I participating site upon IRB approval of the Phase I aspect of the trial.

The date and time of AZD1775 administration, the start time of chemotherapy (for day 1), and actual draw times must be entered into the ECOG-ACRIN Samples tracking system and must be provided in the documentation submitted with the blood samples.

LABELING: All samples are to be labeled with the ECOG-ACRIN protocol number EA2131, the ECOG-ACRIN patient ID number, **date, time point** (e.g. C1D1-0) **of collection**, and type of material (plasma EDTA). Pre-printed labels, provided in the kits, with a unique Custom ID will be used on all sample and aliquot tubes.

When applying the label, place the label in a vertical position. Do not wrap the label around the tube horizontally. Place the label as close to the cap as possible, but do not adhere the label to the cap of the tube. Do not cover any written information with the label.

11.1.1 Submission Schedule

Sample submission schedule is outlined in table format in Section 7.1.1.

Blood samples will be collected into 2 mLvacutainers containing EDTA and processed to isolate the plasma at:

- Cycle 1, Day 1: Time points will be at 0 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr and 24 hrs (Day 2, 0 min) from the time of first AZD1775 administration. Patients are to bring their day 2 dosage to take AFTER the 24 hour draw.
- Cycle 1, Day 16: Time points will be at 0 min, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr and 24 hrs (Day 17) from the administration of first AZD1775 administration. Note, the 24 hour (day 17) draw is strongly encouraged but not required. Patients are to arrive at the clinic prior to time they are to take their day 16 dose.

The collected plasma samples are to be batched at ≤ -70°C and shipped on dry ice at the end of cycle 1, upon collection of all samples from a single patient.

11.1.2 Preparation and Shipping Guidelines

Blood samples are to be processed within 30 minutes of the draw and the collected plasma placed in the freezer (≤ -70°C) as quickly as possible.

Please label and track the collection of these samples carefully, as the collection times will impact assessment of the samples.

Time of administration of AZD1775, start of first chemotherapy IV (day 1 only) and actual draw time for each sample must be indicated in the Sample Tracking System.

- Draw 2 mL of peripheral blood into the EDTA **(purple top)** vacutainer tube provided in the kit provided by Covance. Gently invert tube 10 times.
- Place the vacutainer in ice bath immediately. Within 30 minutes of collection, separate plasma in a centrifuge at refrigerated (~ 4°C) at 1500 g for 10 min.
- Pipette roughly equal amounts of plasma into two properly labeled plastic cryogenic tubes and freeze at -20°C or less until shipped.

Packaging instructions:

- **DO NOT SPLIT THE SAMPLES FROM A SINGLE PATIENT ACROSS MULTIPLE SHIPMENTS**.
- All samples must be labeled. No unlabeled samples are to be shipped. When applying the label, place the label in a **vertical** position. Do not wrap the label around the tube horizontally. Place the label **as close to the cap of the cryovial as possible**, but do not adhere the label to the cap of the tube. Do not cover any written information with the label.
- It is strongly recommended that Day 1 and Day 16 samples from a single patient be in separate biohazard bags.
- Do not ship samples from multiple patients together.
- Each biohazard bag within the shipment must be clearly labeled with the protocol number, patient case ID, and day of collection (C1D1 or C1D16).
- MUST be shipped **on dry ice** (sufficient quantity to ensure they remain frozen for at least 72 hours) overnight MONDAY through THURSDAY only. Do not ship on the day before a weekend or holiday.
- Samples must be securely packed in boxes to avoid breakage during transit and double-bagged to contain leaks.
- Ship using the courier shipping label provided in the kit.
- **A fax of the completed *COVANCE Specimen Shipment Pre-Alert Form* (Appendix XII) :**
  - Fax: 1-800-335-1462
  - Email: SMSpecialHandlingIndy@Covance.com
  - Email: Phyllis.Sellars@Covance.com

- Email: Gaelle.Legaud@Covance.com

on the day of sample shipment. The samples being shipped to CCLS should be shipped using the Covance-supplied kit supplies and labeled with the original CCLS barcode label for identification purposes. Place the purple label, if provided, on the outside of the shipper. The samples should be accompanied with a specimen packing list to allow sample reconciliation upon receipt at CCLS. An STS-generated shipping manifest must be submitted with every shipment and an electronic copy of the manifest should be emailed directly to the email addresses above.

Ship to Covance Laboratories at:

Covance Central Laboratory Services
Attn: Phyllis Sellars – Special Handling
8211 SciCor Drive
Indianapolis, Indiana 46214
Phone: 317-271-1200

11.2 ECOG-ACRIN Sample Tracking System

It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

The date and time of AZD1775 administration, start time of chemotherapy, and actual draw time of each sample must be entered into the ECOG-ACRIN Samples tracking system, and be provided with the documentation submitted with the blood samples.

Generic Specimen Submission Form (#2981) will be used in the event that STS is unavailable at time of sample submission as a substitute for the STS-shipping manifest. Indicate the appropriate Lab on the submission form:

- Covance Central Laboratory Services

Retroactively enter all specimen collection and shipping information when STS is available.

11.3 Storage for Future Research

Residual material from the Phase I pharmacokinetic specimens submitted will not be retained for future research. Specimens will be held until specimen and data analyses are completed and then destroyed.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

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12. Phase II Biospecimen Submissions and Research Studies

Sample submissions apply to patients in the Phase II Study (Arms H and I) only.

Specimens are to be submitted from patients on either treatment arm who consent "Yes" to " *I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies described above*" for the research studies outlined in Section 12.1.

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest is to be included with every submission to any receiving laboratory.

All samples and aliquots must be labeled with the protocol number (EA2131), ECOG-ACRIN patient ID number, patient initials, date of collection and sample type.

12.1 Specimen Collection and Submission

12.1.1 Schedule

Specimens must be labeled with the protocol number, ECOG-ACRIN patient sequence number, date AND TIME of collection, and specimen type.

Order form for collection/shipping kits is located in Appendix XIII. Starter kits are NOT available.

Samples are to be submitted as follows:

- Pre-trial diagnostic pathology materials are to be submitted within 2 weeks following randomization. See Section 12.1.2
- Scalp punch biopsy samples (hair follicles) are to be submitted as outlined in Section 12.1.3 upon collection and processing of the day 2 sample. Samples are to be collected at the following timepoints:
  - prior to start of protocol treatment,
  - Cycle 1 Day 2

12.1.2 Submission Tissue

Submitting pathologist and clinical research associate may refer to Appendix I which also outlines the Pathology Submission Guidelines.

The tissue samples are to be labeled with the pathology ID specimen ID as well as containing the information above.

12.1.2.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest.
- Copy of the surgical pathology report.

Biological Material Submission:

- Representative diagnostic or surgical tumor tissue block

NOTE: If a block is unavailable for submission, cores and slides are to be submitted, all cores and slides must be adequately labeled, with slides number sequentially in the order cut. Alternative submission requirement:

- One (1) H&E, and
- Twenty (20) 4 µm unstained air-dried plus slides, and
- One (1) or more core punches (minimum of 4mm). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844-744-2420). Adequately label every slide and core submitted.

12.1.2.2 Shipping Procedures

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. This account is used for all shipment to the ECOG-ACRIN CBPF for any ECOG-ACRIN trial. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

Pathology materials are to be shipped at ambient temperature within 2 weeks of patient randomization.

Ship to the E-A CBPF at:

MD Anderson Cancer Center
Department of Pathology
Tissue Qualification Laboratory for ECOG-ACRIN
Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Tel: 844-744-2420
Fax: 713-563-6505
Email: eacbpf@mdanderson.org

12.1.3 Submissions of Scalp Biopsies

Questions regarding shipments are to be directed to the ECOG-ACRIN CBPF. Questions regarding performance of the scalp biopsies are to be directed to Erin Hohler at (216) 286-3889 / (216) 386-3890.

Samples are to be collected prior to start of protocol treatment and Cycle 1, Day 2 of treatment.

12.1.3.1 Specimen preparation

Hair Follicles (Scalp Punch Biopsy)

Patient is to be instructed not to apply any topical agents to the biopsy area within 72 hours prior to the procedure (local anesthetic is allowed). Make sure the processing set-up is complete before collecting the scalp punch biopsy.

- Complete and adhere the labels provided on all collection vials with date of specimen collection and patient identifiers.
- Obtain the biopsy from the scalp area 2 inches behind the ears between the top of the ear to middle of the ear.
- Prepare the site with an alcohol wipe or alcohol swab.
- OPTIONAL: If local anesthetic is needed, inject the site of biopsy with 1% lidocaine with 1:100,000 epinephrine as local anesthetic.
- Using the thumb and forefinger of your nondominant hand, stretch the skin at the biopsy site.
- Use a 4-mm skin punch biopsy instrument to push vertically into the biopsy site and then rotate the instrument to cut through the skin into the subcutaneous fat. As you go through the skin into the fat, a decrease in resistance will be felt.
- Push down with your fingers around the biopsy site and the biopsy specimen should lift up. Carefully grasp the biopsy specimen with forceps and lift up. Use sharp tissue scissors to cut the subcutaneous base of the biopsy specimen.
- Apply direct pressure to the biopsy site to achieve hemostasis and then close the site with steristrips or a sterile adhesive dressing. Have a suture kit available in case a suture needs to be placed to close the wound. Load needle driver with 5-0 prolene and place 1-2 sutures. Cut sutures about 5 mm from skin surface
- Place the biopsy specimen into 10% neutral buffered formalin (NBF). Transfer the recently obtained skin punch biopsy to the container of 10% NBF as soon as possible (0-30 min of removal). The formalin solution should be at least 10 times the volume of the specimen. Seal with parafilm and place in a biohazard bag.
- Store at room temperature until shipping. DO NOT FREEZE.
- Samples for an individual patient are to be batched and shipped together for pre-treatment and post-treatment (Cycle 1, Day 2) samples.

- Adequately label every specimen submitted.

12.1.3.2 Shipping procedures

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. This account is used for all shipment to the ECOG-ACRIN CBPF for any ECOG-ACRIN trial. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

Ship the scalp punch biopsy samples at ambient temperature with the STS-generated shipping manifest MONDAY through THURSDAY only, via overnight courier o the E-A CBPF at:

MD Anderson Cancer Center
Department of Pathology
Tissue Qualification Laboratory for ECOG-ACRIN
Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Tel: 844-744-2420
Fax: 713-563-6505
Email: eacbpf@mdanderson.org

12.1.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Any case reimbursements associated with specimen submissions may not be captured if specimens are not logged into STS. Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

Generic Specimen Submission Form (#2981v2) will be required only if STS is unavailable at time of sample submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all submissions when STS is available.

12.1.5 Use of Specimens in Research

Specimens will be distributed for the research studies defined in Section 12.2 per patient consent.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained in an ECOG-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but are not limited to, extradition of plasma, serum, DNA and RNA.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

12.2 Phase II Research Studies

We propose a comprehensive approach to predict efficacy of Nab-Paclitaxel, gemcitabine and AZD1775. Subjects in the phase II portion of the study will have tumor tissue and scalp punch biopsies collected. An initial panel of biomarkers, described briefly below, is planned and additional markers will be added as they are identified.

Priority of tissue use:

1. p53 mutational analysis
2. Pharmacodynamic biomarkers for AZD1775

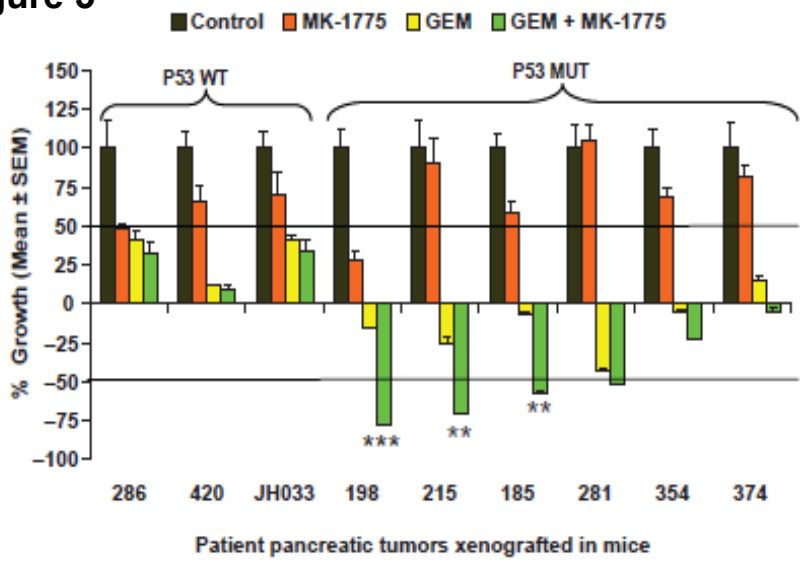
12.2.1 Evaluation of p53 mutation status by DNA sequencing

As discussed in Section 1.6.1, p53 status will be assessed on pre-treatment tumor tissue of patients in Arms H and I as studies have suggested preferential killing of p53-deficient cells with S-/G2-checkpoint inhibitors.[27] However, some studies have also suggested p53-proficient tumors are killed with S-/G2-checkpoint inhibitors.[28-31] Combination of AZD1775 and gemcitabine potentiates the efficacy of gemcitabine in established human pancreatic cancer xenografts.[23] Nine individual patient-derived low passage pancreatic cancer xenografts (3 with wild-type p53 and 6 with deficient p53 [mutant]) were implanted in athymic mice. Five of 9 xenografts treated with gemcitabine and 6 of 9 xenografts treated with combination of

gemcitabine and AZD1775 produced complete tumor growth inhibition resulting in tumor shrinkage.[23] Combination treatment caused greater than 50% regression in tumor size in 4 of 6 xenografts with p53-deficient tumors (Figure 5).[23] The p53 pathway can also be inactivated by genetic or epigenetic events that occur upstream or downstream of p53.[32] Therefore, it is important to assess the integrity of the p53 pathway to determine optimal timing of administration of S-/G2-checkpoint inhibitors and for correlations to be drawn between p53 functional status and tumor response.[32]

Figure 5: Combination of AZD1775 and gemcitabine potentiates the efficacy of gemcitabine in established human pancreatic cancer xenografts. Tumor growth inhibition was observed in the p53-wild type tumors treated with AZD1775 and gemcitabine compared to control; however, combination treatment caused greater than 50% regression in tumor size in 4 of 6 xenografts with p53-deficient tumors.[23]

Figure 5



The discrepancies between preferential killing of p53-deficient vs. -proficient tumors with S/G2 checkpoint inhibitors may be explained by dosing schedules and the integrity of the p53 pathway in the cell lines being treated.[32] In models of Chk1, loss of viability is observed when cells knocked down for Chk1 are exposed to antimetabolites to activate S-phase checkpoint and then released from the S-phase block. This response is independent of p53 status and suggests that p53-proficient tumors could potentially be targeted by concurrent administration of an antimetabolite and a Chk1 inhibitor.[29,32] The differential response of p53 proficient- vs. p53-deficient tumors to combination therapy is most readily observed when cells treated with a DNA-damaging agent are given time to arrest at the G2-checkpoint and then exposed to Chk inhibitors. Under these conditions only p53-deficient cells are observed to enter a lethal mitosis.[32,101] The p53 pathway can also be inactivated by genetic or epigenetic events that occur upstream or downstream of p53.[32] We would expect similar

changes using a Wee1 inhibitor such as AZD1775. Therefore, it is important to assess the integrity of the p53 pathway to determine optimal timing of administration of S-/G2-checkpoint inhibitors and for correlations to be drawn between p53 functional status and tumor response.[32]

p53 mutational analysis will be performed using the Ion AmpliSeq™ Cancer Hotspot Panel v2 (Ion Torrent/Life Technologies) as described.[102,103] This cancer panel targets 50 oncogenes and tumor suppressor genes, including the *TP53* gene. The test uses 207 primer pairs in a single reaction, requiring only 10ng of input DNA from FFPE samples. Briefly, Amplicons averaging 154 bp will be purified (Agencourt AMPure XP, Beckman Coulter), quantified (2100 Bioanalyzer DNA 7500, Agilent Technologies), prepared and enriched for sequencing on the Ion Sphere Particles™ (ISPs) using the Ion OneTouch™ 200 Template Kit v2 (Life Technologies) in the Ion OneTouch™ 2 System (Life Technologies). Templated ISPs will be quantified (Qubit® 2.0, Life Technologies) and loaded into an Ion 318™ Chip (Life Technologies) to be sequenced on the Ion PGM™ using the Ion PGM™ Sequencing 200 Kit v2 (Life Technologies). Signal processing and base calling will be performed with Torrent Analysis Suite version 3.4.2. FASTQ files generated from the Ion Torrent PGM™ Server will be aligned to the Hg19 version of the human genome (The Broad Institute bundle download 2.5) using the Burroughs-Wheeler Alignment algorithm as implemented in the BWA software package v.0.7.5a[104]. MuTect v.1.1.4[105] and the Ion Reporter™ Software (Life Technologies) will be used to identify somatic point mutations in aligned reads. Genetic variants will be functionally annotated using ANNOVAR v.2013Jul28[106] and proprietary software developed by GenomOncology (www.genomoncology.com). Variants will be filtered dynamically to focus on features of biological interest, including (i) filtering out all variations present in dbSNP, (ii) only showing variations that alter protein function, (iii) only showing variations in genes found in the COSMIC cancer gene database, in a subset of COSMIC by cancer type, in a subset of the Gene Ontology, in a subset of pathways from the NCI/Nature pathway set, or any combination of these parameters.

These studies will be performed at the University Hospitals Translational Laboratory (UHTL), a CLIA/CAP accredited laboratory specialized in deep sequencing assays at University Hospitals Case Medical Center/Case Western Reserve University.

12.2.2 Evaluation of pharmacodynamic biomarkers of AZD1775

In response to DNA damage, cells undergo cell cycle arrest due to the presence of cell cycle checkpoints, mainly in the G_1 and G_2 phases. Checkpoint pathways operating at the G_1 phase are frequently lost in cancer cells due to mutation of the p53 tumor suppressor gene, which is common in pancreatic cancer. Cells lacking functional p53 would not be anticipated to arrest at the G_1 checkpoint and would depend on the G_2 checkpoint to permit DNA repair prior to undergoing mitosis. Thus, G_2 checkpoint abrogation should preferentially kill p53-deficient cancer cells by removing the only checkpoint that protects these cells from premature entry into mitosis in response to DNA damage. Pre-clinical data using gemcitabine and AZD1775 pancreatic cancer xenografts strongly supports this rationale.[23]

Wee1 is the major kinase phosphorylating the Tyr-15 site of Cdc2 and Wee1-dependent phosphorylation of Cdc2 maintains the Cdc2/cyclin B1 complex in an inert form. Cdc2 initiates mitosis, which is the ultimate target of DNA replication and repair checkpoints. [23] It has been demonstrated that AZD1775 treatment strongly inhibited phosphorylation of Tyr-15 of Cdc2, the primary substrate of Wee1. [23] Tumor cells treated with gemcitabine induces G_2 arrest, which correlates with an increased Cdc2 inhibitory phosphorylation at Tyr-15 and prevents mitotic entry as evidenced by decreased phospho-histone $H3^{Ser10}$ (p-$HH3^{Ser10}$)[23] However, the decreased Cdc2 inhibitory phosphorylation at Tyr-15 caused by AZD1775 treatment indicates that AZD1775 has the ability to abrogate the G_2 arrest induced by gemcitabine and promote mitotic entry as demonstrated by enhanced p-$HH3^{Ser10}$. [23] Loss of Cyclin B1, a marker of G2 phase in combination AZD1775 and gemcitabine treatment compared to control and gemcitabine-treated pancreatic tumors, indicate the exit from G2 phase arrest.[23]. The levels of phospho-$H2AX^{Ser139}$ (γ-H2AX) were used as a surrogate for unrepaired DNA damage.[107] γ-H2AX expression was clearly elevated in the combination AZD1775 and gemcitabine treatment group compared to gemcitabine-treated tumors, indicating the persistence of unrepaired DNA damage in the tumors.[23] Therefore, the pre-clinical observations provide mechanistic support to the potential biomarkers which will be investigated in this study.

Immunohistochemistry (IHC) to biomarkers in the Wee1 signaling pathway will be performed in pre-treatment tumor tissue and pre- and post-treatment hair follicles from scalp punch biopsies to determine the treatment effects and target engagement of AZD1775. A summary of the markers of interest that will be investigated are as follows:

Biomarker	Purpose
Phospho-$Cdc2^{Tyr15}$ (p-$Cdc2^{Tyr15}$)	Primary substrate of Wee1 and indicates target engagement by AZD1775.
Phospho-histone $H3^{Ser10}$ (p-$HH3^{Ser10}$)	Measure of mitotic entry
Cyclin A2	Marker of S-, G_2- and prophase cells.
Phospho-Chk1 (p-Chk1) Phospho-$H2AX^{Ser139}$ (γ-H2AX)	Measure of DNA damage
Cleaved caspase 3	Measure of cell death

We would expect that the addition of AZD1775 to gemcitabine and Nab-Paclitaxel will: decrease p-$Cdc2^{Tyr15}$ expression indicating abrogation of G_2 arrest, increase p-$HH3^{Ser10}$ and decrease in cyclin A2 expression as the cells enter mitosis, increase p-Chk1 and γ-H2AX reflecting the presence of unrepaired DNA damage and increase cleaved caspase 3 expression as a marker of apoptosis.

Additional information on the markers of interest:

- Phospho-Cdc2^{Tyr15} (p-Cdc2^{Tyr15}) - This should provide a direct indication of drug activity, if drug is on board at the time of sampling.
- Phospho-histone H3^{Ser10} (p-HH3^{Ser10}) - This is a mitotic marker that is increased >10 fold in mitotic cells. We expect that we can measure the mitotic index on H&E sections alone, but in the event that they are rare (e.g., in hair follicles), we will use this marker which detects all mitotic stages.
- Cyclin A2 - This will mark S, G_2, and prophase cells. If mitotic cells are rare in the hair follicle sections, the ratio of cyclin A2 positive to cyclin A2 negative cells in the follicle should provide a measure of cell cycle perturbation, which we expect both from gemcitabine and Nab-Paclitaxel and from AZD1775.
- Phospho-Chk1 (p-Chk1) and Phospho-H2AX^{Ser139} (γ-H2AX) - These are both measures of DNA damage. Phospho-Chk1 is an activation marker for cells that have an activated G_2 checkpoint. It is possible that the activity of Chk1 could antagonize the activity of Wee1. Both in the normal cell cycle and in the DNA damage response, these two enzymes act in concert to delay entry to mitosis. In the presence of a Wee1 inhibitor, the activity of Chk1 could prevent the intended action of Wee1 inhibition. Therefore, we will monitor individual patient activity of Chk1 Phospho-H2AX^{Ser139} is a direct measure of DNA damage downstream of ATR and ATM. This should be directly correlated with Chk1 activation and related to the level of apoptosis.
- Cleaved caspase 3 - This will be used to evaluate the extent of induced programmed cell death.

12.2.3 Immunohistochemistry (IHC) Method

Formalin-fixed paraffin embedded (FFPE) tissues will be cut at 5um and mounted on charged slides for evaluation by IHC. Slides will be baked in an oven at 60° C to melt paraffin, remove underlying moisture, and keep tissue sections adhered to the slide. Further deparaffinization and rehydration of tissue sections will be carried out by immersion through xylenes, graded ethanols, and finally dH2O. Testing of antigen retrieval (AR) methods will include steamer (low heat), pressure cooker (high heat), and/or no retrieval, in addition to AR buffers with different chemistries (Citrate & Tris) and pHs (6 & 9). Endogenous peroxidase activity will be quenched by treating sections with a 3% H2O2 solution. Blocking of charged protein activity and reduction of non-specific background will be achieved by using a proprietary blocking reagent. Titration of individual antibodies will be performed according to dilution ranges specified on vendor datasheets as a starting basis. Additional titration will be performed when necessary. Horseradish peroxidase (HRP) conjugated secondary antibody polymers will be used to detect the target antigen-antibody bound complexes. 3, 3’ diaminobenzidene (DAB) will be

used as the chromogen to visualize the target proteins under basic light microscopy.

We plan on purchasing and validating the primary antibodies to phospho-Cdc2^{Tyr15} (Bioss Inc., Cell Signaling Technologies or BD Biosciences), phospho-histone H3^{Ser10} (Cell Signaling Technology), cyclin A2 (Novus Biologicals, Novacastra or BD Biosciences), phospho-Chk1 (Cell Signaling Technology), phospho-H2AX^{Ser139} (Cell Signaling Technology or BD Biosciences) and cleaved caspase 3 (Cell Signaling Technology, currently used at Case Western and validated).

Assays for validation including appropriate tissue, cell and intracellular (localization) expression, specificity and antibody titration will be performed on known positive and negative control tissues based on manufacturer recommendations and published peer-reviewed literature. Hence, the antibodies may be subject to change based on the validation assays. If available from researchers, known gene tested positive and negative cell line pellets can be included. Western blot analysis for single band expression can be performed if not already demonstrated by manufacturer, provided cell lysates are available. The Case Comprehensive Cancer Center IHC Core is not a CLIA regulated or certified facility. The tests performed in this facility are <u>for research purposes only</u>.

<u>Analysis of IHC evaluation</u>

- Tumor tissue

  Immunohistochemical markers will be evaluated in tumor tissue. Those proteins that may have both cytoplasmic and nuclear expression that are dependent on cell cycle and/or mutational alterations such as Chk-1 and Cyclin A2, will be scored and averaged for both components in a minimum of 3 (20x) fields for relative intensity (0-3+; representing respectively: negative , low , moderate and strong) and approximate distribution in quartiles (< 25%, 26-50%, 51-75%, > 75%). Immunohistochemical stains that are confined to nuclear expression (p-Cdc2^{Tyr15}, p-HH3^{Ser10}and γ-H2AX) are best enumerated (number of positive nuclei/ 5-10 HPF). Cleaved caspase 3 may be semiquantitatively evaluated as a number of apoptotic cells in 3 separate 0.4 mm linear basal layer hair follicle epithelium units, and expressed in quartiles as above. The number of fields may need to be adjusted due to the size of the biopsy specimens.

- Hair follicles

  Immunohistochemical markers will be evaluated in hair follicle epithelium from scalp biopsies. Those proteins that may have both cytoplasmic and nuclear expression that are dependent on cell cycle and/or mutational alterations such as Chk-1 and Cyclin A2, will be scored and averaged for both components in a minimum of 3 (20x) fields for relative intensity (0-3+; representing respectively: negative, low , moderate and strong) and approximate distribution

in quartiles (< 25%, 26-50%, 51-75%, > 75%) of basal layer keratinocytes. Immunohistochemical stains that are confined to nuclear expression (p-Cdc2^{Tyr15}, p-HH3^{Ser10}and γ-H2AX) are best enumerated (number of positive nuclei/ basal layer keratinocyte). Cleaved caspase 3 may be semiquantitatively evaluated as a number of apoptotic cells in 3 0.4 mm linear basal layer hair follicle epithelium units, and expressed in quartiles as above. The number of fields may need to be adjusted due to the size of the biopsy specimens.

12.3 Sample Inventory Submission Guidelines

Inventories of all samples submitted, be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory via STS. Inventories of specimens allocated, and used for any approved research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston

12.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data submitted quarterly is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates.

13. Electronic Data Capture

Please refer to the EA2131 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. List of Required Materials for EA2131
2. Instructional memo to submitting pathologists

List of Required Material

EA2131:	A Phase I and Randomized Phase II Study of Nab-Paclitaxel/Gemcitabine with or without AZD1775 in Treatment-Naïve Metastatic Adenocarcinoma of the Pancreas

The following materials are to be submitting within one month of registering the patient to the trial:

1. Pathology specimens:

   Diagnostic tumor tissue block - open biopsy or core needle biopsy specimens preferred, although cytology cell blocks will be accepted.

   NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned. If blocks are not available, contact the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) to obtain alternative submission guidelines.

2. Forms and reports:

   The following items are to be included with the pathology materials:

   - Institutional Surgical Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981) completed
   - ECOG-ACRIN Sample Tracking System (STS) manifest. If STS is not available at time of submission, submit the completed ECOG-ACRIN Generic Specimen Submission Form (#2981) and retroactively enter the submission information in STS when available.

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists.)

3. Mail pathology materials to the CBPF at:

   MD Anderson Cancer Center
   Department of Pathology
   Tissue Qualification Laboratory for ECOG-ACRIN
   Room G1.3586
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility Office by telephone 844-744-2420 or by email at eacbpf@mdanderson.org.

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for EA2131: A Phase I and Randomized Phase II Study of Nab-Paclitaxel/Gemcitabine with or without AZD1775 in Treatment-Naïve Metastatic Adenocarcinoma of the Pancreas*

The patient named on the attached ECOG-ACRIN Generic Specimen Submission Form (#2981) has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for research studies.

Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being *used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.*

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 or by email at eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG-ACRIN web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

Patient Capsule Calendar

Capsule Calendar Directions

1. Take your scheduled dose of each capsule.
2. If you forget, the missed capsules will not be taken later.
3. Please bring the bottle, or any leftover capsules and your capsule calendar to your next clinic visit.

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Instructions for taking AZD1775:

- Take AZD1775 one hour prior or two hours after a meal.
- On days of chemotherapy, take AZD1775 at the same time or just before the start of chemotherapy.
- On days when you do not have chemotherapy, take AZD1775 about 24 hours after your previous dose.
- Swallow each capsule whole with a full glass of water.
- Do not crush, chew or open the capsules. If capsule is broken and the powder of the capsules gets on skin, wash the exposed area with as much water as necessary. Inform investigator or nurse if that occurs.

Patient Capsule Calendar

ECOG-ACRIN patient no.: _____ Patient's Initials: _____

Agent name: AZD1775, 25 mg capsules, by mouth, taken on days 1, 2, 8, 9, 15 & 16

Take AZD1775 one hour prior or two hours after a meal.

Day	Date			# of 100 mg pills taken	# of 25 mg pills taken	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Signature of patient or the person administering the oral medication:

_____ Date: _____

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Appendix IV

CRADA/CTA

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.”):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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.

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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: 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.

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Appendix V

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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[redacted]

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

[redacted]

[redacted]

[redacted]

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Appendix VII

Medications That May Cause QTc Prolongation

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. AZD1775 may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20
Lithium	24 hour (10-50)		7
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Protiptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hr	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	60	
Voriconizole	6 hours; dose dependent		
Ziprasidone	7 hr	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

*****Weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (*e.g.*, concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

1. Physician's Desk Reference 2002

2. Facts and Comparisons (update to June 2005)
3. The Pharmacological Basis of Therapeutics 9th Edition, 1996

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Appendix VIII

Information On Possible Interactions With Other Agents For Patients And Their Caregivers And Non – Study Health Care Team

[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.]

The patient _____ is enrolled on a clinical trial using the experimental agent **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.*

[redacted], it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

[redacted]

- [redacted]

[redacted]

[redacted]

- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/main-table/ or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:

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  - If you take acetaminophen regularly: If you are an adult under 65 years of age, you should not take more than 8 extra strength tablets a day or 12 regular strength tablets a day. If you are older than 65 years of age, you should not take more than 4 extra strength tablets a day or 7 regular strength tablets a day. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
  - [redacted]

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

  _____

  and he or she can be contacted at

  _____.

INFORMATION ON POSSIBLE DRUG INTERACTIONS

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

[redacted]

[redacted]

➢ Your study doctor's name is _____ and can be contacted at _____.

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Appendix IX

Information for Local Radiology Team – Quality Control for Images

[Note to investigators and study coordinators: This appendix describes the data necessary for the FDG- and FLT-PET/CT sub-studies. It consists of a procedural "checklist" to be kept on-hand in the radiology department for the study imaging technologist and radiologist to use in quality control review of images prior to submission to the American College of Radiology (ACR) Imaging Core Laboratory. Consideration of these procedures will reduce queries in imaging data submission and ensure data integrity. If you have questions, contact the core lab at 215-923-1737.]

Checklist for PET/CT Image Quality Control

Upon Participant Arrival (FDG-PET/CT Only)

Have you checked participant fasting state and blood glucose levels prior to administration of fluorodeoxyglucose (FDG)?

NOTE: Fasting and blood glucose measurements are not needed for FLT PET/CT scans.

- ✓ Has it been confirmed and documented that the participant fasted for > 4 hours prior to arrival to the facility?
- ✓ Was the serum glucose concentration < 200 mg/dL and documented?

SUV Calculations

Standard uptake values (SUVs) will be used as the quantitative measurement to define response to therapy in the imaging sub-studies. The following are necessary to ensure accurate SUV measures.

- ✓ Time of Injection and Scan Start Time
  - Have the time of injection and the scan start time been properly recorded? If the PET scanner software performs decay correction for the time interval between injection and imaging, check whether the time of injection and the start time of the scanner have been correctly entered.
- ✓ Injected Dose
  - Has the injected dose been correctly calculated and entered in the DICOM header of the PET data set?
  - Is the time between radiotracer injection and start of the PET emission scan within the specifications of the imaging protocol? **NOTE:** The time between injection of the radiotracer and PET emission scan start time should be targeted at 60 minutes with an acceptable window of 50 to 70 minutes.
- ✓ Body Weight
  - Has the body weight of the participant been correctly recorded and entered into the DICOM header of the PET data set? **NOTE:** The patient's height and weight

must be measured; verbal relay by the patient is not acceptable for this data element.

Follow-up Scans

The tracer uptake time for follow-up scans should be matched as closely as possible to the baseline scans with a targeted window of +/- 5 minutes (with an acceptable window of +/- 10 minutes). **NOTE:** The time between injection of the radiotracer and PET emission scan start time should be targeted at 60 minutes with an acceptable window of 50 to 70 minutes.

✓ **FDG-PET/CT Follow-up Scans**

- Is the difference in mean liver SUV between the baseline and follow-up scan less than 1.0? (Check by placing a large circular region of interest [ROI, diameter ≥ 5 cm] in normal liver tissue for mean SUV.)
- Is the mean liver SUV between 1.5 and 4.0 (≥ 1.5 and ≤ 4.0)?
- If mean liver SUV is < 1.5 or > 4.0, then check the scanner calibration and cross calibration of the dose calibrator and PET scanner.

Review for Artifacts in Reconstructed Images

✓ Did you check for beam hardening artifacts in the CT scan? Are there any metal implants or other structures with high density in the abdomen or pelvis?

- Do the implants cause beam hardening artifacts in CT that are visible on the reconstructed PET emission images?
- Are the beam hardening artifacts overlying the tumor region?

Participant Movement

✓ Is there any visible mis-registration between the CT scan and the reconstructed PET emission images?

In addition to using quality control review findings to improve future imaging studies for the trial, issues found during review (artifacts, movement, reasons for outliers in SUV requirements, etc.) should be noted in the comments field on the PET Technical Assessment Form for the study.

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Appendix X

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on AZD1775 or within 28 days of the patient's last dose of AZD1775 must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office - Boston. Please contact the ECOG-ACRIN Operations Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.*"

It must be reported via CTEP-AERS as Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A disorder characterized by cessation of life occurring during the first 28 days of life*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to AZD1775 must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*General disorders and administration - Other (neonatal loss)*"under the System Organ Class (SOC) "General disorder and administration".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

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Appendix XI

Phase I AZD1775 Pharmacokinetic Collection and Shipping Kits

Each kit will contain the materials (vacutainers, cryovials, shippers, shipping labels) for the collection and submission of samples for a single patient

Two starter kits are to be ordered by the site upon site activation (IRB approval) of the Phase I aspect of the trial. Do not split contents from a single kit between patients.

To order collection kits, complete the kit order form (page 2 of this appendix) and Fax to Zemotak as indicated on the form.

Kits should be shipped to the site at the contact indicated below, unless otherwise notified.

PHASE I INSTITUTION CONTACT INFORMATION	Site Address for Shipping Kits
Case Comprehensive Cancer Center (Site # OH029)	
Investigator: Jennifer Eads, MD • (216) 844-6031 • jennifer.eads@uhhospitals.org Nurses/CRA: Carol E. Smith RN, BSN, CCRP • (440) 816-6067, carol.smith@UHHospitals.org **Lab Coordinator for KITS: Erin Hohler** • **(216) 844-5562** • **Erin.hohler@UHhospitals.org**	Erin Hohler University Hospitals Seidman Cancer Center Translational Research Core 11100 Euclid Avenue, Seidman 3608 Cleveland, Ohio 44106-5061
Fox Chase Cancer Center	
Investigator: Efrat Dotan, MD • (215) 728-8128, efrat.dotan@fccc.edu C. Rebecca Marlow RN, BSN, MBA, CCRP • (215) 214-1451, becky.marlow@fccc.edu **Kit Contact: R. Katherine Alpaugh, PhD.** • **P**: 215 214-1634, F: 215 214-1635, RK_Alpaugh@fccc.edu	R. Katherine Alpaugh, PhD. Fox Chase Cancer Center Protocol Support Laboratory 333 Cottman Avenue P2009 Philadelphia, PA 19111 USA
Northwestern University	
Investigator: Al B Benson III • (312) 926-3023, a-benson@northwestern.edu CRA: Erin Alonso • (312) 695-4168, erin.alonso@northwestern.edu **Kit Contact:** • **Elena Ramos, Elena.ramos@northwestern.edu** • **312-503-3384, ecogpcorl@northwestern.edu**	Northwestern University (Site #: IL036) Path Core Facility/ Attn: Elena Ramos Robert H Lurie Comprehensive Cancer Center Northwestern University 710 North Fairbanks Court, Olson 8421/31 Chicago IL 60611
University of Pennsylvania	
Investigator: Peter O'Dwyer, MD • (215) 662-7268, peter.odwyer@uphs.upenn.edu Nurses/CRA: Maryanne Redlinger, RN • (215) 662-7452, maryann.redlinger@uphs.upenn.edu	
Vanderbilt Ingram Cancer Center	
Investigator: Dana B. Cardin, MD • (615) 936-6925, dana.backlund@vanderbilt.edu Nurses/CRA: Shaunita A. Michael, RN, BSN • (615) 343-0798, shaunita.a.michael@vanderbilt.edu **Lab Coordinator for KITS: Megan M. Cook** • **P: 615-936-3428, F: 615-936-7626** • **megan.m.cook@vanderbilt.edu**	Megan M. Cook Laboratory Manager – Biospecimen Team, CTSR Vanderbilt-Ingram Cancer Center 634 PRB Nashville, TN 37232-5310

EA2131 PHASE I AZD1775

Pharmacokinetic Collection and Shipping Kit Order Form

Starter kits for two patients may be ordered by the site upon IRB approval.

To request kits for the EA2131 PHASE I PK blood draws, shipping material or documents, the site/CRA can directly go to the online kit ordering:

http://www.covance.com/kitordering

or

Contact the investigator support team: Phyllis.Sellars@Covance.com and Gaelle.Legaud@Covance.com

Comments:

Protocol specific notes:

- Specimens will be submitted to Covance using the Covance-Provided Kits.
- PK Collection time points from start of AZD1775 administration:
  - Cycle 1 Day 1 at 0 min, 1 hr, 2hr, 4hr, 6hr, 8hr, 24hr (Day 2 0min)
  - Cycle 1 Day 16 at 0 min, 1 hr, 2hr, 4hr, 6hr, 8hr, 24hr (Day 17)

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Appendix XII

Covance Specimen Shipment Pre-Alert Form

Upon submission of samples to Covance, complete the form and Fax as instructed.

COVANCE
THE LABORATORY SCIENCE COMPANY

SPECIMEN SHIPMENT PRE-ALERT FORM
Protocol # _ _____

Directions: Please complete the information below. A fax of this form and an email containing all shipping details must be sent to the below recipients on the day of sample pick-up. The samples being returned to CCLS should be shipped using the Covance-supplied kit supplies and labeled with the original CCLS barcode label for identification purposes. Place the purple label, if provided, on the outside of the shipper. The samples should be accompanied with a specimen packing list to allow sample reconciliation upon receipt at CCLS. An electronic copy of the specimen packing list should be emailed directly to the email addresses below.

Fax: 1-800-335-1462 (USA) or 1-317-616-2314 (International)
Emails: SMSpecialHandlingIndy@Covance.com, Phyllis.Sellars@Covance.com and Gaelle.Legaud@Covance.com

* Please send an email to all listed recipients.

Shipment Date: _____

Carrier Name: _____

Airbill Number: _____

Shipment Description (check all applicable boxes)
☐ Frozen ☐ Refrigerant
☐ Ambient ☐ Other: _____

Shipper's Contact Name: _____

Company: _____

Phone: _____

Consignee Name/Department : _____

Ship the package to the following address:
Covance Central Laboratory Services
Attn: Phyllis Sellars – Special Handling
8211 SciCor Drive
Indianapolis, Indiana 46214
Phone: 317-271-1200

↓ CCLS USE ONLY ↓

POD Information:
Date and Time: _____ **Signature:** _____
TD employee Initials: _____

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Appendix XIII

EA2131 PHASE II Collection and Shipping Kits Order Form

Use this form to request kits for the EA2131 PHASE II specimen kits. Starter kits ARE NOT AVAILABLE. Kits are to be ordered upon registration of the patient to the trial.

FAX Completed form **to Zemotak-International at (800) 815-4675**.

Date: _____

Case ID of the Patient: _____

Kit is to be shipped to:

Institution Contact: _____

Phone number for contact: _____

E-mail for contact: _____

Institution Address:

_____

_____

_____

NOTE: Questions are to be directed to the ECOG-ACRIN CBPF– at (844) 744-2420 or eacbpf@mdanderson.org

Comments: