SUMMARY OF CHANGES- Protocol

#	Section	Comments
1.	N/A	Formatting and editorial changes made throughout the protocol (e.g., page numbers).
2.	Title Page	Protocol version date revised to reflect current changes.
3.	Schema 5.1	Sections revised to notify that AZD8186 60 mg. tablets will expire and treatment needs to be completed by April 30, 2022.
4.	Schema 5.3 5.4	Sections revised to notify that Part 2 and Part 3 will no longer open after Part 1 is completed.
5.	6	Section revised to indicate that patients cannot be dose reduced to dose level -1. Doses should be reduced by 60 mg.
6.	8.1.1	Section revised on how AZD8186 is supplied.
7.	Table 7	Contact information updated in regards to AZD8186 PK collection/notification.

NCI Protocol #: 10131

Local Protocol #: 18-237

ClinicalTrials.gov Identifier: TBD

TITLE: A Phase 1 Study of AZD8186 in Combination with Docetaxel in patients with *PTEN* mutated or *PIK3CB* mutated advanced solid tumors, potentially amenable to docetaxel

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Participating Organizations:

Part 1 Dose escalation cohort
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LAO *restricted to*:

- **MD017**/ JHU Sidney Kimmel Comprehensive Cancer Center
- **NY016** / Memorial Sloan Kettering Cancer Center
- **NY478** / Memorial Sloan Kettering Westchester
- **NJ299**/ Memorial Sloan Kettering Monmouth

LAO-TX035/ University of Texas MD Anderson Cancer Center LAO
LAO *restricted to:*

- **TX035/** University of Texas MD Anderson Cancer Center

LAO-NCI/ National Cancer Institute LAO

Part 2 Pharmacodynamic expansion cohort/ Part 3 Disease specific expansion cohort
Open to all sites in LAO Participating Organizations table:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO

LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
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NCI-Supplied Agent(s): AZD8186, NSC# 785347
Commercially- Supplied Agent: Docetaxel, NSC# 628503

[redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / Version 1 / 04/21/2017
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Amendment / Version 3 / 07/26/2017
Amendment / Version 4 / 10/26/2017
Amendment / Version 5 / 12/13/2017
Amendment / Version 6 / 03/23/2018
Amendment / Version 7 / 06/12/2018
Amendment / Version 8 / 07/05/2018
Amendment / Version 9 / 08/02/2018
Amendment / Version 10 / 12/06/2018
Amendment / Version 11 / 03/18/2019
Amendment / Version 12 / 08/29/2019
Amendment / Version 13 / 10/08/2019
Amendment / Version 14 / 12/03/2019
Amendment / Version 15 / 05/20/2021

SCHEMA

This will be a Phase I, multi-part, multicenter, non-randomized, open-label study designed to evaluate the safety, tolerability and preliminary activity of AZD8186 in combination with Docetaxel in patients with *PTEN* mutated or *PIK3CB* mutated advanced solid tumors. In this study, patients who have received any number of prior therapies in the metastatic disease setting will be treated with the combination of AZD8186 twice daily (BID) orally (PO), 5 days on, 2 days off every week, combined with Docetaxel intravenous (IV) on day 1 of a 21 day cycle, until progression of disease (POD), unacceptable toxicity or withdrawal from study. All treatments will be administered in the outpatient setting. The primary objectives are to determine the MTD or RP2D of AZD8186 when administered in combination with docetaxel and assess the safety and tolerability of the combination. Secondary endpoints include objective response rate (ORR), clinical benefit rate (CBR) at 24 weeks and to investigate the drug-drug interaction between docetaxel and AZD8186.

Per the drug manufacturer AstraZeneca, clinical supply of AZD8186 60 mg tablets will expire on April 30, 2022 (based on the planned expiration date extension). Supplies can be used until the terminal lot shelf life dating is reached or the NCI inventory is exhausted. All patients must complete their last treatment on or before April 30, 2022, and the study will be closed to accrual and treatment to coincide with this expiration date.

Parts 2 and 3 will no longer open following completion of the Part 1 Dose escalation cohort.

Figure 1 Overall Study Schema

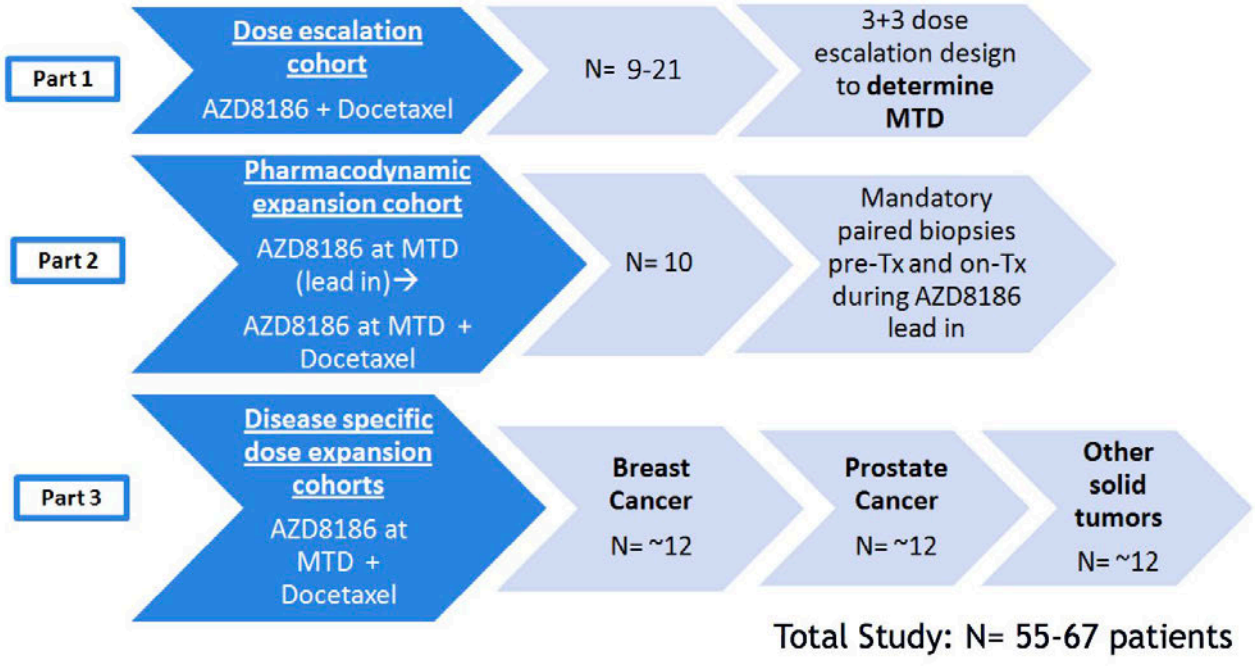
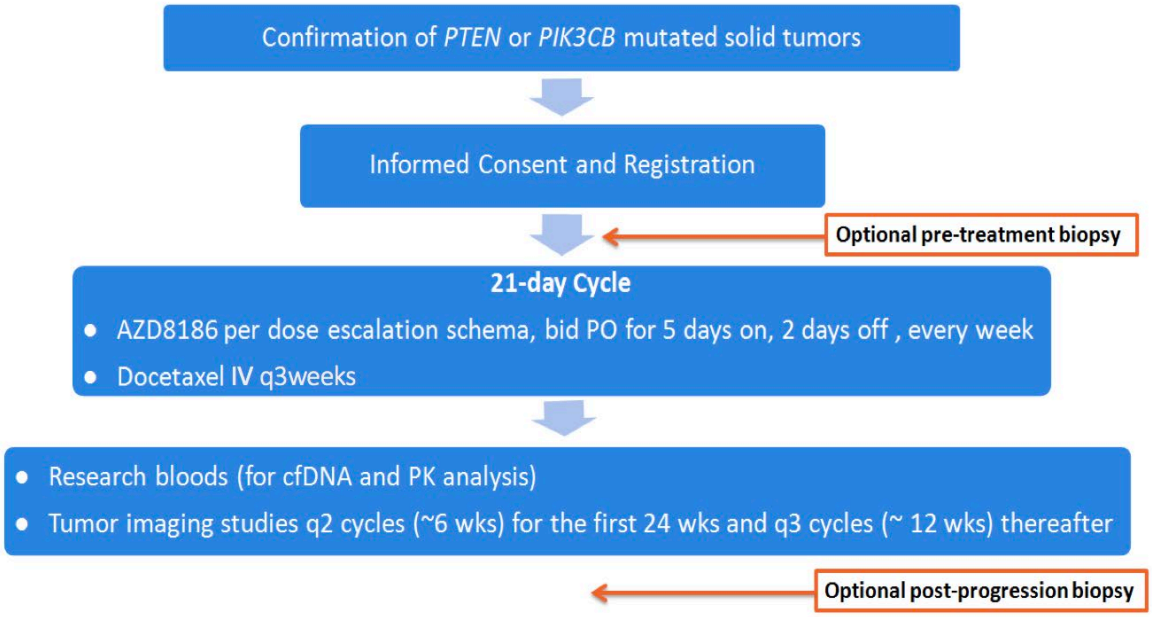


Figure 2 Part 1: Dose escalation cohort schema



(n= 9 -21)

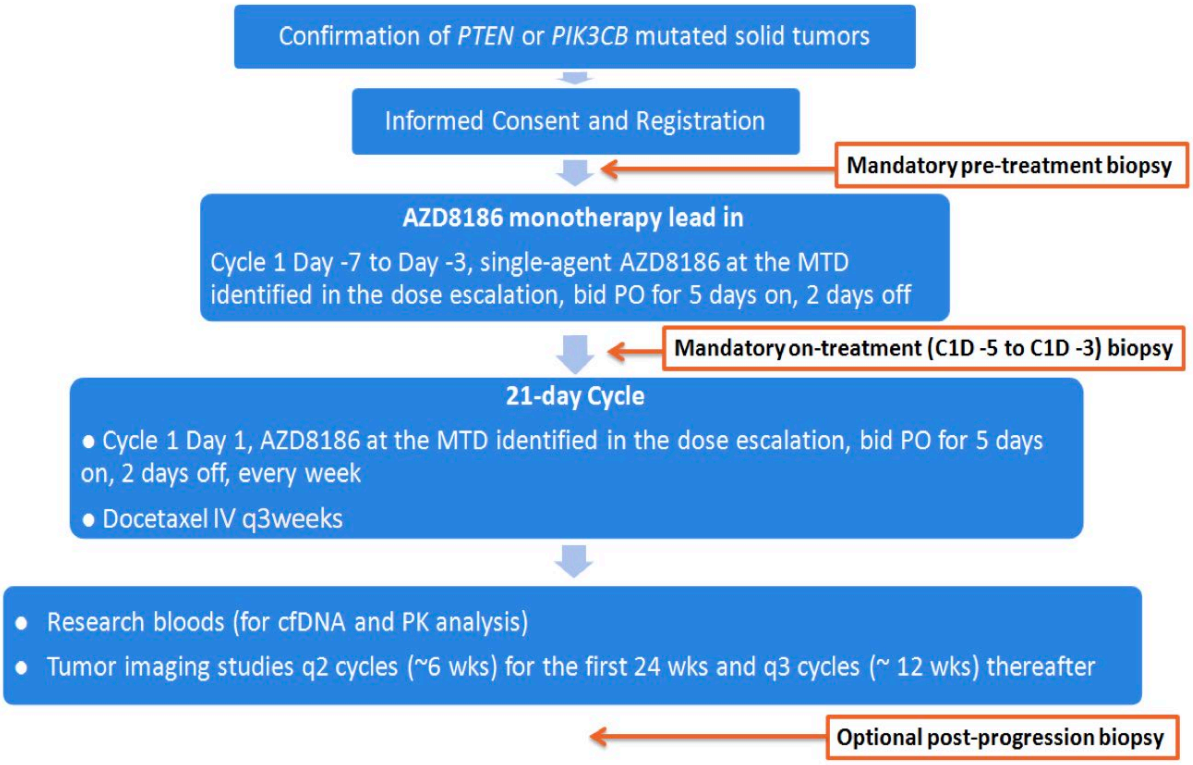
Dose Escalation Schedule

Dose Escalation schema		
Dose Level	**Dose**	
	AZD8186 BID PO, 5 days on, 2 days off every week **(mg)**	**Docetaxel** IV on day 1 of a 21-day cycle (mg/m^2)
-1*	30	75
-1B*	60	60
Starting dose level 1*	60	75
2*	120†	75

Please refer to Section 5.5 for DLT definition.
†AZD8186 dosed at 90mg bid 5 days on /2 off may be explored, as directed by the emerging safety profile of this agent.
*Prophylactic growth factor support with docetaxel should be administered during the first cycle of therapy per institutional guidelines and per the provider's discretion on subsequent cycles. Since the protocol was amended to include the use of prophylactic growth factor during DL-1B, patients who experienced a DLT of neutropenia or neutropenic fever at this dose level prior to the implementation of prophylactic growth factor maybe replaced.
Note: DL -1B was added in an amendment based on the emerging safety profile

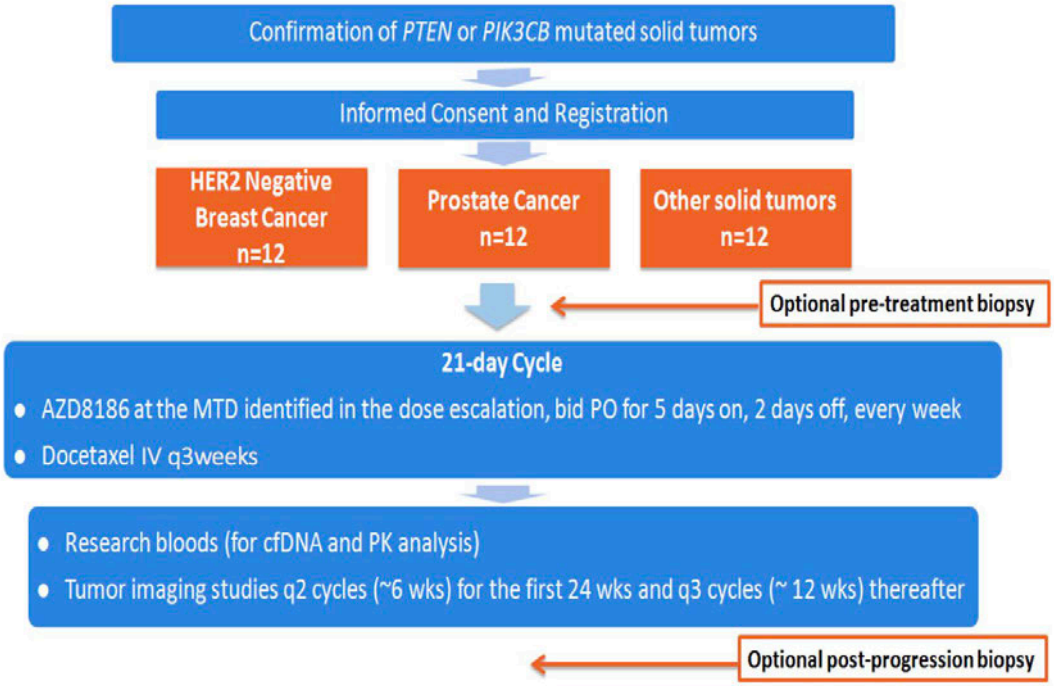
Dose Re-escalation:
The use of prophylactic growth factor with Cycle 1 was added given emerging safety data demonstrating neutropenia as the predominant dose-limiting toxicity. In the event that Dose Level -1B is deemed tolerable with or without the use of growth factor, dose re-escalation can occur to Dose Level 1 and subsequently Dose Level 2 with the ongoing use of prophylactic growth factor.

Figure 3 Part 2: Pharmacodynamics expansion cohort schema



(n= 10)

Figure 4 Part 3: Disease specific expansion cohort schema


Confirmation of PTEN or PIK3CB mutated solid tumors
Informed Consent and Registration
HER2 Negative Breast Cancer n=12
Prostate Cancer n=12
Other solid tumors n=12
Optional pre-treatment biopsy
21-day Cycle
AZD8186 at the MTD identified in the dose escalation, bid PO for 5 days on, 2 days off, every week
Docetaxel IV q3weeks
Research bloods (for cfDNA and PK analysis)
Tumor imaging studies q2 cycles (~6 wks) for the first 24 wks and q3 cycles (~ 12 wks) thereafter
Optional post-progression biopsy

(n=36)

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the MTD or RP2D of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

1.1.2 To assess the safety and tolerability of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity. Although the clinical benefit of this drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.1.1 To assess the objective response rate (ORR) of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

1.2.1.2 To assess the clinical benefit rate at 24 weeks of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

1.2.2 To investigate a drug-drug interaction between docetaxel and AZD8186 and correlate drug exposure with pharmacodynamics response

1.3 Exploratory Objectives

1.3.1 Examine the pattern of co-mutated genes in *PTEN* or *PIK3CB* mutated tumors and their association with treatment response or resistance.

1.3.2 Describe possible mechanisms of acquired resistance to PI3Kβ inhibition.

1.3.3 Evaluation of protein expression of the PTEN gene and its association with treatment response or resistance.

1.3.4 Examine isoform-specific AKT inhibition and other downstream target modulation from PI3Kβ inhibition with AZD8186.

2. BACKGROUND

2.1 Study Disease(s)

This phase I study will be open to patients with all solid tumor types harboring a *PTEN* or *PIK3CB* mutation.

PTEN deficiency (from gene loss, frameshift deletions, epigenetic down-regulation or protein degradation) is a frequent event in many cancer subtypes including prostate, breast, lung, gastric and endometrial cancer, melanoma and glioblastoma.[1,2] Among one of the largest institutional series (n=15,000) of sequenced metastatic tumors using a CLIA NGS assay called MSK-IMPACT,[3] genomic alterations in *PTEN* have been identified in 8% of patients (See **Figure 5**, below, Oncoprint from cbioportal.org and **Figure 6**, below showing the most frequently affected tumor types).[4,5] In addition the table below **Figure 6** illustrates the most frequently altered tumor types as identified within the TCGA dataset.[2]

Figure 5 *PTEN* oncoprint

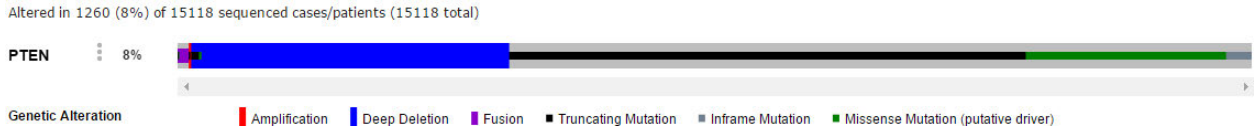
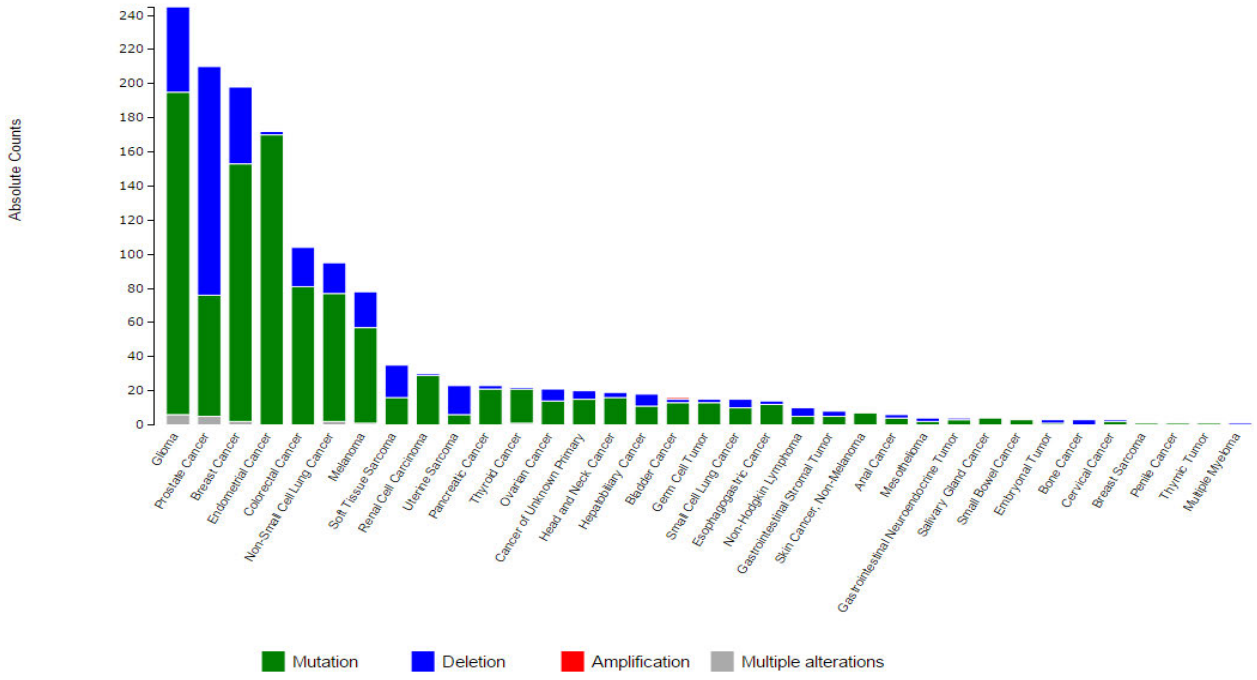


Figure 6 Cancer types Summary: *PTEN*



Frequencies of *PTEN* genetic lesions across cancer subtypes[2]

Cancer Type	% of tumors with *PTEN* mutation or homozygous loss (# altered/total)
Bladder	4.1% (4/97)
Lower Grade Glioma	5.3% (9/169)
Breast	7.47% (57/760)
Cervical	13.9% (5/36)
Colorectal	6.3% (14/221)
Glioblastoma Multiforme	41.9% (99/236)
Head & Neck SCC	2.6% (8/302)
Renal clear cell	3.4% (10/290)
Renal papillary	3% (3/100)
Lung Adenocarcinoma	3.9% (5/129)
Lung SCC	11.2% (20/179)
Ovarian	7.28% (23/316)
Prostate	13.6% (14/103)
Sarcoma	2.9% (6/207)
Melanoma	12.4% (28/225)
Stomach	11.3% (13/115)
Thyroid	1.9% (6/318)
Uterine	66.3% (159/240)

Mutations in *PIK3CB*, although rare have been reported[6] and out of 15,000 sequenced metastatic tumors at MSKCC, ~1.6% patients have been identified to have alterations in *PIK3CB*. (See **Figure 7**, below, Oncoprint from cbioportal.org and **Figure 8**, below showing the most frequently affected tumor types).[4,5]

Figure 7 *PIK3CB* oncoprint

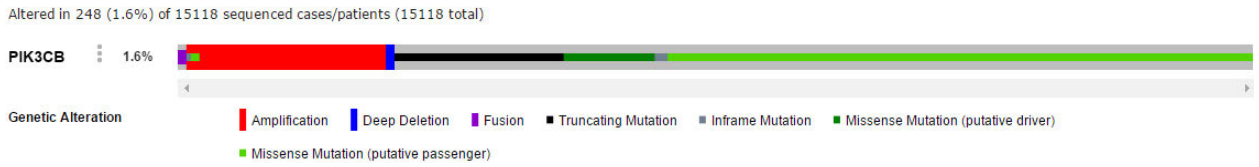
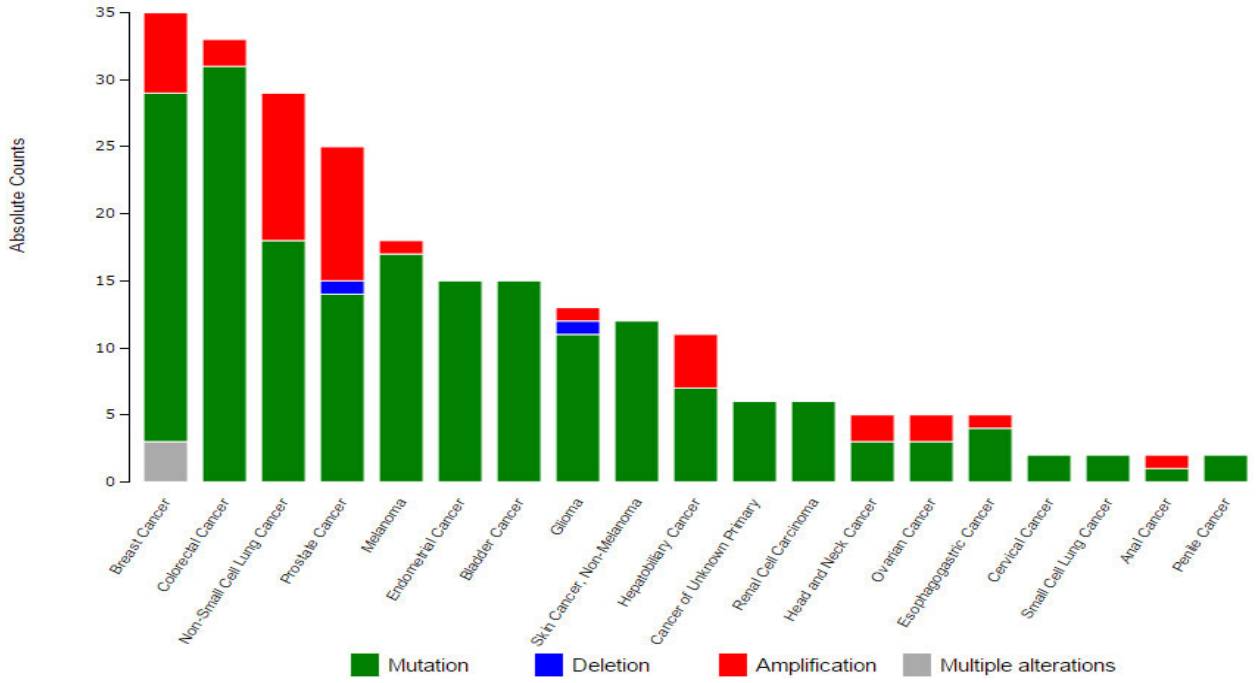


Figure 8 Cancer types Summary: *PIK3CB*



2.2 CTEP IND Agent

2.2.1 **AZD8186**

AZD8186 is a potent selective inhibitor of PI3Kβ/δ being developed as an oral anti-tumor agent with an initial focus on patients with PTEN-deficient tumors. For more detail on non-clinical and clinical studies with this agent please refer to the most up to date version of the investigator brochure.

2.2.1.1 **Summary of Non-clinical studies**

In nonclinical models, PD activity of AZD8186 manifested as reductions in phospho-AKT, phospho-PRAS40 and Foxo-3a nuclear translocation (signaling events downstream of PI3Kβ), leading to inhibition of cellular proliferation in cell line assays in vitro and growth inhibition in xenografts in vivo.

2.2.1.1.1. Pharmacology summary

The principal findings from the non-clinical pharmacology studies are summarized below:

- AZD8186 targets PI3Kβ and δ. Cells become dependent on PI3Kβ signaling when they lose appropriate regulation of the pathway through loss of PTEN function. This can occur at the gene level through gene deletion, or mutation, or through down regulation of the protein relative to normal levels through transcriptional or post-translational effects. For the purposes of this document, the collective drivers of loss of PTEN function are defined as PTEN deficient.
- Isolated enzymes within the PI3K family bind AZD8186 with tight binding kinetics. As a result, cell based assays are more discriminating for the relative potency of the molecule versus different PI3K family members. With this caveat, in vitro biochemical enzyme studies show AZD8186 to be a potent inhibitor of PI3Kβ (4 nM) with additional activity versus PI3Kδ (12 nM), and selectivity over PI3Kα (35 nM), and PI3Kγ (675 nM). Broad profiling versus 2 extensive kinase panels covering up to 442 kinases (and including multiple lipid kinases) showed AZD8186 to have little potency against any other kinase (concentration >1 μM).
- In vitro cellular assays show AZD8186 to inhibit phosphorylation of protein kinase B, pAKT (473) with a concentration giving 50% of the drug-induced inhibitory effect (IC50) of 3 nM in the PI3Kβ dependent PTEN null, cell line MDAMB-468. AZD8186 inhibited phosphorylation of pAKT (thr308) with an IC50 of 725 nM in the PI3Kα dependent PTEN wild-type cell line BT474. Additional activity versus PI3Kδ was observed with AZD8186 inhibiting pAKT (ser473) with an IC50 of 17 nM following stimulation of JEKO cells with immunoglobulin M (IgM). AZD8186 showed comparable suppression of pAKT in a range of PTEN null cells lines with IC50 ranging from (10 to 460 nM).
- In a broad cell panel screen (124 cell lines) AZD8186 inhibited the growth of a number of cell lines with IC50 ranging from 20 to 1000 nM. While activity was seen in both PTEN null and PTEN wild-type cell lines, PTEN null were enriched in the sensitive group.
- In vivo AZD8186 inhibited growth of PTEN null tumor xenografts following oral treatment. Robust anti-tumor activity was observed when animals were dosed in the range of 25 mg/kg to 50-mg/kg continuous dosing (all dosed twice daily [BD]). Activity was also achieved following treatment with 10 mg/kg to 30 mg/kg BD AZD8186 in the presence of 1-aminobenzotriazole (ABT). ABT is a cytochrome p450 inhibitor used to reduce the clearance of AZD8186, and generate a pharmacokinetic (PK) profile that has a flatter profile than that achieved with standard BD dosing.
- In nonclinical models, AZD8186 was effective when used in combination with docetaxel both with continuous and intermittent dosing schedules.
- AZD8186 gives increased combination benefit with inhibitors of the PI3Kα isoform. Increased tumor responses were seen when HCC70 tumors were treated with AZD8186 and AZD8835 (a PI3Kα/δ inhibitor). In the human prostate carcinoma cell line (LNCaP) model,

AZD8186 combines with BYL719 (a PI3Kα inhibitor) to give increased tumor growth suppression.

- AZD8186 combines with blockade of androgen signaling to give increased anti-tumor responses in PTEN protein null androgen-receptor (AR)-positive tumor models. AZD8186 with surgical castration (in PC346 tumor xenografts) or AZD8186 combined with enzalutamide (in the LNCaP model or prostate cancer genetically engineered mouse model [GEMM] model) regressed tumors. AZD8186 also combined well in vitro with the androgen signaling modulator enzalutamide. A triple combination of AZD8186, BYL719 and enzalutamide gave the greatest tumor response, suggesting comprehensive pathway suppression in combination with AR inhibition gives greatest benefit in prostate cancer models.
- AZD8186 combines with inhibitors of mammalian target of rapamycin (mTOR) signaling. In HCC-70, 786-0 (renal cancer), and Karpas-422 (diffuse large B-cell lymphoma) (DLBCL) the combination of AZD8186 and AZD2014 (mTORC1/2 inhibitor) gave tumor regressions. In 786-0, the combination of everolimus (RAD001 mTORC1 inhibitor) with AZD8186 gave tumor regression. In HCC70, AZD8186 gave increased combination benefit when combined with AZD6244, an inhibitor of the mitogen activated protein kinase (MAPK)/EKT pathway.
- Nonclinical data indicates that with intermittent scheduling, efficacy in HCC70 tumors is maintained when AZD8186 is dosed 5 days out of 7 days as monotherapy. When used in combination, other schedules of AZD8186 are effective, with 4 to 5 days dosing per week generally being optimal (25 mg/kg to 50 mg/kg BD). However, in combination with AZD2014, it is possible to reduce both dose and duration of exposure further while maintaining efficacy.
- PI3Kβ is important in regulating ligand-induced platelet activation following activation of specific G-protein coupled receptors (GPCRs). Consistent with activity versus PI3Kβ, AZD8186 inhibited murine and human platelet aggregation in ex vivo assays.
- One major metabolite (M1) of AZD8186 has been investigated. M1 shows equivalent in vitro activity to AZD8186 in PI3Kα, PI3Kβ, PI3Kδ cell based assays.
- In a secondary pharmacodynamics screen of 186 molecular targets, AZD8186 had activity within 30-fold of the highest predicted human free maximum plasma drug concentration (Cmax) at 3 targets. Of these, only the inverse agonism at the dopamine D2S receptor may have potential to translate into central nervous system (CNS) symptoms if clinical free Cmax exposures exceed 5 μM.
- AZD8186 is active at the human *Ether-a-go-go*-Related Gene (hERG) cardiac channel in vitro, with 39% inhibition of the hERG tail current at a concentration 110μM.
- In a conscious telemetered dog cardiovascular study, AZD8186 caused minor transient increases in PR interval and systolic and diastolic arterial blood pressure, but these changes were small in magnitude and considered not to be adverse.
- In mice, assessments of respiratory function, using whole body plethysmography, and CNS function, using a modified Irwin screen, showed no changes related to administration of AZD8186.
- Following single oral dosing, AZD8186 caused dose- related inhibition of stomach emptying in mice, with no effects on gastrointestinal (GI) transit.

2.2.1.1.1. Non-clinical pharmacokinetics and drug metabolism summary

The absorption, distribution, metabolism, and excretion of AZD8186 have been studied in mouse and dog in vivo following oral administration and in mouse, dog, and human in vitro. The animal species and strains used were the same as those used in the toxicology program. The compound has been used in in vitro studies designed to determine protein binding, cross species metabolism and interactions with human cytochrome P450 (CYP) and transporter enzymes. Toxicokinetic monitoring of the 1-month toxicology studies were performed according to Good Laboratory Practice (GLP). Exposures have been achieved in the clinic equivalent to that required for efficacy in mouse xenograft models.

- In mice and dogs oral absorption was rapid with maximum plasma concentrations generally 10 min to 2 h following administration. Increase in the exposure over the dose range studied was less than proportional with dose. In mice, a decrease in exposure on Day 28 compared to Day 1 was observed. In dogs exposure was generally higher on Day 28 versus Day 1.
- Mean percentage free AZD8186 was 9.66, 9.56, 27.6, 33.6 and 15.2% in mouse, rat, rabbit, dog, and human plasma respectively.
- Following incubation with mouse, dog and human hepatocytes, AZD8186 was primarily metabolized to oxidized and dealkylated products followed by conjugation to glucuronic acid and/or sulphate. All 6 metabolites formed in human hepatocytes were observed in incubations with mouse and dog hepatocytes. A demethylated metabolite AZ13472080 (M1), is equipotent with AZD8186 in vitro, and has been observed in plasma of mice, dogs and humans dosed with AZD8186. In vitro CYP3A4 was the principal cytochrome P450 responsible for human metabolism in a panel of 6 isoforms. AZD8186 related material irreversibly binds to human hepatocytes.
- In vitro, AZD8186 is a reversible inhibitor of human CYP2C9 with an IC50 of 29 μM. Reversible inhibition (IC50) of the other human cytochrome P450s (CYP) exceeded 30 μM. Time-dependent inhibition of CYP enzymes was not observed. AZD8186 did not inhibit human P-glycoprotein (P-gp). AZD8186 inhibited human organic anion transporter protein 1B1(OATP1B1) with an IC50 of 19 μM. AZD8186 is an inducer of CYP3A4 and to a lesser extent CYP2B6 in vitro. No induction of CYP1A1/2 was observed. The induction potential of AZD8186 at therapeutic doses is predicted to be low.
- In conclusion:
    - AZD8186 undergoes predominantly Phase 1 metabolism to multiple oxidation and dealkylation products followed by conjugation. All metabolites identified in human hepatocytes were observed in mouse and/or dog hepatocytes indicating the suitability of these species for assessing the toxicology of AZD8186.
    - Dealkylation of AZD8186 to M1 is a major route of metabolism in mouse and dog in vitro. M1 is an equipotent metabolite of AZD8186 with a similar selectivity profile against other PI3K isoforms. In the 1-month toxicology studies, it was circulating at low levels in mouse (generally <20% parent) but higher levels in dog (approximately 50 to 165% parent). M1 is circulating in plasma of patients dosed with AZD8186 but at lower levels than AZD8186.

- AZD8186 is cleared/ metabolized predominantly by CYP3A4. There is therefore a risk that the PK of AZD8186 may be affected by co-administration with inducers and/or potent inhibitors of CYP3A4.
- AZD8186 is a weak inhibitor of CYP2C9 (IC50 29 μM) and OATP1B1 (IC50 19 μM). Based on the predicted human exposures of AZD8186 the use of sensitive substrates of CYP2C9 and OATP1B1 has been restricted in the clinical study. Assessment of the drug-drug interaction risk based on the observed interim human plasma concentrations at 240 mg BD supports this assessment for CYP2C9 interactions but suggests the risk of OATP1B1 interactions is low.
- AZD8186 is an inducer of CYP3A4 and to a lesser extent CYP2B6 in vitro. Currently Day 19 and Day 1 exposures in patients for AZD8186 up to 240 mg BD are very similar, suggesting there is no significant induction of CYP3A4. An early assessment of the potential of AZD8186 to induce CYP3A4 in the clinical study will be conducted using 4-hydroxy-β-cholesterol as a marker of CYP3A4 metabolism.
- Human free exposures of AZD8186 achieved in the clinic are within the range required for efficacy in the nude mouse.

2.2.1.1.2. Toxicology summary

Nonclinical safety evaluation studies conducted with AZD8186 include oral toxicology studies of up to 1 month in duration in mice and dogs, a battery of in vitro and in vivo genetic toxicity studies and an in vitro phototoxicity assessment.
Key findings from the studies are summarized below:

- Dosing AZD8186 for up to 1 month was associated with hepatic changes in dogs and mice. In dogs, dosing for up to 14 days was associated with minimal hepatocyte degeneration, sinusoidal dilatation and increased sinusoidal leucocytes, with associated increases in plasma liver enzyme activities (alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT] and glutamate dehydrogenase [GLDH]). After dosing for 1 month at similar dose levels, hepatocellular single cell necrosis, inflammation and pigmented macrophages, with more marked increases in plasma liver enzyme activities, were seen. Reversibility of the plasma liver enzyme increases and histopathology was demonstrated after a1 month recovery period. Pigmented macrophages, inflammation and fibrosis noted in the liver of some recovery animals was considered to indicate resolution of earlier liver changes in these animals. In mice, inflammatory cell infiltration in the liver, sometimes accompanied by areas of hepatocellular degeneration and/or necrosis, was seen following dosing for 1 month. Small increases in liver enzymes were seen in some individual mice dosed with AZD8186, but did not correlate with the histopathological changes in the liver. Similar inflammatory changes of lesser severity were seen in a few mice following a 1-month recovery period, suggesting reversibility.
- Dosing AZD8186 in dogs for up to 1 month was associated with single cell necrosis or degeneration of lymphocytes, reduced lymphocytes and/or inflammation in the lymphoid tissues in the GI tract, thymus mesenteric lymph node, and tonsils and in the splenic white pulp. Changes in the bone marrow (increased myeloid: erythroid ratio, increased or decreased cellularity) and thymus (hypocellularity, lymphocyte single cell necrosis), and increases in peripheral white blood cell (WBC) counts (especially neutrophils and monocytes), were also apparent. In mice, dosing for up to 1 month produced changes in the mesenteric and/or mandibular lymph nodes (increased histiocytes, lymphocytolysis, reduced

lymphocytes), bone marrow (increased histiocytes) and spleen (hypocellularity) in individual animals. Lymphoid organ and hematology changes showed evidence of reversibility in both species following a 1-month recovery period.

- Dosing AZD8186 in dogs and mice for up to 1 month was associated with testicular tubular degeneration, with associated reductions in testis weight and changes in the epididymides. Following a 1-month recovery period, partial reversibility of the testis changes was seen for mice although in dogs testicular tubular degeneration was still apparent. In mice, a reduction in ovary weight, with no histopathological correlate, was also seen following dosing AZD8186 for 1 month.
- There was no evidence of rash or any other changes suggestive of potential hypersensitivity type reactions in the nonclinical toxicology studies when AZD8186 was dosed continuously for up to 1 month in mice and dogs.
- Dosing AZD8186 to dogs for 1 month was associated with sporadic fecal changes
- A dose level of 30 mg/kg BD to dogs for 1 month was associated with elevated neutrophils, monocytes and C-reactive protein; there were no changes to inflammatory cytokine release or lymphocyte subsets noted.
- At all dose levels in the dog, treatment related findings were present in the lymphoid system in the GI associated lymphoid tissue (GALT). The findings were minimal to mild single cell necrosis of lymphoid follicles and minimal to mild inflammatory cell infiltration associated with the GALT These changes recovered after 28 days off-dose.
- AZD8186 causes inhibition of adenosine diphosphate (ADP)-stimulated platelet aggregation in dog whole blood ex vivo, without any adverse effects on bleeding in dogs or mice in vivo.
- The majority of these changes were considered likely to be related to pharmacology, in particular resulting from inhibition of PI3K β and/or PI3K δ.
- AZD8186 also caused small increases in plasma glucose in mice and dogs, which suggested that plasma exposures in these animals were sufficient to transiently inhibit PI3Kα.
- AZD8186 was not genotoxic in vitro in the Ames and mouse lymphoma assays or in vivo in a mouse bone marrow micronucleus assay.
- AZD8186 absorbs in the ultraviolet (UV) spectrum (290 to 700 nm) and was positive in an in vitro 3T3 Neutral Red Uptake phototoxicity test, indicating a potential phototoxicity risk.

2.2.1.2 **Summary of Clinical Data**

AZD8186 is currently under evaluation in 1 ongoing AstraZeneca-sponsored clinical study
(D4620C00001), a Phase 1 study to assess safety, tolerability, PK, and preliminary anti-tumour activity in patients with advanced castration-resistant prostate cancer (CRPC),
squamous non-small cell lung cancer (sqNSCLC), triple-negative breast cancer (TNBC) and
patients with known PTEN-deficient advanced solid malignancies, as monotherapy

and in

combination with abiraterone acetate or vistusertib (mTOR inhibitor).

This study dosed its first patient on 10 July 2013 and as of 02 May 2019, 147 patients have been dosed with AZD8186 and 7 dose levels have been investigated under 3 different BD dosing schedules (5 days on, 2 days off; 2 days on, 5 days off, continuous) either as monotherapy or in combination with abiraterone or vistusertib. Patients have received doses ranging from 30 to 360 mg BID alone and in combination with either AZD2014 or abiraterone. There have been 16 separate dosing regimens in total (12 monotherapy, 4 combination). Dose limiting toxicities (DLTs) of rash have occurred at the 360 mg and 300 mg dose levels. Additionally, Grade 3 diarrhea and colitis occurred at 180 mg dose levels.

The most common treatment related, adverse events have been in the Gastrointestinal (GI) tract (including diarrhea, nausea, vomiting and potentially abdominal pain), skin, immune system/apparent hypersensitivity. These adverse events have been monitorable, reversible and mild in nature.

Hypersensitivity, pyrexia/chills, hepatic effects, inhibition of platelet aggregation, phototoxicity, reproductive toxicity and drug-drug interaction and lymphoid effects have been identified as important potential risks and will continue to be closely monitored as the ongoing phase I clinical trial progresses.

The hypersensitivity-like reactions including rash, chills, fever sometimes accompanied by gastrointestinal symptoms are of unknown etiology. This group of adverse events has substantial overlap with known AEs associated with PI3Kδ inhibitors including fever, rash, diarrhoea and anaphylactic reactions. As such, it is possible that the hypersensitivity-like events may be pharmacologic mechanism-related, specifically due to PI3Kδ (±PI3Kβ) inhibition.

2.2.1.2.1. Pharmacokinetics

The preliminary pharmacokinetics of AZD8186 and its N-demethylated active metabolite (M1) have been characterized in patients after single and multiple BD dosing (5 days on, 2 days off) over the dose range 30, 60, 120, 180, 240, 300 and 360 mg.

AZD8186 appeared rapidly in plasma after single or multiple oral administration with peak plasma concentrations attained at around 1.5 h. Following the time to reach maximum plasma concentration (tmax), levels declined in a bi-phasic manner with a mean terminal half-life of 1.8 to 4.3 h following a single dose.

A dose proportional increase in AZD8186 exposure was observed in the dose range tested. Geometric mean Cmax and area under the plasma concentration-time-curve from zero to 12h after dosing (AUC(0-12)) increased in a dose proportional manner following single and multiple dosing.

Following an intermittent 5 days on; 2 days off schedule there was minimal accumulation with mean accumulation ratio (Rac) of 1.17 (Day 19/Day 1 AUC(0-12)). These results are consistent with the

short half-life of AZD8186, and further suggest a low likelihood of autoinduction of metabolizing enzymes that might affect its own clearance.

The metabolite (M1) was detected in the plasma of all patients with a similar profile to that of the parent drug, but at a lower level (approximately 40%, independent of dose, to date).

Overall, the metabolite increased with dose in a similar manner to that of the parent drug after single or multiple dosing.

2.2.1.2.2. Pharmacodynamics

Acute reduction of pAKT S473 and pGSK3β was observed in platelet-rich plasma of patients treated with a single dose of AZD8186. This reduction was maintained for 8 hours in patients treated with an AZD8186 single dose (30 or 60 mg), and for 24 hours in patients treated with at least 120 mg.[7]

2.2.1.2.3. Safety and efficacy

Preliminary findings from 147 dosed patients from data cut off of 02 May 2019:

Safety and tolerability

Most patients (143/147 [97.3%]) experienced an AE, and most patients (117/147 [79.6%]) experienced an AE that was considered by the investigator to be causally related to AZD8186. Over half the patients (91/147 [61.9%]) experienced an AE of CTCAE Grade 3 or higher. Twenty-six of the 147 patients (17.7%) had an AE leading to discontinuation. Of the 147 patients, 61 (41.5%) patients experienced an SAE and 29 (19.7%) patients experienced an SAE that was considered by the investigator to be causally related to AZD8186. The AEs include those from doses that were later deemed to be non-tolerable due to dose limiting toxicities (DLTs).

- The most frequently reported AEs (affecting >20% patients) were diarrhoea reported by (69/147 [46.9%]), nausea (62/147 [42.2%]), fatigue (54/147 [36.7%]), vomiting (51/147 [34.7%]), decreased appetite (40/147 [27.2%]), pyrexia (34/147 [23.1%]), increased aspartate aminotransferase (31/147 [21.1%]) and increased alanine aminotransferase (30/147 [20.4%]).
- In Study D4620C00001 to date, the SOCs with the most SAEs were GIdisorders (29 events), Infections and infestations (25 events), General disorders and administrative site conditions (23 events), and Respiratory, thoracic, and mediastinal disorders (11 events). The most frequently occurring PTs (with ≥3 SAEs) were pyrexia (15 events), diarrhoea (8), pneumonia (6), colitis (6), vomiting (5), AST increased (5), ALT increased (4), anaemia (4), nausea (4), sepsis (4), back pain (4), confusional state (4), haematuria (3), pulmonary embolism (3), lower respiratory tract infection (3), and dehydration (3).
- At this early stage of clinical development, patient numbers in each dose group are low, and it is difficult to draw conclusions.

- There have been no AEs leading to death reported in the clinical programme to date. All deaths have been reported up to the data cut-off for this IB have been identified as being due to disease progression.
- Three patients have experienced confirmed partial responses, according to RECIST. One patient was administered AZD8186 as monotherapy, and 1 patient was administered AZD8186 in combination with vistusertib, and 1 patient was administered AZD8186 in combination with abiraterone

Preliminary efficacy

At this stage, only a small number of patients have been enrolled to determine efficacy, as the clinical programme is still evaluating the optimal dose and schedule.

Three patients have experienced confirmed partial responses, according to RECIST, as follows:

- Highly refractory mCRPC Part A patient with known PTEN and KRAS mutations on 2/5 schedule at 120 mg BD a (maximal 32% tumour reduction versus baseline). The patient is now off-study due to disease progression (on study >83 weeks).
- mCRPC Part D1 patient (germline BRCA-2 and AR mutations) on 5/2 schedule 30 mg BD plus vistusertib 100 mg 2/5 schedule. The patient is now off-study due to disease progression (on study for >55 weeks).
- Abiraterone/enzalutimide naïve PTEN proficient mCRPC Part C1 cohort 2 patient (120 mg AZD8186 BD 5/2/ plus 1000 mg abiraterone QD) had confirmed PR by CT (51% reduction in target lesions) and PSA.

Investigation of the safety and tolerability of AZD8186 alone and in combination with abiraterone acetate is continuing in expansion cohorts in patients with mCRPC.

2.2.1.2.4. Precautions for use

The risks associated the AZD8186 are as follows from 147 dosed patients from data cut off of 02 May 2019:

<u>Identified risks</u>
Rash
Diarrhea and colitis

<u>Potential risks</u>
Hypersensitivity
Possible drug interactions
Platelet aggregation/bleeding risk

Lymphoid effects
Hepatic effects
Phototoxic potential
Reproductive precautions

Summary of previous and ongoing important risks

Risk	Pre-clinical data	Clinical data	Actions
Identified risks			
Rash	No data in pre-clinical studies	Rash has been observed with the use of AZD8186 at a cumulative frequency of 24% (8.8% grade 3) in study D4620C00001. All cases resolved after dose-interruption/dose-reduction.	Recommendations for the management of rash together with dose modification guidance for rash grade ≥ 3 are included in the clinical study protocol.
Diarrhea/Colitis	Evidence in genetically modified mice with a 'kinase-dead' mutation inserted into the PI3Kδ gene. These mice spontaneously develop colitis (Uno et al 2010). However, when these mice are raised in a germ free environment they do not develop colitis (Steinbach et all 2014). If the germ-free mice are transferred to normal environment they do get colitis (Steinbach et all 2014). This data indicates that lacking catalytically active PI3Kδ is a risk factor for colitis, when bowel microbiota are present	Diarrhea has been observed with the use of AZD8186, the majority being mild, self-limited and responsive to anti-motility agents [cumulatively 46.9% (All grades); 8.2% (grade 3); study D4620C00001]. 9 cases of grade 3 colitis/entercolitis were reported, all of which resolved with dose interruption, dose reduction and/or supportive treatment including steriods.	Patients with pre-existing grade 2 or higher chronic diarrhea are excluded from studies with AZD8186. Recommendations for the management of diarrhoea together with dose modification guidance for diarrhoea grade >2 are included in the clinical study protocol. Suspected colitis as the cause of intermittent, chronic or chronic recurrent diarrhoea should be confirmed and treated by standard local practice.
Important potential risks			

Hypersensitivity	No data in pre-clinical studies	Two patient experienced hypersensitivity in study D4620C00001 (one case was Grade 3) and recovered with dose reduction/interruption.	Patients with medically confirmed history of hypersensitivity or allergic reaction to any drug (e.g., penicillin), or anaphylaxis to food allergen(s) are excluded from studies with AZD8186. Hypersensitivity is closely monitored as part of routine pharmacovigilance. Guidance on dose interruption for patients who experience hypersensitivity/ allergic response is included in the clinical study protocol.
Possible drug interactions	AZD8186 may have the potential to induce CYP450 enzymes, particularly CYP3A4, and to inhibit Organic Anion Transporting Polypeptide 1B1 (OATP1B1) and CYP2C9 enzyme.	AZD8186 is predominantly metabolised by CYP3A4 and preliminary PK data from study D4620C00001suggests there is no auto-induction effect following multiple bi-daily dosing (5 on 2 off schedule) over a 3 week treatment period. No toxicity potentially related to drug-drug interaction (DDI) has been observed so far in study D4620C00001.	The concomitant use of AZD8186 with narrow therapeutic index drugs that are metabolized by CYP3A4 or CYP2C9 should be avoided. A list of these drugs is included in the clinical study protocol. Strong and moderate CYP3A4 inducers and inhibitors are prohibited during studies with AZD8186 and a list of these are included in clinical study protocols. Additional monitoring of low-density- lipoprotein (LDL) is advised for patients receiving cholesterol-lowering drugs (eg. statins and ezetimibe).
Hepatic effects	AZD8186 administration was associated with changes in the liver of dogs (including	Cumulatively 12% of patients developed increase in AST and/or ALT (Grade 1/2) and 12% developed a Grade 3 toxicity in study	Patients are required to have adequate baseline hepatic function, with liver enzymes and liver synthetic function

	hepatocyte degeneration/single cell necrosis, increases in plasma liver enzymes) and mice (inflammatory cell infiltration). These changes showed evidence of reversibility following withdrawal of AZD8186.	D4620C00001, all of which resolved after dose interruption/reduction. One patient developed Grade 4 ALT/ Grade 3 AST elevation in combination with abiraterone, resulting in an interruption of study therapy. There was negative rechallenge with AZD8186, and positive rechallenge with abiraterone. The event resolved upon continuation of AZD8186 and discontinuation of abiraterone.	monitored closely throughout study treatment. Persistent grade 2 or higher occurrence of elevation of transaminases and bilirubin or evidence of impaired liver function in patient will result in interruption of treatment with AZD8186 immediately until all abnormaities return to normal or to their baseline state.
Inhibition of Platelet Aggregation (bleeding risk)	AZD8186 was shown to inhibit ADP-stimulated platelet aggregation in dog whole blood, without any adverse effects on bleeding observed in vivo. These changes were considered likely to be related to pharmacology, in resulting from inhibition of PI3K β and/or PI3K δ. These changes showed evidence of reversibility following withdrawal of AZD8186.	Cumulatively, a total of 14 events of hematuria (13 grade 1 or garde 2 severity, 1 grade 3 severity), 1 report of grade 1 or grade 2 hemoptysis, and 2 reports of grade 1 or grade 2 epistaxis were observed. All of these events were assessed as unrelated to AZD8186 except for 2 events of haematuria which were assessed as related to AZD8186 by the reporting investigator.	Thrombolytic therapy is not permitted during the study period. Anti-platelet agents should be interrupted in patients with significant evidence of bleeding, bleeding risk or 7 days prior to any biopsies or surgical procedures and restarted afterwards.
Phototoxicity	AZD8186 absorbs in the UV spectrum (290 to 700 nm) and was positive in an in vitro 3T3 Neutral Red Uptake phototoxicity test at the in vitro IC50 for a positive phototoxicity signal (7.7 mg/ml, 16.8 μmol/L). This suggests that AZD8186 exhibits a	No effects observed to date.	Patients will be required to follow UV-light precautions, including: protective clothing, sunglasses and Sun Protection Factor (SPF) 45 or greater sunscreen when outdoors; and sun bed avoidance.

	weak phototoxic potential.		
Reproductive toxicity	AZD8186 administration was associated with testicular tubular degeneration in dogs and/or mice. The changes seen in the testis in both species may be related to PI3K β inhibition, as male mice expressing a catalytically inactive PI3K p110β subunit have been shown to develop testicular hypotrophy and impaired spermatogenesis, leading to defective fertility.	No effects observed to date.	Conception must be avoided during exposure to AZD8186. Strict contraceptive guidance is included in the clinical study protocols. Women of childbearing potential and men will be required to agree to use adequate contraception during the study period and for 4 weeks (women) and 1 week (men) after the last dose of study drug. Male subjects should similarly abstain from sperm donation for 6 months after the last dose of study drug.
Lymphoid Tissue changes (Blood and lymphatic disorders)	In dogs and mice, changes were observed in a variety of lymphoid tissues (including lymphocyte single cell necrosis-degeneration), increases in peripheral white blood cell counts. PI3K isoforms, in particular PI3Ks β, δ and γ, have multiple non-redundant roles within the immune system, including neutrophil and lymphocyte development and function. The changes seen in the primary and secondary lymphoid organs of mice and/or dogs dosed with AZD8186 may, therefore, be a consequence of inhibition of PI3K β	Cumulatively, thrombocytopenia, anaemia, neutropenia and lymphopenia were reported as follow: -thrombocytopenia: 3 cases (2.04%) of Grade 1/2, 3 cases (2.04%) of Grade 3, 1 case (0.7%) of Grade 4. Of these 7 events, 3 were assessed as related to AZD8186. None of the events were serious. -anaemia: 18 cases (12.2%) of Grade 1/2, 8 cases (5.4%) of Grade 3. Of these 26 events, 13 were assessed as related to AZD8186. 4 events were serious and 1 was related to AZD8186. -neutropenia/neutrophil count decreased: 8 cases (5.4%) of Grade 1/2 and 3 cases (2.0%) of Grade 3. Of these 11 reports, 8 were assessed as related to AZD8186. A single report was serious and related	Patients are required to have adequate bone marrow reserve and organ function at study entry and these parameters will be monitored throughout study.

and PI3K δ.	to AZD8186 therapy. -lymphopenia/lymphocyte count decreased: 5 cases (3.4%) of grade 1/2, 9 cases (6.1%) of grade 3, 1 case (0.7%) of grade 4. Of these 15 cases, 6 were assessed as related to AZD8186. None of the events were serious.

2.2.1.2.5. Rationale for the proposed starting dose, dose escalation scheme.

From the ongoing phase I study, AstraZeneca has declared a RP2D of AZD8186 at 60 mg po bid on a 5 day on/2 off weekly schedule. AZD8186 was tested on this schedule at doses as high as 340 mg po bid. Toxicities of rash, fever, chills, and colitis were seen with these higher doses. Across the ongoing phase I study, doses as high as 340 mg BD AZD8186 have been explored on the 5/2 monotherapy schedule and as high as 120 mg BD on the continuous (declared as tolerated) and 240 mg BD on the 2/5 schedule (also declared as tolerated). In addition AZD8186 at 120mg BD is currently being explored with full dose abiraterone and vistusertib (AZD2014, TORC1/2 inhibitor). Based on pharmacodynamic data, 30mg is considered to be the lowest effective dose, as a result the proposed starting dose for combination with docetaxel is 60mg.

Dose Escalation Schedule

Dose Escalation schema		
Dose Level	**Dose**	
	AZD8186 BID PO, 5 days on, 2 days off every week **(mg)**	**Docetaxel** IV on day 1 of a 21-day cycle **(mg/m^2)**
-1*	30	75
-1B*	60	60
Starting dose level 1*	60	75
2*	120†	75

Please refer to Section 5.5 for DLT definition.
†AZD8186 dosed at 90mg bid 5 days on /2 off may be explored, as directed by the emerging safety profile of this agent.
*Prophylactic growth factor support with docetaxel should be administered during the first cycle of therapy per institutional guidelines and per the provider's discretion on subsequent cycles. Since the protocol was amended to include the use of prophylactic growth factor during DL-1B, patients who experienced a DLT of neutropenia or neutropenic fever at this dose level prior to the implementation of prophylactic growth factor maybe replaced.
Note: DL -1B was added in an amendment based on the emerging safety profile

2.3 Other Agent(s)

Docetaxel

Docetaxel, a semi-synthetic analog of paclitaxel, acts by disrupting the microtubule network leading to apoptosis and cell death. Docetaxel is used as a single agent and in combination with multiple other chemotherapies in the treatment of many solid tumors including Breast, ovarian, lung, head & neck, bladder, esophageal, cervical, and endometrial cancers.
The most common adverse events with the administration of docetaxel ate infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluids retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions and myalgia (Taxotere product information).

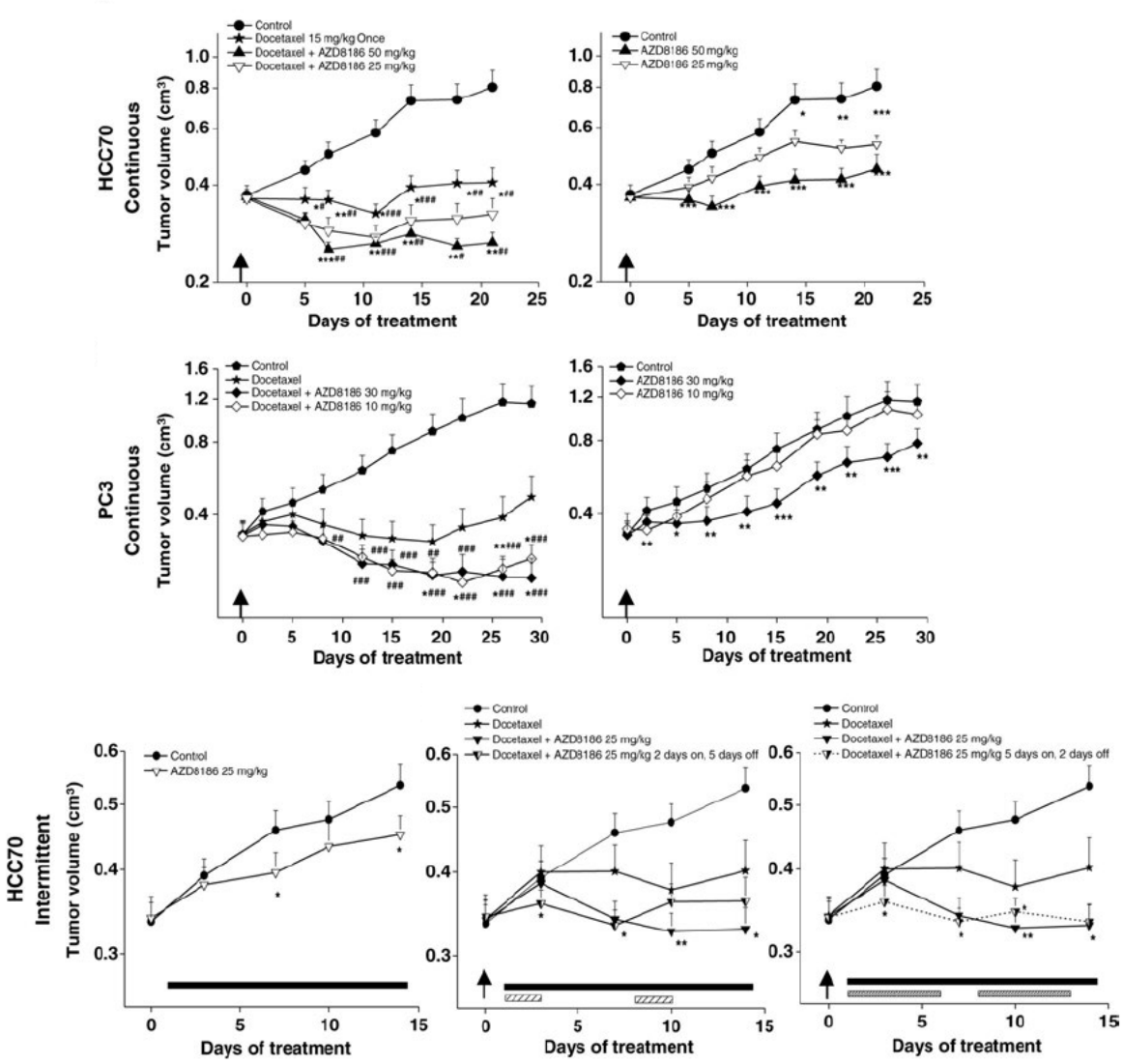
An established standard of care dose (75mg/m^2 Docetaxel on day 1 of a 21-day cycle) was chosen as the starting dose level for this agent. This dose is used in most solid tumors treated with docetaxel either as a single agent or in combination with other chemotherapies.

2.4 Rationale

The PI3K/AKT/mTOR signaling network is a critical regulator of many cellular processes, including proliferation, survival and transformation. PI3K–AKT pathway dysregulation is a hallmark of various cancers, seen in up to 50% of all solid tumors.[10-12] Among other mechanisms, aberrant pathway activation can arise from somatic mutations in *PIK3CA*, *AKT1* or from loss/inactivation of the *PTEN* suppressor gene.[13-15]

The lipid kinases PI3Kα, β, γ & δ are key regulators of this network.[16] Different isoforms of PI3Ks have been shown to play key roles in distinct tumor types, often linked with genetic alterations in genes encoding other components of the network. Furthermore, the PI3K enzymes are critically controlled by the tumor suppressor PTEN, a lipid phosphatase that reverses the action of PI3Ks.[17] PTEN additionally has a nuclear role in promoting chromosome stability and DNA repair and therefore, loss of PTEN function increases genomic instability.[2,18,19] Indeed, PTEN has been linked to poor outcome and therapeutic resistance in a number of cancers and as such offers a potential therapeutic target.[1,2,20-29]

PTEN deficient tumors may have increased dependence on PI3Kβ activity requiring p110β for growth and signaling through the PI3K pathway and thus may be sensitive to PI3Kβ inhibition.[30-32] AZD8186 is a potent and selective small molecule inhibitor of PI3Kβ with additional activity against PI3Kδ. PTEN-deficient tumors have been identified to have dependency on AKT2 for survival.[33] AZD8186 has been shown to inhibit AKT pathway activation, modulate pathway biomarkers and inhibit growth of breast and prostate tumor models.[34] Although AZD8186 has demonstrated limited single-agent activity in PTEN-null and PI3Kβ-driven preclinical models, it is likely to be more clinically effective in combination with other targeted agents or cytotoxic chemotherapy. Indeed, AZD8186 administered on an intermittent schedule with a single dose of docetaxel improved tumor growth inhibition in both PTEN-deficient prostate cancer and triple-negative breast cancer (TNBC) xenograft mouse models (**Figure 9,** below).[34]



In addition to *PTEN*, activating mutations of *PIK3CB*, the gene (formally known as *PIK3B*) encoding PI3Kß protein, although rare are being reported such as the E633K mutation in *PIK3CB*, found in a patient derived breast tumor, as well as D1067V, found in a lung cancer patient, have been reported to activate the PI3K/AKT pathway.[6,35] *PIK3CB* missense mutations, copy number gains and translocation have also been reported in a cohort of metastatic castrate-resistant prostate cancer.[36]

We propose that targeting *PTEN* mutated or *PIK3CB* mutated solid tumors with the PI3Kβ and PI3Kδ inhibitor, AZD8186 in combination with docetaxel, represents a mechanistically rational combination strategy to overcome therapeutic resistance in this largely poor prognosis group of cancers.

2.5 Correlative Studies Background

2.5.1 **Targeted genomic sequencing of formalin-fixed, paraffin-embedded tumor and tumor-derived plasma cell free (cf) DNA samples with the MSK-IMPACT assay**

2.5.1.1 Background

2.5.1.1.1. The MSK-IMPACT platform is an enterprise-grade targeted hybrid-capture next generation sequencing (NGS) assay examining 468 genes (current panel version) commonly mutated in cancer,[3] with a proven track record of generating high coverage (>500X) data in formalin-fixed paraffin-embedded (FFPE) specimens with as little as 15ng of genomic DNA.[37] Using a version of MSK-IMPACT optimized for cfDNA-based studies, the Center for Molecular Oncology (CMO) at MSKCC has successfully prepared sequence libraries with as little as 2ng cfDNA.[38] This platform has readily detected somatic mutations in cfDNA, captured tumor heterogeneity and provided a real-time readout of clonal and subclonal dynamics and evolution.[39]

2.5.1.2 DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor tissue from fresh pre-treatment biopsies or archival specimens and post-progression tumor biopsies along with a matched normal blood specimen collected pre-treatment will be evaluated for mutations in established cancer-related genes using the MSK-IMPACT assay. Serial cfDNA samples collected on study will also be evaluated for emerging mutations using MSK-IMPACT. cfDNA will be isolated from the plasma compartment of blood collected in Streck tubes.

2.5.1.3 Integrated biomarker

2.5.1.3.1. Retrospective central confirmation of the molecular alteration (an inactivating *PTEN* mutation or activating *PIK3CB* mutation) in **pre-treatment biopsy specimens or archival tumor specimen** (*pre-treatment biopsy required if archival tumor tissue is unavailable)*

2.5.1.4 Exploratory biomarker

2.5.1.4.1. Hypotheses:

2.5.1.4.1.1. Co-mutational profile will potentially modify response to AZD8186 in *PTEN/ PIK3CB* mutated tumors

2.5.1.4.1.2. In patients that initially respond to AZD8186, the durability of these responses will be limited by mutations that drive acquired resistance.

2.5.1.4.1.3. Aims:

2.5.1.4.1.3.1. Examine the pattern of co-mutated genes in pre-treatment biopsy specimens or archival tumor specimens of patients with *PTEN/ PIK3CB* mutated tumors and their association with treatment response or resistance

2.5.1.4.1.3.2. Monitor the emergence of new somatic alterations or resistant subclones in the **cfDNA and post-progression tumor biopsies** of patients with *PTEN/ PIK3CB* mutated tumors who initially respond to AZD8186, thereby describing potential mechanisms of acquired resistance to therapy.

2.5.2 **Multiplex quantitation of Akt pathway signaling proteins in flash frozen pre- and on-treatment biopsy specimens with the Luminex multiplex assay (**Integrated biomarker)

2.5.2.1 Background:

2.5.2.1.1. Investigators (Dr Srivastava, lab PI) at the Pharmacodynamics Assay Development and Implementation Section (PADIS) laboratories of DCTD, NCI have extensive experience in developing validated multiplex immunoassays suitable for quantifying apoptotic biomarkers.[40] Using validated immunoassays for pharmacodynamic biomarkers of MET signaling, they succeeded in quantifying pharmacodynamic response of the MET/HGF receptor to MET inhibitors.[41] Dr Srivastava's group have since developed Luminex multiplex assays to monitor the pharmacodynamics of multiple classes of drugs targeting the PI3K-AKT-mTOR-rpS6 pathway. This multiplex assay examines isoform-specific AKT inhibition and other downstream target modulation from PI3Kβ inhibition.

2.5.2.1.2. The preclinical time-course study of this assay evaluating the molecular target responses to AZD8186 in PTEN mutant cell lines HCC70 and PC3 is ongoing at the Biological Testing Branch, NCI, the results of which will be presented at AACR-NCI-EORTC (Herrick, Srivastava et al 2017). First, highly selective isoform- or phospho-specific antibodies were developed for AKT1/2/3 and pRPS6(S235) and their specificity validated using a combination of techniques involving isoform-specific CRISPR knock-out cell lines, cancer cells treated with selective drugs and epitope-peptide competition. Multiplex sandwich immunoassays were then developed on the Luminex platform by using isoform-specific antibodies for capture and biotinylated antibodies for detection of total protein or phosphorylated residues. Recombinant proteins were used as calibrators. Dr Srivastava's lab multiplexed the analysis of biomarkers in the PI3K-AKT-rpS6 pathway (Table 1 below)

Table 1. Composition of multiplex panels

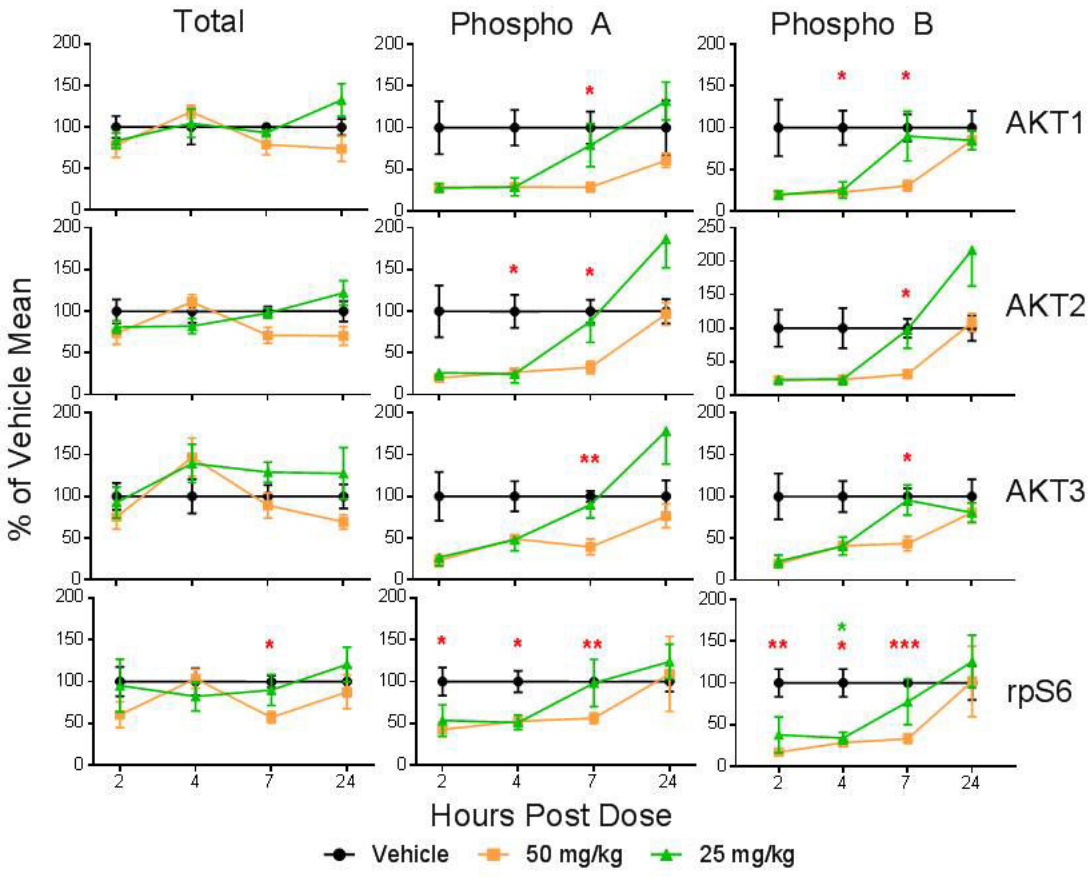
Total	Phospho A	Phospho B
1. Total AKT1 2. Total AKT2 3. Total AKT3 4. Total rpS6	1. pS473 AKT1 2. pS474 AKT2 3. pS472 AKT3 4. pS235 rpS6	1. pThr308 AKT1 2. pThr309 AKT2 3. pThr305 AKT3 4. pS240/244 rpS6

Prelimanry results:

- Using PTEN-null cancer cell lines (HCC70, MDA-MB-468, PC-3) treated with AZD8186, they found that the multiplex assays measure 70-90% reduction in target phosphorylation with high precision (CV < 15%). They also demonstrated that the AKT and rpS6 phospho-signals appear to be stable and quantifiable when biopsies are processed according to clinically-validated biopsy collection and extraction protocols established

previously for phospho c-MET (Appendix I).

- **Changes in AKT and rpS6 phosphorylation in AZD8186 treated PC3 xenografts –** Changes in biomarker levels were analyzed 2, 4, 7 and 24 hours post dose 1 in mice implanted with PC3 xenografts. No significant changes in the total protein levels were detected except for a small change in total rpS6 in the 50 mg/kg treatment group ($p< 0.05$). Significant changes in phosphorylation were observed at 7h for pS473 AKT1 and at 4 and 7h for pThr308 AKT1 ($p<0.05$) for the 50 mg/kg dose. AKT2 phosphorylation at pS473 significantly decreased at 4h and 7h and after 7h for pThr308 AKT2 ($p< 0.05$). Both pS473 and pThr308 AKT3 phosphorylation was reduced at 7h ($p< 0.01$ and $p< 0.5$ respectively). Reduction in rpS6 phosphorylation at pS235 and pS240/244 was observed at 2h, 4h and 7h post dose 1 50 mg/kg ($p<0.05$ 2-4h Phospho A, $p<0.01$ 7h PhosphoA, $p< 0.01$ 2h Phospho B, $p< 0.05$ 25 and 50 mg/kg at 4h and $p<0.001$ 7h).



2.5.2.2 Hypothesis: Testing paired tissue biopsies with this multiplex assay will provide quantitative measurements of the magnitude of drug-induced target suppression and indicate the effectiveness of AZD8186 in suppressing downstream pathway signaling.PI3Kβ inhibition of PTEN-deficient tumors will lead to changes in AKT pathway signaling and downstream target modulation.

2.5.2.3 Aim: Examine isoform-specific AKT inhibition and other downstream target modulation from PI3Kβ inhibition with AZD8186 in patients with *PTEN/ PIK3CB* mutated tumors enrolled in the **pharmacodynamic expansion cohort only,** using **pre- and on-treatment [window: Between C1D -5 to C1D -3, (2-3 hrs post dose)] flash frozen biopsy specimens.** Methods as previously described**.**[40,41]

2.5.3 **Immunohistochemistry-scoring of PTEN protein expression** (Exploratory biomarker)

2.5.3.1.1. Hypothesis: Loss of PTEN surface expression will be associated with inactivating/loss of function mutations in the *PTEN* gene and predict for response to therapy

2.5.3.1.2. Immunostaining of FFPE sections from pre-treatment or archival specimens and post-progression biopsies will be performed with tumor PTEN expression using the H-score formula: 3 × percentage of strongly staining cells+2 × percentage of moderately staining cells+percentage of weakly staining cells, giving a range of 0 to 300.[42] A H-score >10 will be considered positive for PTEN protein expression.[43,44]

2.5.3.1.3.

2.5.4 **Docetaxel and AZD8186 Pharmacokinetics (**Integrated biomarker)

2.5.4.1.1. Background: Clinical Pharmacology of Docetaxel and AZD8186 and Drug-Drug Interaction Potential: Docetaxel is metabolized primarily by CYP3A4 to at least four inactive metabolites and is susceptible to drug-drug interactions.[45] [46] Docetaxel is also a substrate for the drug transporter ABCB1 (P-glycoprotein), encoded by the MDR1 gene.[47] AZD8186 may be a substrate for and induce CYP3A4. Given docetaxel is a narrow therapeutic-index drug with ~40% intersubject variability in drug clearance,[48] there is a potential for reduced docetaxel concentrations when co-administered with AZD8186. Therefore, pharmacokinetic (PK) characterization would help confirm the potential clinical consequences of concurrent docetaxel and AZD8186.

2.5.4.1.2. Hypothesis: The interaction between AZD8186 and docetaxel will not result in clinically meaningful alterations in exposure.

2.5.4.1.3. Aims: To investigate a drug-drug interaction between docetaxel and AZD8186. To correlate drug exposure with pharmacodynamics response.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

3.1.2 Patients must be able to swallow and retain oral medications and be without gastrointestinal illnesses that would preclude absorption of AZD8186.

3.1.3 Unlimited prior therapies allowed

3.1.4 Docetaxel appropriate

3.1.4.1 Patients who have not received prior docetaxel (or other taxane therapy) in the advanced setting are eligible for all cohorts

3.1.4.2 Patients who have previously received docetaxel(or other taxane therapy) in the advanced setting are eligible for the dose escalation cohort only, if anticipated to have maintained taxane sensitivity and in the opinion of the investigator would still benefit from further docetaxel therapy.

3.1.5 Age ≥18 years.

3.1.5.1 Because no dosing or adverse event data are currently available on the use of AZD8186 in combination with Docetaxel in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.6 ECOG performance status ≤2 (Karnofsky ≥60%, see **Appendix A**).

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

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– hemoglobin	≥8 g/L
– platelets	≥100,000/mcL
– total bilirubin*	within normal institutional limits
– AST(SGOT)/ALT(SGPT)	≤1.5 × institutional upper limit of normal
– creatinine	within normal institutional limits OR
– creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.8 *PTEN* or *PIK3CB* mutated advanced solid tumor.

3.1.8.1 *PTEN* loss of function mutation or *PIK3CB* gain of function mutation identified by local CLIA certified next generation sequencing (NGS).

3.1.8.1.1. A curated list of *PTEN* variants with the corresponding literature to support their loss of function is found in **Appendix B** of this LOI.

3.1.8.1.2. A curated list of *PIK3CB* variants with the corresponding literature to support their gain of function is found in **Appendix C** of this LOI

3.1.8.2 Breast cancers patients enrolled on this study must have either:

3.1.8.2.1. Estrogen receptor positive and HER2 negative breast cancer

3.1.8.2.2. Triple negative breast cancer

3.1.9 Adequate archival tissue (metastatic tissue sample is preferable but primary tumor tissue will be acceptable) **or** willing to undergo pre-treatment biopsy (for central confirmation of molecular alteration and PTEN immunohistochemical assessment) if adequate archival tissue is unavailable.

3.1.10 The effects of AZD8186 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of AZD8186 administration.

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

3.1.12 Cohort specific eligibility:

3.1.12.1 Dose escalation cohort:

3.1.12.1.1. Prior receipt of docetaxel is permitted (see 3.1.4.2)

3.1.12.1.2. Measurable disease is not required for enrollment

3.1.12.2 Pharmacodynamic expansion cohort:

3.1.12.2.1. Prior receipt of docetaxel is not permitted (see 3.1.4.1)

3.1.12.2.2. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.12.2.3. Consent to allow mandatory paired (pre- and on- treatment) fresh tissue biopsies if deemed safe to do so for quantitation of Akt pathway signaling proteins

3.1.12.3 Disease specific expansion cohorts

3.1.12.3.1. Prior receipt of docetaxel is not permitted (see 3.1.4.1)

3.1.12.3.2. Patients (excepting the prostate cancer patients) must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.12.3.3. Breast cancers patients enrolled on this study must have:

3.1.12.3.3.1. Metastatic or advanced (incurable and unresectable) HER2 negative breast cancer regardless of estrogen receptor status (both hormone receptor positive and triple negative patients are eligible)

3.1.12.3.3.2. Received hormonal therapy, as appropriate based on their hormone receptor status. Hormone receptor positive patients who have not received endocrine therapy for recurrent/metastatic disease are eligible, permitted their physician feels they are not appropriate for first line endocrine therapy, for example for high risk visceral metastatic disease.

3.1.12.3.4. Prostate cancers patients enrolled on this study (applies to all prostate cancer patients treated on parts 1, 2, and 3) must have:

3.1.12.3.4.1. Metastatic or advanced (incurable and unresectable) castration resistant metastatic cancer

3.1.12.3.4.2. Received at least one additional line of anti-androgen therapy with abiraterone or enzalutamide.
3.1.12.3.4.3. Measurable disease is not required for enrollment

3.2 Exclusion Criteria

3.2.1 HER2 positive breast cancer.

3.2.2 Prior treatment with PI3K/AKT inhibitors.

3.2.3 Any known concurrent *RAF* or *PIK3CA* mutation.

3.2.4 Patients who have had chemotherapy, radiotherapy, immunotherapy or anticancer agents within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of the first dose of study treatment, except hormonal therapy with LHRH analogues for medical castration in patients with prostate cancer and breast cancer, which are permitted

3.2.5 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1)

3.2.6 Patients who are receiving any other investigational agents.

3.2.7 Patients with known, untreated or unstable brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients with treated brain metastases are eligible if the metastases have been radiographically and clinically stable for at least one month. If on steroids for this indication, the patient must be on a stable dose for at least one month.

3.2.8 History of clinically significant allergic reactions attributed to compounds of similar chemical or biologic composition to AZD8186 or Docetaxel or to Docetaxel itself.

3.2.9 Patients receiving any medications or substances that are strong inhibitors and/or strong or moderate inducers of CYP3A4 are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. [**Appendix D**: patient information sheet]

3.2.10 Existing bleeding or condition associated with increased risk of bleeding
3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled hypertension, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.12 Pregnant women are excluded from this study because AZD8186 is a PI3K inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with AZD8186, breastfeeding should be discontinued if the mother is treated with AZD8186. These potential risks may also apply to other agents used in this study.

3.2.13 HIV-Patients positive for human immunodeficiency virus (HIV) are NOT excluded from this study, but HIV-positive patients must have:

- A stable regimen of highly active anti-retroviral therapy (HAART) that does not include strong inhibitors and strong or moderate inducers of CYP3A4
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
- A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test

3.3 Inclusion of Women and Minorities

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

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	1	1	1	1	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	7	7	2	2	**18**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
White	12	12	2	2	**28**
More Than One Race	2	2	2	2	**8**
Total	**22**	**22**	**7**	**7**	**58**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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

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

Documentation Required	IVR	NPIVR	AP
CV (optional)	✔	✔	✔

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

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

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

4.1.1 Site Registration

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

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

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

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

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

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

be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Participating Organizations:

Part 1 Dose escalation cohort
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO *restricted to:*

- **MD017**/ JHU Sidney Kimmel Comprehensive Cancer Center
- **NY016** / Memorial Sloan Kettering Cancer Center
- **NY478** / Memorial Sloan Kettering Westchester
- **NJ299**/ Memorial Sloan Kettering Monmouth

LAO-TX035/ University of Texas MD Anderson Cancer Center LAO
LAO *restricted to:*

- **TX035/** University of Texas MD Anderson Cancer Center

LAO-NCI/ National Cancer Institute LAO

Part 2 Pharmacodynamic expansion cohort/ Part 3 Disease specific expansion cohort
Open to all sites in LAO Participating Organizations table:

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

4.1.2 Downloading Regulatory Documents

Site registration forms may be downloaded from the *[NCI protocol #10131]* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.

- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MD017 *and protocol #10131.*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.1.3 Requirements For *NCI protocol #10131* Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- A Site initiation visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator, and pharmacist. To schedule a SIV, please email the Protocol Liaison and crocc@jhmi.edu and reference the protocol in the subject line of the email.

4.1.4 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.1.5 Checking **Site** Registration Status

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

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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does

not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.2 Patient Registration

4.2.1 OPEN / IWRS

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

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

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

4.2.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

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

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

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

4.2.3 Patient Enrollment Instructions

Sites must reserve a slot in IWRS and then submit documentation to the study team before their slot request will be approved and they are able to enroll the patient in OPEN.

- A biomarker request form of the patient's mutation must be been signed and approved for eligibility by the Principal Investigator. (**Appendix E**)

4.2.4 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.3 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

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

Enrolled patients will initiate treatment with AZD8186 and Docetaxel beginning Day 1 of Cycle 1, excepting in the pharmacodynamic expansion cohort where patients will begin AZD8186 only on Day -7 (AZD8186 monotherapy lead-in). A cycle is 21 days. See below for details regarding administration of each agent.

Per the drug manufacturer AstraZeneca, clinical supply of AZD8186 60 mg tablets will expire on April 30, 2022 (based on the planned expiration date extension). Supplies can be used until the terminal lot shelf life dating is reached or the NCI inventory is exhausted. All patients must complete their last treatment on or before April 30, 2022, and the study will be closed to accrual and treatment to coincide with this expiration date.

Prophylactic growth factor support (i.e., G-CSF or peg G-CSF) with docetaxel should be administered during the first cycle of therapy per institutional guidelines and per the provider's discretion on subsequent cycles.

While on study, patients will return for assessments every week during the first cycle, then every 3 weeks.

Patients that require discontinuation of one study agent (AZD8186 or Docetaxel), but meet criteria to continue the other study agent (AZD8186 or Docetaxel) may do so after discussion with the study chair.

Docetaxel can be discontinued and AZD monotherapy continued if the patient develops intolerable G2 or greater toxicity deemed related to docetaxel (including but not limited to nail toxicity, edema, weight gain, and neuropathy).

During screening, every 6 weeks (±7 days) for the first 24 weeks then every 12 weeks (±7 days), and at the end of study, patients will have tumor imaging studies (a CT or MRI of the abdomen and pelvis and a CT of the chest) performed.

A patient will be permitted to have a new cycle of therapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

Beyond the DLT period, it will be acceptable for a new cycle of therapy (and all associated tests and procedures) to be delivered within a 3 day window before and after the protocol defined date.

Table 2 Regimen Description

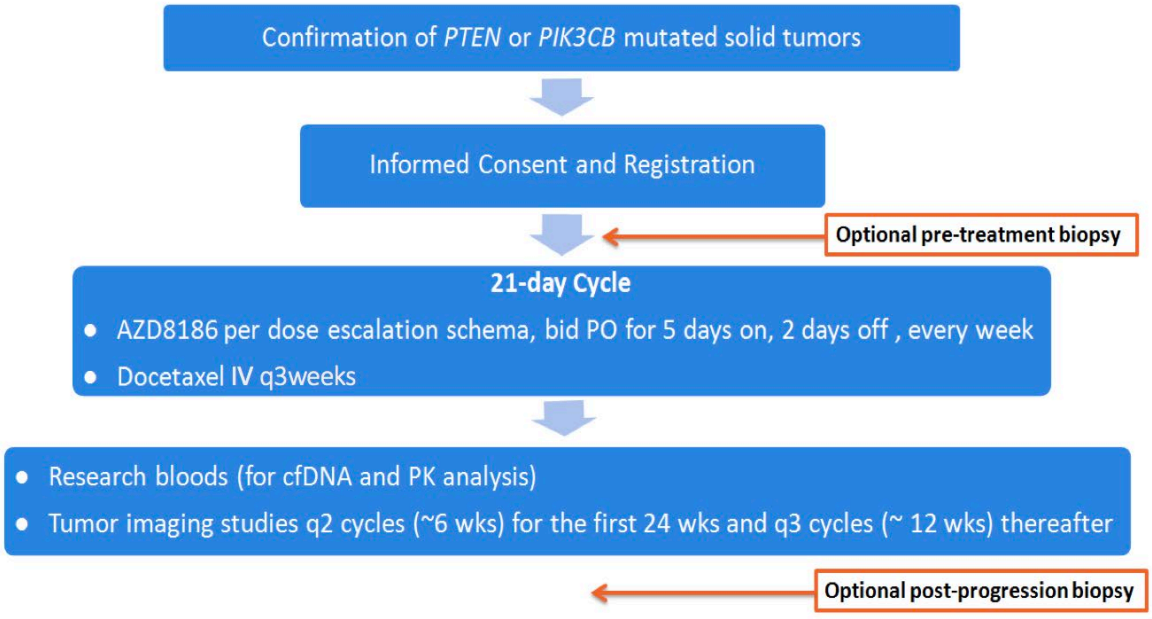
Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Docetaxel	Premedicate according to institutional guidelines. Recommended pre-medication with dexamethasone 8 mg orally twice daily x 3 days (or at the discretion of the investigator), to begin the day before treatment (6 doses) Recommend close observation for hypersensitivity reactions, especially during the first and second infusions, including an assessment of vital signs (body temperature, pulse rate, respiration rate, blood pressure) and weight prior to administration and monitoring of patient continuously during and up to 2 hours from the end of the the infusion on C1D1 and C2D1.	** in NS or D5W	IV over 1 hour	Day 1	21 days (3 weeks)

AZD8186	Taken at approximately the same time each day on an empty stomach and approximately 12 hours apart	** tablet	PO in the a.m. and p.m. (water only for at least 2 hours prior and 1 hour after each dose)	Starting on Day 1, administered for 5 days on, 2 days off, every week, (*Pharmacodynamic expansion cohort only, start on* ***Day -7***)	
***Doses as appropriate for assigned dose level.*					

The patient will be requested to maintain a medication diary of each dose of medication (Appendix F). The medication diary will be returned to clinic staff at the end of each course. Missed doses should be recorded in the pill diary but will not be considered deviations to the protocol.

5.2 Part 1: Dose escalation cohort

Figure 2 Dose escalation cohort schema



(n= 9 -21)

Dose Escalation Schedule

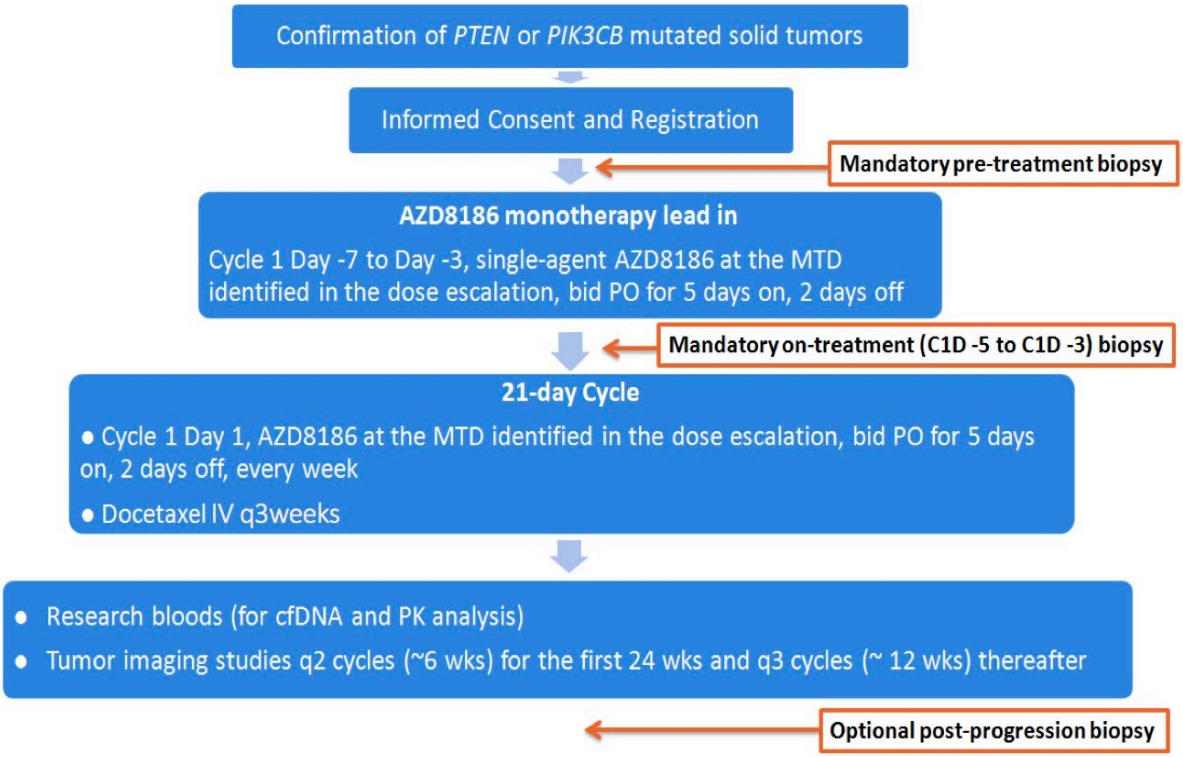
Dose Escalation schema		
Dose Level	**Dose**	
	AZD8186 BID PO, 5 days on, 2 days off every week **(mg)**	**Docetaxel** IV on day 1 of a 21-day cycle **(mg/m^2)**
-1*	30	75
-1B*	60	60
Starting dose level 1*	60	75
2*	120†	75

Please refer to Section 5.5 for DLT definition.
†AZD8186 dosed at 90mg bid 5 days on /2 off may be explored, as directed by the emerging safety profile of this agent.
*Prophylactic growth factor support with docetaxel should be administered during the first cycle of therapy per institutional guidelines and per the provider's discretion on subsequent cycles. Since the protocol was amended to include the use of prophylactic growth factor during DL-1B, patients who experienced a DLT of neutropenia or neutropenic fever at this dose level prior to the implementation of prophylactic growth factor maybe replaced.
Note: DL -1B was added in an amendment based on the emerging safety profile

- DLT evaluation period: 21 days (i.e. the duration of cycle 1)
- Patients will be **evaluated weekly during the DLT evaluation period:**
  - C1D1, C1D8 (± 1 day), C1D15 (± 1 day), C2D1 (± 1 day).

5.3 Part 2: Pharmacodynamic expansion cohort: NO LONGER OPEN

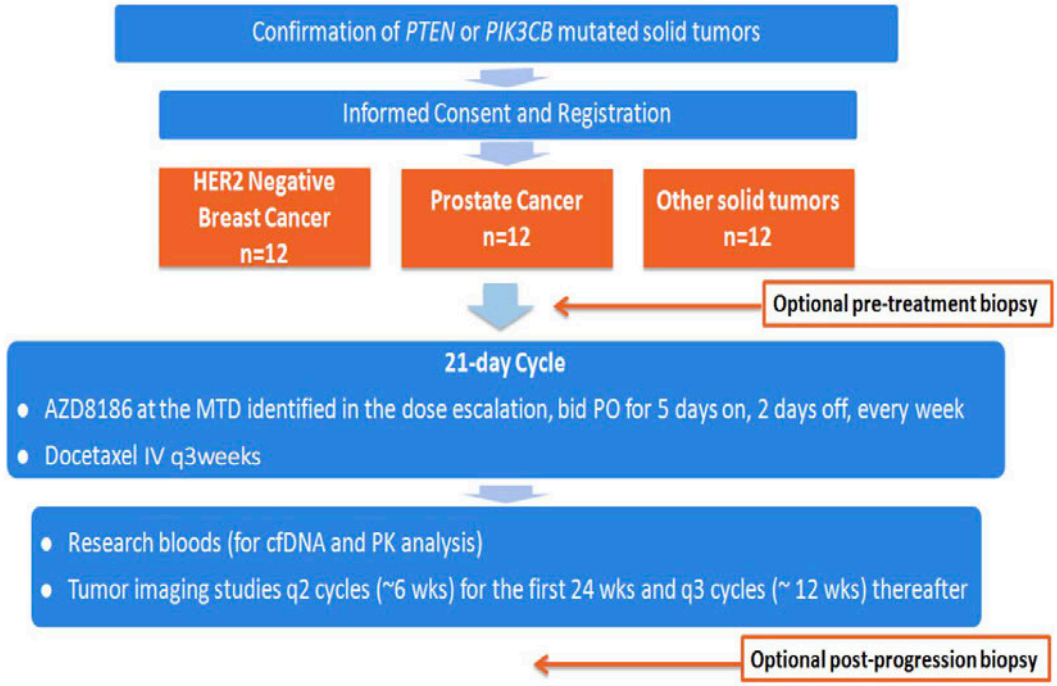
Figure 3 Pharmacodynamic expansion cohort schema



(n= 10)

5.4 Part 3: Disease specific expansion cohort: NO LONGER OPEN

Figure 4 Disease specific expansion cohort schema



(n=36)

5.4.1 AZD8186

Please refer to the regimen description, Table 2.
Note that for the pharmacodynamic expansion cohort specifically, patients will begin AZD8186 only on Day -7 (AZD8186 monotherapy lead-in).

AZD8186 will be taken orally twice daily at approximately the same time each day on an empty stomach (water only for at least 2 hours prior and 1 hour after each dose) and approximately 12 hours apart for 5 days on, 2 days off every week.

5.4.2 Docetaxel

Please refer to the regimen description, Table 2.

Administration of Docetaxel will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Anaphylactic precautions should be observed during Docetaxel administration. Premedication in order to prevent the onset of hypersensitivity reaction (HSR) and to reduce and/or delay the occurrence of skin toxicity and fluid retention related to docetaxel, will be according to institutional guidelines with recommendations detailed in the regimen description, **Table 2**. Additional antiemetic premedication may be employed at the discretion of the investigator.

Sites should consult the manufacturer's instructions for docetaxel for complete prescribing information (including warnings, precautions, contraindications and adverse reactions) and follow institutional procedures for the administration of docetaxel.

5.5 Definition of Dose-Limiting Toxicity

A DLT is defined as any treatment related toxicity (i.e., not attributable to the disease or disease-related processes under investigation) during the first 21 days of multiple dosing (i.e. from dosing on cycle 1, day 1 until dosing would be due on day 22), which includes:

1. Hematological toxicities as follows:
    a. Grade 4 neutropenia (ANC < 500 cells/mm3) lasting longer than 7 consecutive days despite growth factor support
    b. Grade 3 neutropenia of any duration accompanied with fever ≥ 38.5°C and/or systemic infection
    c. Grade 3 thrombocytopenia with bleeding
    d. Any other confirmed and clinically significant hematological toxicity ≥ Grade 4 (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).

2. Non-hematological toxicity ≥ Grade 3 including:
    a. Laboratory abnormalities (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).
    b. QTc prolongation (> 500 msec corrected using Fridericia's formula) in the presence of normal serum potassium

3. Hepatotoxicities as follows:

    a. Elevations of ALT or AST by 3-fold or greater above the upper limit of normal with elevation of serum total bilirubin of greater than 2× the upper limit of normal, without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal).
    b. No other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.
4. Any other toxicity i.e., greater than at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of the dosing schedule of more than 14 days.
5. Any event, including significant dose reductions or omissions, judged to be a DLT by the Investigator.

A DLT excludes:

1. Alopecia of any grade
2. Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal anti-emetic and/or anti diarrheal prophylaxis and/or treatment).

All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above. Patients who do not complete 75% of the study drug (AZD8186) during the DLT period due to reasons other than drug toxicity will be replaced.

Table 4 Dose escalation decision rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose

	administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3*	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the maximally tolerated dose (MTD)/ recommended phase 2 dose (RPD2). At least 6 patients must be entered at the recommended phase 2 dose.

* If Dose Level -1B is not deemed tolerable due to neutropenia, 3 more patients can be treated at this dose level with growth factor support.

5.6 Dose Expansion Cohorts

Once Part 1: Dose escalation cohort of the study is completed and the MTD/RP2D is reached, parts 2 and 3 will be opened concurrently and an additional 46 patients will be treated at the MTD. For the expansion cohorts, patients will continue to be monitored for occurrence of DLT during the DLT period (cycle 1, as defined for the dose escalation cohort above).
DLT data from the first 6 consecutively enrolled subjects to Parts 2 or 3 will be combined with DLT data from the 6 subjects treated at the MTD in Part 1. If, at any point, 4 or more total DLTs are observed across the combined 12 patients, further enrollment will be halted as the safety stopping rule will have been met. At this point, the study would be amended in consultation with the board to ensure ongoing subject safety.Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

5.7 General Concomitant Medication and Supportive Care Guidelines

Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Because there is a potential for interaction of AZD8186 with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs (including the use of supportive care medications or premedications such as dexamethasone), over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. For example, the potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors.

It is probable that AZD8186 is predominantly eliminated via CYP3A4 metabolism; therefore CYP3A4 inhibitors or inducers may increase or decrease exposure to AZD8186, respectively. Strong and moderate inhibitors or inducers of CYP3A4/5 should not be combined with AZD8186. Weak inhibitors or inducers of CYP3A4/5 are permitted but caution should be exercised and patients monitored closely for drug interactions. Dexamethasone is a weak CYP3A4 inhibitor but is required per standard of care premedication for docetaxel. Dexamethasone 8 mg orally twice daily x 3 days is recommended to decrease both HSR and fluid retention rate in patients receiving docetaxel every 21 days (**Table 2 Regimen**).

Check the study agent Investigator's Brochure for potential sources of drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. **Appendix D** (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following: Chemotherapy, hormonal therapy (except LHRH analogues for medical castration in patients with breast or prostate cancer, which are permitted), immunotherapy, radiotherapy, investigational agents, or herbal therapy.

Supportive care and other medications considered necessary for the patient's well being may be given at the discretion of the investigator.

5.7.1 Anticoagulation or thrombolytic therapy

The use of vitamin K antagonists is not permitted on the study. Patients requiring anti-coagulation should be given standard or low molecular weight heparins, or factor Xa inhibitors.

5.7.2 Recombinant Granulocyte Colony Stimulating Factor (G-CSF)

Primary prophylactic administration should be given with Cycle 1 and with subsequent cycles per investigator discretion

5.7.3 Blood transfusions

No primary prophylactic administration (for or during the first cycle) is permitted. Blood transfusions may be administered during subsequent cycles.

5.7.4 Bone modifying agents

The use of bisphosphonates and RANK ligand inhibitors are permitted on the study.

5.8 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.9 Duration of Follow Up

Patients will be followed for *a <u>minimum</u> of 30 days* after removal from protocol treatment or until death, whichever occurs first.

Patients removed from protocol treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients who discontinue for reasons other than progression should be imaged when they come off protocol treatment and then every 3 months until progression of disease or beginning of alternative anticancer therapy.

6. DOSING DELAYS/DOSE MODIFICATIONS

Investigator judgment is required for all dose modifications. Reductions in AZD8186 and/or docetaxel may be appropriate depending on the clinical context. If the adverse event is more clearly related to Docetaxel based on the known toxicity profile of this drug, then dose reductions of 20% decrements (where dose level -1 is 60mg/m2 and dose level -2 is 45/mg/m2) according to the

approved product information (prescribing information) should be used, whilst maintaining the AZD8186 dose and schedule. Patients cannot be dose reduced to dose level -1. When patients require dose modification due to toxicity possibly related to AZD8186, the dose should be decreased by 60 mg (i.e., 120 mg BID can have a single dose reduction to 60 mg BID). If more than 2 dose reductions are required, AZD8186 should be discontinued.

If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

If a patient experiences any of the following listed below, dosing will be interrupted and supportive therapy administered as required in accordance with local practice/guidelines:

- Any of the following AEs not attributable to the disease or disease-related processes under investigation: CTCAE grade 2 or higher maculopapular rash, chills, fever, hypersensitivity/allergic response, or any other immune mediated AE such as colitis
- And/or any other CTCAE grade 3
- And/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation (refer to Section 5.5 for DLT definition).

If the toxicity resolves or reverts to ≤ CTCAE grade 1 within 21 days of onset and there are no safety concerns for retreatment, AZD8186 and/or Docetaxel may be restarted at the same dose or a lower dose using the rules below for dose modifications.

If the toxicity does not resolve to ≤ CTCAE grade 1 after 21 days of dose interruption, then the patient should be permanently discontinued from AZD8186 and Docetaxel (withdrawn from the study) and observed until resolution of the toxicity. NOTE: Patients that require discontinuation of one study agent but meet criteria to continue the other study agent may do so after discussion with the study chair.

On resolution of toxicity within 21 days:

- If a further episode of the same AE subsequently requires dose interruption, AZD8186 and/or Docetaxel must restart at one dose level lower on improvement of the AE.
- If a different AE subsequently requires dose interruption, AZD8186 and/or Docetaxel may restart at the same or one dose level lower on improvement of the AE at the discretion of the Investigator and agreement with the Principal investigator.

Table 6 Dose modifications

Nausea	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose

Nausea	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
	May consider holding until ≤ Grade 1. Resume at same dose level.	
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose May consider holding until ≤ Grade 1. Resume at same dose level.	No change in dose
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Recommendations for treatment of diarrhea/colitis

Patients should be made aware of the risk of diarrhea while receiving treatment with AZD8186. Patients should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically.

As soon as the first liquid stool occurs, patients should start treatment with loperamide immediately (to be administered per package information and usual clinical practice) and also take electrolyte-containing fluids. Patients should inform their study doctor. Loperamide should not be administered for more than 48 consecutive hours.

Infectious diarrhea should be excluded by standard of care investigations, for example, caused by infections with C. difficile or Salmonella. If positive, patients must be treated according to local practice.

Hospitalization is recommended for management of diarrhea under the following circumstances:

- Diarrhea associated with fever

- Diarrhea requiring intravenous hydration
- Diarrhea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Suspected drug-induced colitis as the cause of diarrhea of chronic (i.e. >3 loose stools per 24 hours for more than 4 weeks), intermittent or chronic recurrent course, should be confirmed by standard of care investigations including colonic tissue biopsy and treated by standard local practice including high-dose steroids with tapering down of the dose over 3-4 weeks.

Diarrhea or colitis	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold, reassess 24-48 hrs later. Once ≤ Grade 1 (within 21 days), resume at same dose level.	No change in dose
Grade 3	Hold, reassess 24-48 hrs later. Once ≤ Grade 1 (within 21 days), resume at one dose level lower.** If unresolved , hospitalize (if not already) with GI consult	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Should not be administered for more than 48 consecutive hours. Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Recommendations for treatment of rash

Patients who develop Grade 1 or 2 changes in their skin condition should be treated with the Investigator's choice of antihistaminergic drugs, over the counter moisturizing cream or ointment, local antihistamines and/or topical or systemic steroids. If bacterial infection is suspected, local and/or systemic antibiotics may be added.

For Grade 3 rash, topical and/or systemic steroids with or without topical and/or systemic antibiotics (to be considered if bacterial infection is suspected) are indicated, together with dose modifications as described in section 5.9.2; short courses (mod days) of corticosteroid treatment at doses that do not exceed 100 mg per day of prednisone or equivalent may be given.

Example treatments:

- Topical steroids: triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone proprionate 0.05%, alclometasone 0.05%
- Topical antipruritics: pramoxine 1%; doxepin 5% cream

- Oral antihistamines: loratidine, cetirizine, fexofenadine; diphenhydramine 25-50 mg every 8h; hydroxyzine 25 mg every 8h
- Topical antibiotics: clindamycin 1-2%; erythromycin 1-2%; metronidazole 1%; silver sulphadiazine1%
- Oral antibiotics: doxycycline 100 mg BD; minocycline 100 mg BD; tetracycline 500 mg

Hematologic Dose Modifications

Neutropenia	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	No change in dose	Hold* until ≤ Grade 1. Resume at one dose level lower and/or initiate G-CSF, if not given prophylactically.**
Grade 4	Hold* until ≤ Grade 2. Resume at one dose level lower and/or initiate G-CSF if not given prophylactically. **	Hold* until ≤Grade 1. Resume at one dose level lower and/or initiate G-CSF if not given prophylactically..**
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should permanently discontinue docetaxel.		

Thrombocytopenia	**Management/Next Dose for AZD8186**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Hold* until ≤ Grade 1. Resume at one dose level lower.**	Hold* until ≤ Grade 1. Resume at one dose level lower.**
*Patients requiring a delay of >3 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.		

With recurrence of G4 neutropenia/thrombocytopenia or a G3 febrile neutropenia event despite one docetaxel dose reduction, the participant should be removed from docetaxel chemotherapy.

Additional hemostatic criteria for AZD8186 dosing

Patients requiring anti-coagulation should be given standard or low molecular weight heparins, or factor Xa inhibitors. Vitamin K antagonists are not permitted during the study period. If the patient is on an anti-platelet agent, this will be interrupted in line with the investigator's usual practice if

there is significant evidence of bleeding or bleeding risk. Similarly, during the study period, anti-platelet agents should be stopped 7 days prior to any biopsies or surgical procedures and restarted afterwards.

If the patient is showing clinical benefit and the above improve to baseline or to the normal range treatment with AZD8186 may be permitted to restart at a de-escalated dose at the discretion of the Investigator.

Hepatic Toxicity

- Hold docetaxel if bilirubin > ULN, or if AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. If laboratory abnormalities improve sufficiently to resume, decreased docetaxel dose by 1 dose level.
- Hold AZD8186 for Grade 2 bilirubin, or Grade 3 ALT and/or AST elevation. If the toxicity resolves or reverts to ≤ CTCAE grade 1 within 21 days of onset and there are no safety concerns for retreatment, AZD8186 and may be restarted at the same dose or a lower dose using the rules for dose modifications.
- If no recovery after 3 weeks, participant will be removed from study treatment.

Dose Modifications for Docetaxel Infusion (Allergic/Hypersensitivity) Reactions

- In the event of an infusion reaction, follow the Institutional Guidelines of each site and/or the recommendations shown in the tables below, based on the grade of the reaction.
- To identify the grade of a reaction, refer to the list below adapted from the General Disorders and Administration Site Conditions section of the NCI CTCAE Version 4.0:
    - **Grade 1:** Mild transient reaction; infusion interruption not indicated; intervention not indicated.
    - **Grade 2:** Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids indicated for ≤24 hours).
    - **Grade 3:** Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae **Note:** any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.
    - **Grade 4:** Life-threatening consequences; urgent intervention indicated.

Docetaxel Infusion Reactions	**Management/Next Dose for *[Agent Name]***
≤ Grade 1	Interruption or intervention not indicated. Slow the rate of infusion of the drug until resolution of symptoms, then resume at the planned infusion rate.
Grade 2	Interrupt the infusion. Follow institutional guidelines or give steroids (e.g. Dexamethasone 8 mg IV), diphenhydramine 50 mg IV, and/or an H2 blocker (e.g. Ranitidine 50 mg IV) after consultation with the attendant physician. Resume after recovery of symptoms at a slower

Docetaxel Infusion Reactions	**Management/Next Dose for *[Agent Name]***
	rate, and then increase incrementally toward the initial rate. If the reaction reoccurs, stop the infusion and do not administer the remaining volume.
Grade 3 or 4	Stop the infusion. Treat the participant as per grade 2 reaction above. Discontinue docetaxel permanently.

Docetaxel Dose Modifications for Neurotoxicity

- For grade 4 neurotoxicity, the participant should be removed from study treatment.
- For grade 3 neurotoxicity, docetaxel should be held until toxicity resolves to ≤ grade 1. Resume docetaxel at a dose reduction of one level.

Docetaxel Dose Modifications for Fluid Retention

- There are no dose reductions for fluid retention. Participants should be treated with salt restrictions and diuretics.
- More aggressive therapy depends on the clinical situation. In severe situations, the Investigator, with the participant, should determine if it is in the participant's best interest to continue or discontinue study treatment.

Docetaxel Dose Modifications for Mucositis

- For grade 4 mucositis (life-threatening), the participant should be removed from study treatment.
- For grade 3 mucositis present on Day 1 of a cycle, docetaxel should be held until toxicity resolves to grade 1. Resume docetaxel at a dose reduction of one level.
- If the grade 3 mucositis does not resolve within 3 weeks, the participant should be removed from study treatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below).

Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

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

7.1.1 CAEPRs for CTEP IND Agent

7.1.1.1 CAEPR for AZD8186

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
AZD8186 (NSC 785347)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text.
This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for AZD8186.

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

Version 1.2, August 29, 2019[1]

Adverse Events with Possible Relationship to AZD8186 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	
CARDIAC DISORDERS	
Sinus tachycardia	
GASTROINTESTINAL DISORDERS	
Abdominal distension	
Abdominal pain	
Colitis	*Colitis (Gr 3)*
Constipation	
Diarrhea	*Diarrhea (Gr 3)*
Dry mouth	
Nausea	*Nausea (Gr 2)*
Vomiting	*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Chills	

Adverse Events with Possible Relationship to AZD8186 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Edema limbs	
Fatigue	*Fatigue (Gr 2)*
Fever	*Fever (Gr 2)*
INFECTIONS AND INFESTATIONS	
Urinary tract infection	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Bruising	
Fall	
INVESTIGATIONS	
Activated partial thromboplastin time prolonged	
Alanine aminotransferase increased	
Alkaline phosphatase increased	
Aspartate aminotransferase increased	
Electrocardiogram QT corrected interval prolonged	*Electrocardiogram QT corrected interval prolonged (Gr 2)*
GGT increased	
Lymphocyte count decreased	
Neutrophil count decreased	
Weight loss	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Anorexia	*Anorexia (Gr 2)*
Dehydration	*Dehydration (Gr 2)*
Hyperglycemia	
Hypoalbuminemia	
Hypocalcemia	
Hypokalemia	
Hypomagnesemia	
Hyponatremia	
Hypophosphatemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	
Back pain	
Pain in extremity	
NERVOUS SYSTEM DISORDERS	
Dizziness	
Dysgeusia	
Headache	
PSYCHIATRIC DISORDERS	
Insomnia	
RENAL AND URINARY DISORDERS	
Hematuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Cough	
Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	

Adverse Events with Possible Relationship to AZD8186 (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
Dry skin	
Rash maculo-papular	***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS	
Hot flashes	
Hypertension	
Hypotension	

[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.

Adverse events reported on AZD8186 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD8186 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrioventricular block first degree
IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - Cholesterol high
RENAL AND URINARY DISORDERS - Urinary retention
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (angioedema)

Note: AZD8186 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 Adverse Event List(s) for Commercial Agent(s)

Docetaxel

- *Cardiac*: arrhythmias, pericardial effusions.
- *Hematologic*: dose-related neutropenia, leukopenia, thrombocytopenia, anemia.
- *Metabolic*: hypoglycemia, hypernatremia.
- *Gastrointestinal*: nausea and vomiting, diarrhea, oral mucositis, pancreatitis, esophagitis.
- *Neurologic*: reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures.
- *Hypersensitivity:* hypersensitivity (local or general skin rash, flushing, pruritus, drug fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea).
- *Dermatologic*: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes.

- *Hepatic:* increased transaminase, alkaline phosphatase, and bilirubin, hepatic failure, hepatic drug reaction.
- *Pulmonary*: dyspnea with restrictive pulmonary syndrome, pleural effusions.
- *Other*: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites, fever, flu-like symptoms.

Please refer to the package insert for the comprehensive list of adverse events with this agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for SAE reporting only. This study will continue to utilize CTCAE version 4.0 for routine toxicity reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and 5.0. A copy of the CTCAE version 4.0 and 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

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

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour

notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

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

7.3.3 Expedited Reporting Guidelines

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

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

Death due to progressive disease should be reported as **Grade 5 "Disease Progression"** in the system organ class (SOC) "General disorders and afministration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy loss"** under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

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

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or

subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

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

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

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

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Secondary Malignancy

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

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

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

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

Loading of the pathology report is required.

7.6 Second Malignancy

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

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent

8.1.1 AZD8186 (NSC #785347)

Chemical Name: 8-[(1R)-1-(3,5-difluoroanilino)ethyl]-N,N-dimethyl-2-morpholino-4-oxo-chromene-6-carboxamide

Other Names: none

Classification: PI3K beta and delta inhibitor

Molecular Formula: $C_{24}H_{25}F_2N_3O_4$ **M.W.:** 457.42

Approximate Solubility: AZD8186 solubility is 0.16 mg/mL at pH 1.5, 0.08 mg/mL at pH 6.6 and 0.11 mg/mL in Fasted State Simulated Intestinal Fluid.
Mode of Action: AZD8186 is a potent and oral inhibitor of phosphatidylinositol 3-kinase (PI3K), selective for beta and delta isoforms. The PI3K/AKT/mTOR signaling pathway is a critical regulator of proliferation, survival and transformation of cells. This pathway is frequently de-regulated is human cancers and is suitable to targeted therapy.

Description: AZD8186 is a crystalline powder.

How Supplied: AstraZeneca supplies and CTEP, NCI, DCTD distributes AZD8186 as film-coated tablets containing 30 mg and 60 mg of AZD8186. Tablets are packaged in 36-count HDPE bottles with an induction seal and child-resistant cap. Supplies of 30 mg tablets can be used until the terminal lot shelf life dating of November 30, 2021 is reached or the NCI inventory is exhausted. Supplies of 60 mg tablets can be used until the terminal lot shelf life dating of April 30, 2022 is reached or the NCI inventory is exhausted.

Tablet excipients include mannitol, colloidal silicon dioxide, di-calcium phosphate (anhydrous), sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulfate and magnesium stearate. The tablets are film coated with Opadry.

Storage: Store intact bottles below 30° C.

If a storage temperature excursion is identified, promptly return AZD8186 to less than 30° C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

Repackaging is not allowed and tablets must be dispensed in the original container. If exact quantity must be dispensed, then extra tablets should be removed, documented as waste and destroyed immediately.

Route and Method of Administration: Oral. Take on an empty stomach with water only for at least 2 hours prior and 1 hour after each dose.

Potential Drug Interactions: In vitro studies demonstrate AZD8186 is predominantly metabolized by CYP3A4/5 and CYP1A2 and to a lesser extent by CYPs 2C8, 2C9, 2D6 and 2C19. Avoid concomitant administration of potent CYP3A4/5 and CYP1A2 inducers/inhibitors.

In vitro studies suggest AZD8186 is a weak inhibitor of CYP2C9 and OATP1B1 and an inducer of CYP3A4/5 and to a lesser extent for CYP2B6. No enzyme induction was observed for CYP1A1/2 and no inhibition was observed for CYP 1A2, 2C8, 2B6, 2C19, 2D6, 3A4/5 and P-glycoprotein. Avoid concomitant administration of sensitive substrates of CYP2C9, CYP3A4/5, CYP2B6 and OATP1B1 since there is a potential for drug-drug interaction.

Patient Care Implications: Based on preclinical toxicology, AZD8186 is expected to affect platelet aggregation. Bleeding risk should be considered before starting treatment and monitored throughout study treatment, both clinically and with standard hematology and coagulation testing. Anti-coagulants or thrombolytic therapy should be restricted. Anti-platelet agents may be permitted, but these should be interrupted if there is significant evidence of bleeding or bleeding risk. Anti-platelet agents should be stopped 7 days prior to any biopsies or surgical procedures and restarted afterwards.

Patients will be required to follow UV-light precautions, including use of protective clothing, sunglasses and sunscreen with SPF 45+ when outdoors and should be counseled to avoid tanning beds.

Availability

AZD8186 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD8186 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

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

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

Study agent must be ordered after patient is registered to the treatment arm as no starter supplies are available for this study.
Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

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

8.1.2.3 Useful Links and Contacts

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

8.2 Commercial Agent: Docetaxel

Docetaxel

Please refer to the FDA approved and appropriate package insert for the standard comprehensive mixing instructions and adverse drug reaction information for Docetaxel.

Provided below are the details for Taxotere®, but sites may use the docetaxel formulation that is available to them, either concentrate or solution (brand or generic) and refer to the appropriate package insert.

Product description*:*

Taxotere® is a semisynthetic analog of paclitaxel using a precursor extracted from the needles of the European yew tree. Taxotere®'s high affinity for binding to microtubules enhances tubular polymerization, leading to inhibition of mitosis and cell division. Taxotere® is a cell-cycle specific agent with activity in the mitotic phase. Taxotere® is a member of the taxoid family. The molecular weight is 861.94 Da.

Product form: Taxotere® is formulated in polysorbate 80 and commercially available.
Solution preparation:

Storage and Stability: Storage and stability may vary by manufacturer, refer to specific prescribing information. Follow USP 797 recommendations for beyond use dates based on the level of risk for preparation.

Docetaxel 10 mg/mL: Store intact vials between 2°C to 25°C (36°F to 77°F).Protect from bright light. Multi-use vials (80 mg/8 mL and 160 mg/16 mL) are stable for up to 28 days after first entry when stored between 2°C to 8°C (36°F to 46°F) and protected from light. Solutions diluted for infusion should be used within 4 hours of preparation, including infusion time.

Docetaxel 20 mg/mL concentrate/solution:

Taxotere: Store intact vials between 2°C to 25°C (36°F to 77°F). Protect from bright light. Solutions diluted for infusion in D5W or NS in non-PVC containers should be used within 6 hours of preparation, including infusion time, when stored between 2°C to 25°C (36°F to 77°F) or within 48 hours when stored between 2°C to 8°C (36°F to 46°F).

Generic formulations: Store intact vials between 2°C to 25°C (36°F to 77°F). Protect from light. Multi-use vials are stable for up to 28 days after first entry when stored between 2°C to 8°C (36°F to 46°F) and protected from light. Solutions diluted for infusion in D5W or NS should be used within 6 hours of preparation, including infusion time. Actual recommendations may vary by generic manufacturer; consult manufacturer's labeling.

Non-alcohol formulation: Store intact vials at 20°C to 25°C (68°F to 77°F). Protect from light. After the first use and following multiple needle entries and withdrawals, multi-use vials (80 mg/4 mL and 160 mg/8 mL) are stable for up to 28 days when stored between 2°C to 8°C (36°F to 46°F) and protected from light. Solutions diluted for infusion in NS or D5W are stable for 24 hours when stored between 2°C to 8°C (36°F to 46°F).

Docetaxel lyophilized powder (Docefrez): Store intact vials between 2°C to 8°C (36°F to 46°F). Protect from light. Allow vials (and provided diluent) to stand at room temperature for 5 minutes prior to reconstitution. After reconstitution, may be stored refrigerated or at room temperature for up to 8 hours. Solutions diluted for infusion in D5W or NS should be used within 6 hours of preparation, including infusion time. According to the manufacturer, physical and chemical in-use stability of the infusion solution (prepared as recommended) has been demonstrated in non-PVC bags up to 48 hours when stored between 2°C and 8°C (36°F and 46°F).

Two-vial formulation (generic; concentrate plus diluent formulation): Reconstituted solutions of the two-vial formulation are stable in the vial for 8 hours at room temperature or under refrigeration. Solutions diluted for infusion in NS or D5W in polyolefin containers should be used within 4 hours of preparation, including infusion time.

Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Preparation:

One-vial formulations: Further dilute for infusion in 250 to 500 mL of NS or D5W in a non-DEHP container (eg, glass, polypropylene, polyolefin) to a final concentration of 0.3 to 0.74 mg/mL. Gently rotate and invert manually to mix thoroughly; avoid shaking or vigorous agitation.

Non-alcohol formulation: Use a 20 gauge needle to withdraw docetaxel from the vial; dilute in 250 mL of NS or D5W to a final concentration of 0.3 to 0.74 mg/mL. If docetaxel dose is >200 mg, use a larger volume of infusion fluid to maintain a final concentration of 0.3 to 0.74 mg/mL. Mix by gentle manual rotation.

Taxotere: Use **only** a 21 gauge needle to withdraw docetaxel from the vial (larger bore needles, such as 18 gauge or 19 gauge needles, may cause stopper coring and rubber precipitates). If intact vials were stored refrigerated, allow to stand at room temperature for 5 minutes prior to dilution. Inspect vials prior to dilution; solution is supersaturated and may crystalize over time; do not use if crystalized.

Two-vial formulation (generic; concentrate plus diluent formulation): Vials should be diluted with 13% (w/w) polyethylene glycol 400/water (provided with the drug) to a final concentration of 10 mg/mL. Do not shake. Further dilute for infusion in 250 to 500 mL of NS or D5W in a non-DEHP container (eg, glass, polypropylene, polyolefin) to a final concentration of 0.3 to 0.74 mg/mL. Gently rotate to mix thoroughly. Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

Route of administration:

The Taxotere® dilution for infusion should be administered intravenously over approximately 1-hour per institutional standards, under ambient room temperature (below 25°C) and lighting conditions.

Use non-PVC (polyvinylchloride) tubing only; filter not required.

Infusion control device required for all infusions.

Agent Ordering:

Taxotere® is commercially available and will not be provided.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biospecimen collections will be performed in accordance with the Schedule of Procedures detailed in the study calendar (Section 10). All specimens should be processed, packaged and shipped according to **Table 7** and the Specimen Collection and Shipping Guidelines and SOPs in (Appendix H and Appendix I). Memorial Sloan Kettering (PI: Michael F. Berger, PhD; Michael Roehrl, MD), the Pharmacodynamics Assay Development and Implementation Section (PADIS) laboratories of DCTD, NCI (PI: Apurva Srivastava**,** PhD) and the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins (PI: Michelle Rudek, PharmD, PhD) will act as the receiving sites for biomarker specimens as outlined in **Table 7**, below.

Archival and/or Fresh Tumor Tissue:
Fresh pretreatment (screening) and/**or** archival tumor tissues are mandatory for central confirmation of the required molecular alteration and PTEN IHC analysis.

Fresh pre- and on-treatment biopsies are mandatory for the pharmacodynamic expansion cohort. Post-progression biopsies are optional but strongly encouraged for all cohorts.

Tumor samples should be provided in the form of a formalin-fixed paraffin-embedded block. Alternatively, unstained slides (as detailed in Appendix H sample requirements) should be provided. Bone metastases, final needle aspirates, cytology specimens and alcohol-fixed specimens are not suitable.

Whole Blood for Germline DNA:
Blood will be obtained during the study (preferably acquired during screening, at the same time as hematology, serum chemistry, and plasma samples are taken).

Note: Paired analysis of tumors and patient-matched normal samples will be performed for the sole purpose of unambiguous detection of somatic mutations. Germline DNA will not be annotated for pathogenic mutations. Testing will not be conducted in a CLIA lab but at the MSKCC centre for molecular oncology and as such, results will not be returned to the patient.

Plasma for Biomarker Analysis of cfDNA:
Serial plasma samples for subsequent exploratory biomarker analyses will be collected from each patient at every study visit.

Guidelines for whole blood collection for germline DNA and plasma cfDNA are provided in the Appendix H.

9.1 Exploratory Correlative Studies

9.1.1 Targeted genomic sequencing with MSK-IMPACT of formalin-fixed, paraffin-embedded tumor and tumor-derived plasma cell free (cf) DNA samples.

MSK uses a custom, hybridization-based capture panel (MSK-IMPACT)[3] to detect single nucleotide variants, small indels, copy number alterations, and structural variants from matched tumor-normal sequence data. There have been three versions of the panel: version 1 containing 341 genes, version 2 containing 410 genes, and the current version containing 468 genes. Specimens are reviewed by a pathologist to ensure tumor cellularity of at least 10%. Tumors are sequenced to an average unique depth of coverage of approximately 750X. Reads are aligned using BWA, flagged for duplicate read pairs using GATK, and locally realigned using ABRA. Sequence mutations are called using MuTect and reported for >5% allele frequency (novel variants) or >2% allele frequency (recurrent hotspots). Copy number alterations are called using a custom pipeline and reported for fold-change >2. Structural rearrangements are called using Delly. All somatic mutations are reported without regard to biological function. Testing is performed for patients with advanced metastatic cancer across all solid tumor types.

9.1.1.1 **Pre-treatment biopsy specimens or archival tumor specimen** (*pre-treatment biopsy required if archival tumor tissue is unavailable)* will be sequenced to:

9.1.1.1.1. Retrospective central confirmation of the molecular alteration (an inactivating *PTEN* mutation or activating *PIK3CB* mutation) [Integrated Biomarker]

9.1.1.1.2. Examine the pattern of co-mutated genes in *PTEN/ PIK3CB* mutated tumors [Exploratory Biomarker]

9.1.1.2 **Post-progression biopsy specimens and serial cfDNA samples** will be sequenced to:

9.1.1.2.1. Monitor the emergence of new somatic alterations or resistant subclones [Exploratory Biomarker]

9.1.2 **Immunohistochemistry-scoring of PTEN protein expression** [Exploratory Biomarker]

9.1.2.1 Of pre-treatment biopsy specimens or archival specimens and post-progression biopsies specimens using previously described methods.[50]

9.1.3 **Multiplex quantitation of Akt pathway signaling proteins with the Luminex multiplex assay** [Integrated biomarker]

9.1.3.1 Of flash frozen pre- and on-treatment biopsy specimens using previously described methods (Appendix J).[40,41]

9.1.4 **Docetaxel and AZD8186 Pharmacokinetics [**Integrated biomarker]

9.1.4.1 Docetaxel blood levels will be measured by LC-MS/MS in the blood at the following time points: C1D1**:Pre-treatment; C2D1 Pre-treatment, 30 min. 55 min. after the start of the docetaxel infusion, and 2 hours (~3 hours), 5 hours (~6 hours) post- end of infusion docetaxel infusion, and C2D2 ~24 hours after the start of infusion.
**For Part 2 PD study, this should be pre-study or Day -7

9.1.4.2 AZD8186 blood levels will be measured by LC-MS/MS in the blood at the following time points: C1D1**: Pre-treatment; C2D1 Pre-treatment, 1 hour, 3 hours, and 6 hours post-dosing; C2D2 ~24 hours after the C2D1 dose and prior to the next AZD8186 dose; Starting Cycle 3, a Day 1 Pre-treatment sample should be collected at every scheduled study visit.
**For Part 2 PD study, this should be pre-study or Day -7

Optional samples may be obtained in the event of chronic (lasting ≥7 days) or serious (≥G3 non-hematological, ≥G4 hematological) toxicity, a blood sample should be drawn as close as possible to the time of the event with documentation of the last docetaxel and AZD8186 dose administered.

9.2 Table 7

Collection, Handling and Shipping of biomarker specimens to sites performing correlatives studies

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
Pre-treatment biopsy specimen FFPE Metastatic Tumor (FM01) (Refer to Appendix H – Specimen Guidelines)	Prior to any treatment *Pre-treatment biopsy is mandatory if adequate archival tissue is unavailable.*	Precision Pathology Biobanking Center at MSKCC **Memorial Sloan Kettering Cancer Center** Precision Pathology Biobanking Center (PPBC) 411 E 67th Street Room C-573 New York, NY 10065 **Phone:** 212-639-2296 / 6737
Archival tumor specimen FFPE Metastatic Tumor (FM02) (Refer to Appendix H – Specimen Guidelines)	Prior to any treatment *Not required if* FM01*is submitted*	
Archival tumor specimen FFPE Primary Tumor (FP01) (Refer to Appendix H – Specimen Guidelines)	Prior to any treatment *Not required if* FM01 or FM02 *is submitted*	
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) or PaxGene tube (s) (Refer to Appendix H – Specimen Guidelines)	Prior to or after starting study treatment	
Blood for Plasma cfDNA (PL-SCR, PL-01, PL-02,….) 10mls of blood drawn in 2 x Streck tubes (Refer to Appendix H – Specimen Guidelines)	Screening (SCR) and at every treatment cycle (01,02,…)	Lab Medicine, MSKCC **within 2 days** of specimen collection **Memorial Sloan Kettering Cancer Center** Center for Laboratory Medicine 327 East 64th Street Room C2-004 New York, NY 10065 ATTN: cfDNA Lab **Phone:** 646-608-1034 **E-mail:** zzPDL_LAB_CFDNA_LAB

Docetaxel PK†# 4 or 5 mL green top sodium heparin vacutainer tubes Blood Draw: - Obtain venous blood by standard phlebotomy technique from a peripheral access point. NOTE: Suggest using a minimum 18G needle to avoid sample hemolysis. - Fill-up the tubes as much as possible until blood flow stops. - GENTLY invert each tube several times (8-10 times) immediately after collection to avoid sample hemolysis. - Place samples immediately **on ice** after collection; samples must be processed **within 30 minutes**. Processing instructions: 1. Invert sample 8-10 times immediately before processing. 2. Centrifuge at 2500-3000 rpm for 10 minutes in swinging bucket (SW) or 15 minutes in a fixed angel (FA) rotor at 4ºC in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.	C1D1**: Pre-treatment; C2D1:Pre-treatment, 30 min. 55 min. after the start of the docetaxel infusion, and 2 hours (~3 hours), 5 hours (~6 hours) post- end of docetaxel infusion, and C2D2~24 hours after the start of infusion. **For Part 2 PD study only, this should be pre-study or Day -7	Specimens should be stored and shipped as a batch by participant (more than 1 participant/shipment is acceptable if the site has >1 participant on-study). A participant's samples should be shipped to the APC lab within 1 month of the last sample's collection date. (i.e., if C3D1 sample is collected on 1/1/2017, all of that participant's samples should be at the APC lab by 2/1/2017). The APC lab may contact the study team to request shipment off-schedule. The PK (docetaxel and AZD8186) specimens can be shipped in the same shipment. **Please ship 1-2 aliquots to the APC laboratory. Once receipt is confirmed, the back-up aliquot may be shipped. The back-up can be shipped later** Preparing the shipment -Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", LxWxH). -Please organize the samples by Patient and Time point in the box.

AZD8186 PK†# As for Docetaxel PK above	C1D1**: Pre-treatment; C2D1Pre-treatment, 1 hour, 3 hours, and 6 hours post-dosing; C2D2 ~24 hours after the C2D1 dose and prior to the next AZD8186 dose; Starting Cycle 3, a Day 1 Pre-treatment sample should be obtained at every scheduled study visit **For Part 2 PD study only, this should be pre-study or Day-7	-Do not store in plastic bags (they break on dry-ice and labels will detach). -A copy of each of the pharmacokinetic sample collection forms for the respective patients or a sample list should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them (in addition to sample label) and numbering samples on the sample sheet. -Note the study number, PI, and the drugs used/to be measured. -A name, phone number and email address should be included with samples so that receipt can be acknowledged. -Please notify the lab by email (onc-pharmacology@lists.johnshopkins.edu) or telephone (410-502-7192 or 410-955-1129) at least 24 hours prior to shipment. Shipping - All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. - Overnight shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday. Analytical Pharmacology Core Laboratory* Attn: NCI10131 Docetaxel + AZD8186 Study Samples 1650 Orleans St. CRB1 Rm 184 Baltimore, MD 21231-1000 Phone: 410-502-7192 or 410-955-1129 Fax: 410-502-0895
Pre-treatment biopsy specimen Flash frozen Metastatic Tumor (FZM01) 1-2 cores (Refer to Appendix I)	Prior to any treatment (before Cycle 1 Day -7) *Mandatory*	**Memorial Sloan Kettering Cancer Center** Precision Pathology Biobanking Center (PPBC) 411 E 67th Street Room C-573
On-treatment biopsy specimen Flash frozen Metastatic Tumor (FZM02) 1-2 cores (Refer to Appendix I)	On-treatment window: Between C1D -5 to C1D -3 biopsy, (2-3 hrs post dose).	

Post-progression biopsy specimen FFPE Metastatic Tumor (FM03) (Refer to Appendix H – Specimen Guidelines)	After progression on study.	New York, NY 10065

* Label samples as cfDNA, including study number (NCI10131), unique patient ID (assigned by the consortium), initials, date of collection, draw time, and time point for e.g. SCR (screening), Cycle 1, 2 etc
† Label samples as docetaxel or AZD8186 PK, including study number (NCI10131), unique patient ID (assigned by the consortium), initials, date of collection, draw time, and time point for e.g. SCR (screening), Cycle 1, 2 etc
# Optional samples may be obtained in the event of chronic (lasting ≥7 days) or serious (≥G3 non-hematological, ≥G4 hematological) toxicity, a blood sample should be drawn as close as possible to the time of the event with documentation of the last docetaxel and AZD8186 dose administered.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Baseline radiographic tumor assessment must be done within 30 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. It will be acceptable for a new cycle of therapy (and all associated tests and procedures) to be delivered within a 3 day window before and after the protocol defined date (see Section 5.1).

	Pre-Study	Cycle 1, Day -7*	Cycle 1, Day 1 (±1)	Cycle 1, Day 8 (±1)	Cycle 1, Day 15 (±1)	Cycle 2, Day 1 (±1)	Cycle 2, Day 2	Cycle 3 (and beyond), Day 1 (±3)	Off Study[c]
AZD8186		A*	A	A	A	A	A	A	
Docetaxel			D			D		D	
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X----------							----X
Physical exam	X	X	X	X	X	X		X	X
Vital signs	X	X	X	X	X	X		X	X
Height	X								
Weight	X	X	X		X			X	X
Performance status	X	X	X		X			X	X
CBC w/diff, plts	X	X	X	X	X	X		X	X
Serum chemistry[a]	X	X	X	X	X	X		X	X
PT (INR)/PTT	X	X	X	X	X	X		X	X
Urinalysis	X	X	X	X	X	X		X	X

EKG	X	X	X	X	X	X		X	X
Adverse event evaluation	X	X----------X							X
Tumor assessments	X					Tumor measurements with CT and/or MRI and Bone scan (required for prostate cancer patients only) are repeated every 6 weeks (+/- 7 days) for 24 weeks, then every 12 weeks (+/- 7days) thereafter. Documentation (radiologic) must be provided for patients removed from study for progressive disease. PSA measurement on Day 1 of every cycle as below (required for prostate cancer patients only)			X
PSA (required for prostate cancer patients only)	X		X			X		X	X
B-HCG	X[b]								
Plasma Collection for cfDNA Biomarker Analysis[d]	X		X			X		X	X
Whole blood sample for germline DNA[e]	X								
Docetaxel PK [f]	X					X	X		X
AZD8186 PK [g]	X					X	X	X	X
Fresh Pre-Treatment Biopsy or Archived FFPE Submission[h]	X[d]								
On-Treatment Biopsy [i]		X[e]							
Post-Progression Biopsy [j]									X[f]
		A: AZD8186 assigned dose, BID PO, 5 days on, 2 days off every week,. *Patients enrolled in the pharmacodynamic (PD)cohort will begin on Day -7 D: Docetaxel 75mg/m^2 on Day 1 of a 21-Day cycle a: Na, K, Cl, CO2, BUN, creatinine, Ca, glucose (fasting for 8 hours), total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT b: Serum pregnancy test (women of childbearing potential). c: Off-study evaluation (30 days +/- 7 days after last dose). Patients who discontinue for reasons other than progression should be imaged when they come off study and then every 3 months until progression of disease or beginning of alternative anticancer therapy. d: Plasma will be collected for cfDNA biomarker analysis at every study visit e: Whole blood sample for research (single collection) obtained during study, preferably during screening or within the first cycle of therapy. f: Docetaxel PK: Pre-study or Day -7 (for PD study) or C1D1 pre-treatment (1 sample; overall pre-treatment) C2D1:Pre-treatment, 30 min. 55 min. after the start of the docetaxel infusion, and 2 hours (~3 hours), 5 hours (~6 hours) post- end of docetaxel infusion, and C2D2~24 hours after the start of infusion. g: AZD8186 PK: Pre-study or Day -7 (for PD study) or C1D1: Pre-treatment (1 sample; overall pre-treatment); C2D1: Pre-treatment; C2D2~24 hours after the C2D1 dose and prior to the next AZD8186 dose; Starting Cycle 3, a Day 1 Pre-treatment should be collected at every scheduled study visit h: Archived formalin fixed paraffin embedded (FFPE) tissue or Fresh Pre-Treatment Biopsy specimen (1-2 cores in FFPE along with an additional 1-2 cores flash frozen for the PD cohort only). Biopsy is mandatory for the PD cohort and for patients with insufficient archival material i: Mandatory on-treatment biopsy for the PD cohort, Window:C1D -5 to C1D -3 biopsy, (2-3 hrs. post dose). (1-2 cores flash frozen). j: Optional Fresh Post-progression Biopsy specimen (1-2 cores in FFPE).								

11. MEASUREMENT OF EFFECT

Although the clinical benefit of this drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 6 weeks for the first 24 weeks and every 12 weeks thereafter. In addition to a baseline scan, confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks for the first 24 weeks and every 12 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with AZD8186 and Docetaxel.

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 disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

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

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

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

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

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

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

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

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11.1.4 Response Criteria

11.1.4.1 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 (<1 cm).

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

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

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

11.1.5 Duration of Response

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

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

11.1.6 Progression-Free Survival

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

11.2 Antitumor Effect – Prostate cancer, PCWG3

Therapeutic Response for Prostate Cancer patients

Response and progression will be evaluated in this study using a combination of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1) as described by Eisenhauer et al. 2009 and the guidelines for prostate cancer endpoints developed by the Prostate Cancer Clinical Trials Working Group (PCWG3) described by Scher, et al. 2016.

A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
- A minimum size of 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable 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), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria. Bone lesions should not be recorded as target or nontarget lesions according to RECIST 1.1 criteria.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ (per PCWG3), 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions

RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a $\leq$ 5 mm contiguous reconstruction algorithm. If a 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.

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Ultrasound (US), endoscopy and laparoscopy should not be used to measure tumor lesions. Cytology and histology can be used to differentiate between PR and CR in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD 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. The appearance of one or more new extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of 1 or more new extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started).

Evaluation of Best Overall Response: Patients with Target (+/- NonTarget-) Disease			
Target Lesions	**Nontarget**	**New Lesions**	**Overall**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Best Overall Response: Patients with NonTarget- Disease Only		
Nontarget Lesions	**New Lesions**	**Overall**
CR	No	CR
Non-CR/non-PD	No	Non-
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Duration of Response

Imaging is required for this study at baseline and after every 2 cycles (6 weeks) thereafter. Patients who have been on study at least 24 weeks, may decrease the frequency of disease/ tumor assessments to every 3 cycles (12 weeks). There is a +/- 7 day window for all scans.

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 PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started), including progression in bone per PCWG3 criteria.

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

Duration of Stable Disease
SD 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

PCWG3 Criteria for Assessment of Bone Disease

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016

Imaging of Baseline Bone Disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-methylene diphosphonate radionuclide bone scintigraphy
- Confirm ambiguous results by other imaging modalities (eg, CT or MRI) however only positivity on the bone scan defines metastatic disease to bone

Documentation of baseline bone disease

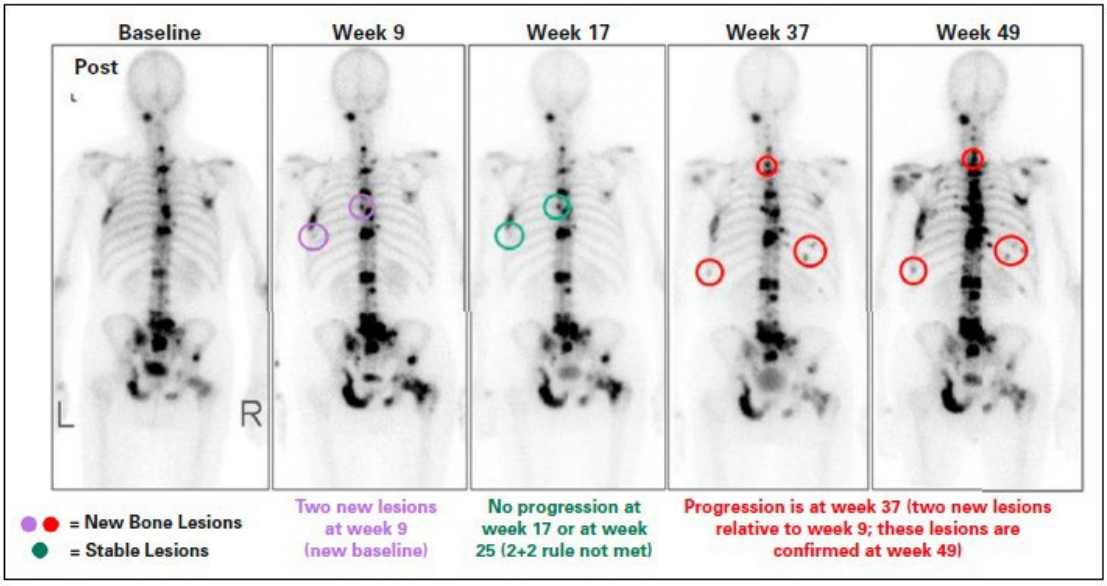
- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial

Following for bone progression during the study

- Exclude pseudoprogression in the absence of symptoms or other signs of progression.
- At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule).

- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented.
- For scans after the first post-treatment scan, at least two new lesions relative to the first post- treatment scan confirmed on a subsequent scan.
- Changes in intensity of uptake alone do not constitute either progression or regression

Controlling for Flare by Applying the 2+2 Rule using the First Post-treatment Scan as Baseline



Date Progression Detected (Visit)	**Criteria for Progression in Bone**	**Criteria for Confirmation of Progression in Bone**
Week 9 (1^{st} on-treatment scan)	Two or more new lesions on bone scan compared to **baseline** bone scan by PCWG3	Two or more new bone lesions compared to Week 9 on bone scan obtained at least 6 weeks after progression identified (or at Week 17 assessment)
Week 17 (2^{nd} on-treatment scan)	Two or more new lesions on bone scan compared to **Week 9** bone scan.	Persistent or increase in number of bone lesions compared to Week 17 assessment on bone scan obtained at least 6 weeks after progression identified (or at Week 25 assessment)

Week 25 and after (3rd on-treatment scan and after)	Two or more new lesions bone scan compared to **Week 9** bone scan	Persistent or increase in number of bone lesions compared to prior assessment on bone scan obtained at least 6 weeks after progression identified (or at next scheduled assessment)

PCWG3 Criteria For Confirmation of Radiographic Progression in Bone by Investigator Assessment (to be used in conjunction with modified RECIST 1.1 criteria for visceral and nodal disease)

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Study Oversight

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

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

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

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

Investigators (or, when unavailable, a qualified representative from each institution) will meet via teleconference every 2 weeks.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

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

In addition, the lead Principal Investigator will have at least bi-weekly conference calls with the site Study Investigators and study teams to review accrual, progress, adverse events, and unanticipated problems.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data

audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

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

12.3 Collaborative Agreements Language

See Appendix G

12.4 Genomic Data Sharing Plan

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Objectives

13.1.1.1 To determine the MTD or RP2D of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

13.1.1.2 To assess the safety and tolerability of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

13.1.2 Secondary Objectives

13.1.2.1 To assess the objective response rate (ORR) of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

13.1.2.2 To assess the clinical benefit rate (CBR) at 24 weeks of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

13.1.2.3 To investigate a drug-drug interaction between docetaxel and AZD8186 and correlate drug exposure with pharmacodynamics response

13.1.3 Exploratory Objectives

13.1.3.1 Examine the pattern of co-mutated genes in PTEN or PIK3CB mutated tumors and their association with treatment response or resistance.

13.1.3.2 Describe possible mechanisms of acquired resistance to PI3Kβ inhibition.

13.1.3.3 Evaluation of protein expression of the PTEN gene and its association with treatment response or resistance.

13.1.3.4 Examine isoform-specific AKT inhibition and other downstream target modulation from PI3Kβ inhibition with AZD8186.

13.1.4 Statistical Considerations for Primary objectives:

In the dose escalation cohort/ portion of the study, a standard 3+3 design will be used to find the maximum tolerated dose (MTD) for the combination of AZD8186 and docetaxel. Initially, three patients will be treated with AZD8186 at dose level 1 [the RP2D identified in the ongoing phase

I study (NCT01884285)] combined with standard approved dose (75mg/m2) of docetaxel. At any given dose level, if none of the initial 3 patients experience DLT by the end of cycle 1 (Day 21), the next dose level will be studied. If one of the initial 3 patients has DLT, 3 additional patients will be treated at the same dose level. Escalation will continue only if there is no additional DLT observed. If 2 or more patients experience DLT at any dose level, the previous dose will be declared the MTD. Should 2 or more patients experience DLTs at the lowest dose level, the study will stop and the treatment regimen will be re-evaluated. If only 3 patients are treated at a dose declared to be the MTD, 3 additional patients will be enrolled and treated at that dose to confirm the MTD. Therefore, at the completion of the dose escalation cohort/ portion, 6 patients will have been treated at the MTD. Patients who withdraw before completing at least 75% of the assigned dose during cycle 1 for reasons other than development of a DLT will be replaced. (See Section 5.2, *Dose escalation schedule/scheme*, Section 5.5 for *Definition of a DLT and* **Table 4** for *Dose escalation decision rules and MTD definition*)

Patient safety and tolerability will be described according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4. All patients who receive any amount of the study drug will be evaluable for toxicity.

Safety evaluation will be conducted throughout the expansion cohort of this study (i.e. the pharmacodynamic expansion cohort and disease specific dose expansion cohorts 1, 2, 3). DLT data from the first 6 consecutively enrolled subjects to Parts 2 or 3 will combined with DLT data from the 6 subjects treated at the MTD in Part 1. If, at any point, 4 or more total DLTs are observed across the combined 12 patients, further enrollment will be halted as the safety stopping rule will have been met. At this point, the study would be amended in consultation with the board to ensure ongoing subject safety.

So if DLT's are seen in:

- 0/6 at MTD in part 1 combined with 4/6 in part 2+3.
- 1/6 at MTD in part 1 combined with 3/6 seen in part 2+3.

The probability of stopping the trial under hypothetical true DLT rates denoted as p is shown below

p	probstop
0.10	0.00710
0.15	0.02720
0.20	0.06611
0.25	0.12549
0.30	0.20383
0.35	0.29725
0.40	0.40038

p	probstop
0.45	0.50717
0.50	0.61161
0.55	0.70835
0.60	0.79315

13.2 Sample Size/Accrual Rate

Proposed Sample Size Minimum: 55 Maximum: 67

Projected yearly accrual rate is estimated at 1-2 patients per month.

13.3 Stratification Factors

N/A

13.4 Analysis of Secondary Endpoints

Antitumor activity:

The secondary objective of this phase I study is to obtain preliminary data of antitumor activity in disease specific cohorts and overall across all cohorts. Efficacy will be measured by the objective response rate (ORR) and Clinical benefit rate (CBR) at 24 weeks of AZD8186 when administered in combination with docetaxel in patients with PTEN or PIK3CB mutated advanced solid tumors.

Given the sample size per cohort, only descriptive statistics will be computed for the secondary objectives. Patient response to AZD8186 and docetaxel will be assessed with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 evaluations of computed tomography (CT) scans performed every 6 weeks (and bone scans and PSA measurement by Prostate Working Group 3 (PCWG3) criteria for the Prostate cancer patients).

A response is defined as any of the following: a response according to RECIST v 1.1, PCWG3 (for patients with measurable visceral and/or nodal disease at baseline) **or** a reduction in the PSA level of 50% or more (for prostate cancer patients without visceral and/or nodal disease at baseline), with a confirmatory assessment at least 4 weeks later.

Clinical benefit rate (CBR) is defined as the proportion of patients with CR, PR, and SD at 24 weeks as defined by modified RECIST Version 1.1. A 90% confidence interval on CBR will be calculated assuming binomial proportions. All patients will be followed up for 24 weeks. Patients who are lost to follow up before 24 weeks will be evaluable for response and counted as non responders.

Efficacy and safety will be reported separately for each disease cohort (cohort 1, 2, 3) as part of the primary analysis and overall when all cohorts are combined (secondary analysis). All patients treated at the MTD will be included in an attempt to answer the question whether this treatment regimen is tolerable and has antitumor activity in this preselected patient population regardless of disease type.

Exposure/response relationships:

Docetaxel[51] and AZD8186 (method TBD) concentrations in subject samples will be quantitatively measured using liquid chromatography/tandem mass spectrometric (LC/MS/MS) method in the Analytical Pharmacology Core Laboratory at the Sidney Kimmel Comprehensive Cancer Center (SKCCC) at Johns Hopkins. For docetaxel, a limited sampling schema will be employed to assess for total exposure since AZD8186 may decrease docetaxel concentrations. For docetaxel, individual PK parameters will be estimated for Cmax, AUC, T1/2, Cl, and V using non-compartmental or compartmental PK methods with the software WinNonlin. For AZD8186, trough concentrations will be assessed to elucidate a minimum exposure. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables will be tabulated and descriptive statistics (e.g., geometric means and coefficients of variation) calculated for each dose level. PK parameters (i.e., T½, Cl, and AUC) will be compared across dose level using nonparametic statistical testing techniques. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity and efficacy) will be analyzed using nonparametric statistics. Significance for comparisons will be at the $p<0.05$ level.

13.5 Exploratory Correlative Analysis

Correlative studies will be performed and summarized using descriptive statistics and graphical displays at pre and post treatment time points. All correlative studies will be considered exploratory.

Retrospective central confirmation of the molecular alteration (an inactivating PTEN mutation or activating PIK3CB mutation) will be described (Integrated biomarker)
Out of all patients enrolled on the study a number/rate of centrally confirmed PTEN and PIK3CB mutated tumors will be reported.

Examine the pattern of co-mutated genes and association with treatment response.
At the patient level, associations of pre-treatment pattern of co-mutated genes (grouped by pathway for e.g. mutations affecting the PI3K-Akt-mTOR pathway – binary covariate) and response (CR/PR at 6 weeks; binary covariate defining responders and non responders) will be assessed. These associations will be performed using non parametric methods such as the Mann Whitney U test due to the small targeted sample size of this proposed study.

Describe possible mechanisms of acquired resistance to PI3Kβ inhibition.
Sequencing data from pre- and post-treatment specimens of patients that initially responded to AZD8186 will be compared to identify newly acquired mutations or DNA copy number alterations. Given that the number of patients and recurrence rate of specific events will be low, this analyses will be primarily descriptive with graphical representation in order to uncover any

trends such as a pathway specific clustering of resistance mutations or second-site mutations or focal amplifications, that might inform potential mechanisms of acquired resistance. Results will be used to generate future hypotheses that will be tested in larger patient samples.

Evaluation of protein expression of the PTEN gene and its association with treatment response or resistance.
We will summarize the expression pattern of PTEN by immunohistochemistry at baseline (archival/pre-treatment specimen) and post-progression on therapy to provide a preliminary assessment on the predictive capacity of this marker in determining responders versus non-responders.

Examine isoform-specific AKT inhibition and other downstream target modulation from PI3Kβ inhibition with AZD8186.

- The proposed number of participants in the PD cohort is accounting for the fact that adequate tissue obtained under the optimal conditions (Appendix I) is unlikely to be achieved in all 10 patients. Tumor heterogeneity, biological variability and inadequate tumor content in pre- and post-treatment biopsies could affect interpretation of lysate based assays. It is estimated that 20-30% of biopsies could be challenging and may influence biomarker interpretation and that biological inter-tumor variability of phospho-proteins will be in the range of 50-70% (for different markers).
- Dr Srivastava (lab PI) has addressed some of the issues related to tumor heterogeneity,[40,41] especially the variable mouse cell infiltration (from 20% to 50% of tumor was mouse content) of tumor and how to use variability data to derive valid interpretation. In addition, to help with interpretation of potential aberrant results due to tumor heterogeneity, Dr Srivastava plans to consider two factors: 1) Using total levels of all biomarkers (AKT1, AKT2, AKT3, and rpS6) as denominator assay to express changes in all phospho-measurements (expressed as ratio of total as done previously); 2) Monitoring if all markers in the multiplex (12 markers) are changing in one direction, if this is the case, results would be interpreted accordingly.
- Determination of exact cut-off above/below which a change in biomarker is considered drug (AZD8186) induced and not due to biological variability is currently underway in Dr Srivastava's preclinical time-course study in two models, PC3 and HCC70 xenografts (detailed in section 2.5.2.1.2) The determination is based on both inter- and intra-tumor variability (n=5-6 mice) and calculated as a "critical difference" using a criterion similar to that defined in clinical laboratories (methodology and cut-off values described in Supplementary data of cited publications).[40,41]
- Dr. Srivistava has observed an effect size modulation of the phosphoproteins of 70-90%, with a relatively high precision (CV < 15%). Given the fact that the AKT isoform studies are highly novel and important, that there are good controls of total protein for AKT1, AKT2, and AKT3, to compare with the phophoepitopes, and that the effect of AZD8186 on all 3 phospho-isoforms seemed to track together with in vivo studies, we have confidence that this small cohort of 10 patients may demonstrate convincing evidence of target modulation.
- In this study we will collect paired (pre- and on-treatment) biopsies and measure percent inhibition on a continuous scale (0-100) aiming to show a 70%-80% decrease in the on-treatment samples.

- 10 patients provide 72-80% power (assuming one sided one sample test for change in the mean with Type I error=0.05) to show a 70%-80% decrease respectively.
- The minimum effect size of 70% incorporates intra-tumor variability

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APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B CURATED LIST OF *PTEN* VARIANTS WITH THE CORRESPONDING LITERATURE TO SUPPORT THEIR LOSS OF FUNCTION

Gene	Alteration	Oncogenicity	Mutation Effect	PMIDs for Mutation Effect
PTEN	A121E	Oncogenic	Loss-of-function	21828076
PTEN	A126D	Oncogenic	Loss-of-function	21828076
PTEN	A126G	Oncogenic	Loss-of-function	21828076
PTEN	A126S	Oncogenic	Loss-of-function	21828076
PTEN	A126V	Oncogenic	Loss-of-function	21828076
PTEN	A34D	Oncogenic	Loss-of-function	21828076
PTEN	A39P	Oncogenic	Loss-of-function	25527629
PTEN	C124N	Oncogenic	Loss-of-function	21828076
PTEN	C124R	Oncogenic	Loss-of-function	9467011, 10866302, 21828076
PTEN	C136Y	Oncogenic	Loss-of-function	10866302
PTEN	C71Y	Oncogenic	Loss-of-function	10866302, 11051241
PTEN	D162G	Oncogenic	Loss-of-function	21828076
PTEN	D162H	Oncogenic	Loss-of-function	23840064
PTEN	D24Y	Oncogenic	Loss-of-function	17213812
PTEN	D252G	Oncogenic	Loss-of-function	25527629
PTEN	D326N	Oncogenic	Loss-of-function	25527629, 21828076
PTEN	D92A	Oncogenic	Loss-of-function	21828076
PTEN	D92E	Oncogenic	Loss-of-function	21828076
PTEN	D92G	Oncogenic	Loss-of-function	21828076
PTEN	D92H	Oncogenic	Loss-of-function	21828076
PTEN	D92V	Oncogenic	Loss-of-function	21828076
PTEN	Deletion	Oncogenic	Loss-of-function	21430697
PTEN	E157G	Oncogenic	Loss-of-function	21828076
PTEN	F154L	Oncogenic	Loss-of-function	19329485
PTEN	F241S	Oncogenic	Loss-of-function	25527629, 21828076
PTEN	F341V	Oncogenic	Loss-of-function	10866302, 11051241
PTEN	F347L	Oncogenic	Loss-of-function	10866302
PTEN	G127E	Oncogenic	Loss-of-function	21828076
PTEN	G127N	Oncogenic	Loss-of-function	21828076
PTEN	G129D	Oncogenic	Loss-of-function	21828076
PTEN	G129E	Oncogenic	Loss-of-function	9811831, 25527629, 9467011, 10866302, 21828076
PTEN	G129R	Oncogenic	Loss-of-function	9811831, 25527629, 10866302, 21828076
PTEN	G165E	Oncogenic	Loss-of-function	21828076
PTEN	G165V	Oncogenic	Loss-of-function	9467011, 21828076
PTEN	G36R	Oncogenic	Loss-of-function	21828076
PTEN	G44D	Oncogenic	Loss-of-function	21828076

PTEN	H118P	Oncogenic	Loss-of-function	25527629, 21828076
PTEN	H123D	Oncogenic	Loss-of-function	21828076
PTEN	H123Q	Oncogenic	Loss-of-function	21828076
PTEN	H123Y	Oncogenic	Loss-of-function	21828076
PTEN	H61D	Oncogenic	Loss-of-function	21828076
PTEN	H93D	Oncogenic	Loss-of-function	21828076
PTEN	H93Q	Oncogenic	Loss-of-function	21828076
PTEN	H93R	Oncogenic	Loss-of-function	21828076
PTEN	H93Y	Oncogenic	Loss-of-function	10866302, 21828076
PTEN	I122L	Oncogenic	Loss-of-function	21828076
PTEN	I122S	Oncogenic	Loss-of-function	21828076
PTEN	I168F	Oncogenic	Loss-of-function	21828076
PTEN	K125E	Oncogenic	Loss-of-function	20926450, 21828076
PTEN	K125L	Oncogenic	Loss-of-function	21828076
PTEN	K125M	Oncogenic	Loss-of-function	21828076
PTEN	K128N	Oncogenic	Loss-of-function	21828076
PTEN	K128Q	Oncogenic	Loss-of-function	25447541
PTEN	K128R	Oncogenic	Loss-of-function	21828076
PTEN	K128T	Oncogenic	Loss-of-function	21828076
PTEN	K62R	Oncogenic	Loss-of-function	20926450, 19457929
PTEN	L112P	Oncogenic	Loss-of-function	25527629, 10866302
PTEN	L112R	Oncogenic	Loss-of-function	10866302
PTEN	L181P	Oncogenic	Loss-of-function	21828076
PTEN	L23F	Oncogenic	Loss-of-function	17213812
PTEN	L325F	Oncogenic	Loss-of-function	19329485
PTEN	M199del	Oncogenic	Loss-of-function	11051241
PTEN	M35R	Oncogenic	Loss-of-function	21828076
PTEN	N48K	Oncogenic	Loss-of-function	25527629, 21828076
PTEN	N94I	Oncogenic	Loss-of-function	21828076
PTEN	P169H	Oncogenic	Loss-of-function	21828076
PTEN	P95L	Oncogenic	Loss-of-function	21828076
PTEN	P95S	Oncogenic	Loss-of-function	19329485
PTEN	P96Q	Oncogenic	Loss-of-function	21828076
PTEN	R130*	Oncogenic	Loss-of-function	24721394
PTEN	R130A	Oncogenic	Loss-of-function	21828076
PTEN	R130G	Oncogenic	Loss-of-function	9811831, 25527629, 10866302, 21828076, 11051241
PTEN	R130K	Oncogenic	Loss-of-function	21828076
PTEN	R130L	Oncogenic	Loss-of-function	25527629, 9467011, 10866302
PTEN	R15K	Oncogenic	Loss-of-function	21828076
PTEN	R15S	Oncogenic	Gain-of-function	17213812

PTEN	R161G	Oncogenic	Loss-of-function	21828076
PTEN	R173H	Oncogenic	Loss-of-function	24721394, 10866302
PTEN	R335*	Oncogenic	Loss-of-function	23475934
PTEN	R335L	Oncogenic	Loss-of-function	21828076
PTEN	S170R	Oncogenic	Loss-of-function	9467011, 10866302
PTEN	T131A	Oncogenic	Loss-of-function	21828076
PTEN	T131I	Oncogenic	Loss-of-function	21828076
PTEN	T131L	Oncogenic	Loss-of-function	21828076
PTEN	T160I	Oncogenic	Loss-of-function	21828076
PTEN	T167A	Oncogenic	Loss-of-function	21828076
PTEN	V217D	Oncogenic	Loss-of-function	21828076
PTEN	V343E	Oncogenic	Loss-of-function	10866302
PTEN	V343L	Oncogenic	Loss-of-function	21828076
PTEN	Y155C	Oncogenic	Loss-of-function	10866302, 21828076, 11051241
PTEN	Y65C	Oncogenic	Loss-of-function	20926450, 19457929
PTEN	Y68D	Oncogenic	Loss-of-function	21828076
PTEN	A121P	Likely Oncogenic	Loss-of-function	10866302
PTEN	C105F	Likely Oncogenic	Loss-of-function	10866302
PTEN	C124S	Likely Oncogenic	Loss-of-function	9811831, 25527629
PTEN	C136R	Likely Oncogenic	Loss-of-function	23475934
PTEN	D107Y	Likely Oncogenic	Loss-of-function	10866302
PTEN	D24N	Likely Oncogenic	Likely Loss-of-function	17213812
PTEN	D331G	Likely Oncogenic	Loss-of-function	10866302
PTEN	D92N	Likely Oncogenic	Loss-of-function	21828076
PTEN	F21A	Likely Oncogenic	Loss-of-function	17213812
PTEN	G165R	Likely Oncogenic	Loss-of-function	10866302
PTEN	G20E	Likely Oncogenic	Loss-of-function	10866302, 17213812
PTEN	G251C	Likely Oncogenic	Loss-of-function	10866302
PTEN	H61R	Likely Oncogenic	Loss-of-function	10866302
PTEN	I32del	Likely Oncogenic	Loss-of-function	10560660, 22817889, 24904117, 9326929, 24293293
PTEN	K289E	Likely Oncogenic	Loss-of-function	10866302
PTEN	K342N	Likely Oncogenic	Loss-of-function	10866302

PTEN	L108P	Likely Oncogenic	Loss-of-function	25527629
PTEN	L345Q	Likely Oncogenic	Loss-of-function	10866302
PTEN	L42R	Likely Oncogenic	Loss-of-function	10866302
PTEN	M134L	Likely Oncogenic	Loss-of-function	10866302
PTEN	N276S	Likely Oncogenic	Loss-of-function	25527629
PTEN	R130Q	Likely Oncogenic	Loss-of-function	10866302
PTEN	R173C	Likely Oncogenic	Loss-of-function	10866302
PTEN	R173P	Likely Oncogenic	Loss-of-function	10866302
PTEN	S10N	Likely Oncogenic	Loss-of-function	10866302
PTEN	S170N	Likely Oncogenic	Loss-of-function	10866302
PTEN	S227F	Likely Oncogenic	Loss-of-function	10866302
PTEN	T401I	Likely Oncogenic	Loss-of-function	10866302
PTEN	Truncating Mutations	Likely Oncogenic	Likely Loss-of-function	17218262, 11237521
PTEN	V133I	Likely Oncogenic	Loss-of-function	10866302
PTEN	Y16C	Likely Oncogenic	Loss-of-function	10866302
PTEN	Y174N	Likely Oncogenic	Loss-of-function	10866302
PTEN	Y27S	Likely Oncogenic	Loss-of-function	10866302
PTEN	Y369G	Likely Oncogenic	Loss-of-function	10866302
PTEN	Y68H	Likely Oncogenic	Loss-of-function	9467011, 23840064, 10866302

APPENDIX C CURATED LIST OF *PIK3CB* VARIANTS WITH THE CORRESPONDING LITERATURE TO SUPPORT THEIR GAIN OF FUNCTION

Gene	Alteration	Oncogenicity	Mutation Effect	PMIDs for Mutation Effect
PIK3CB	E552K	Likely Oncogenic	Gain-of-function	16339315
PIK3CB	D1067Y	Oncogenic	Gain-of-function	26759240
PIK3CB	N553S	Likely Oncogenic	Likely Gain-of-function	18755892, 26000489
PIK3CB	Amplification	Oncogenic	Gain-of-function	26442967, 16432180, 25533673
PIK3CB	D1067V	Oncogenic	Gain-of-function	25982275
PIK3CB	E663K	Likely Oncogenic	Likely Gain-of-function	23734178, 20668451
PIK3CB	E1051K	Likely Oncogenic	Likely Gain-of-function	18755892, 26000489
PIK3CB	ACPP-PIK3CB Fusion	Likely Oncogenic	Likely Gain-of-function	26000489, 16432180
PIK3CB	D1067A	Likely Oncogenic	Gain-of-function	26759240
PIK3CB	R48W	Likely Oncogenic	Likely Gain-of-function	18755892, 26000489

APPENDIX D PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, AZD8186. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

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

AZD8186 interacts with CYP 3A4/5, 1A2, 2C9 and 2B6 and transport protein OATP1B1.

- AZD8186 is broken down by CYP 3A4/5 and 1A2, enzymes that may be affected by other drugs that inhibit or induce these enzymes.
- AZD8186 inhibits CYP2C9 and induces CYP 3A4/5 and 2B6. These enzymes may affect the levels of other drugs in the body that are cleared by these enzymes.
- The protein in question is OATP1B1 and is inhibited by AZD8186 which may affect the ability of other drugs to move in and out of cells.

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

AZD8186 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

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

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

AZD8186 must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4/5, 1A2 or sensitive substrates of CYP 3A4/5, 2C9 and 2B6 and transport protein OATP1B1.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Avoid taking blood thinners or anticoagulants with checking with the study doctor.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking AZD8186.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **AZD8186.** This clinical trial is sponsored by the NCI. **AZD8186** may interact with drugs that are *processed by your liver, or use certain transport proteins in your body*. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement. ➢ Avoid ingesting grapefruit juice, grapefruit, and Seville oranges while taking AZD8186.	**AZD8186** interacts with specific liver enzymes called CYP 3A4/5, 1A2, 2C9, 2B6 and transport protein, OATP1B1, and must be used very carefully with other medicines that interact with these enzymes and transporter. ➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of 3A4/5 and 1A2 or sensitive substrates of CYP 3A4/5, 2C9 and 2B6 and transport protein OATP1B1." ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX E BIOMARKER REQUEST FORM

Please email this form to the Principal Investigator

To be completed by Investigator

1. Request date:____-_____- 20___
   DD MMM YY

2. Site ID:_____/ _____
   (country #) (Site #)

3. Tumor Type: _____

4. Specify the *PTEN/PIK3CB* mutation: _____

5. Attach the genomic test report **ONLY** if the patient has signed generic hospital/institution consent.

   Note: Slot request and patient enrollment cannot be approved until after the Principal Investigator has approved the mutation

Investigator:_____Date:___-__-_ 20___
Signature DD MM YY

To be completed by study Principal Investigator

Mutation and/or Amplification Approved: Yes ☐ No ☐

Sponsor or study PI:_____Date:___-__-_ 20___
Signature DD MM YY

APPENDIX F DRUG ADMINISTRATION DIARY FOR AZD8186

Participant ID: _____ Participant Initials: _____ Dose Level: _____

Cycle #: ___ Cycle Start Date: _____

Instructions:

- Use this diary to record each dose of AZD8186 that you take – write in the date, the number of tablets and the time taken as well as any comments

- Your **AZD8186** dose is: _____ mg **twice a day for 5 days on and 2 days off every week**
  - Take _____ 60mg tablets and_____ 30mg tablets.
  - AZD8186 should be taken on an empty stomach (water only for at least 2 hours prior and 1 hour after each dose) and swallowed whole. Do not split, crush or chew the tablets.
  - If you miss a dose of AZD8186 (not taken within 4 hours of scheduled time), skip the dose and resume taking AZD8186 at the next scheduled time; do not "double up" doses to make up a missed dose.
  - If you vomit after taking AZD8186, do not retake the dose. Mark the vomited dose in the diary. Resume taking AZD8186 at the next scheduled time.

- Whenever possible, all doses should be taken at approximately the same time each day.

- On days that you come to clinic, wait to dose until instructed by your doctor

- Use the comments section to record any side effects or anything else you would like to tell the doctor/research nurse.

- **Please bring the empty bottle or any leftover tablets and this diary to your next clinic visit.**

Participant ID: _____ Participant Initials: ____ Dose Level: ____
Cycle #: ___ Cycle Start Date: _____

Cycle Day	Date		Comments			
		# of 60 mg	# of 30 mg	Time		
				AM	PM	
1						
2						
3						
4						
5						
6	[redacted]					
7						
8						
9						
10						
11						
12						
13	[redacted]					
14						
15						
16						
17						
18						
19						
20	[redacted]					
21						

Completed by: _____ Date: _____
Signature of Participant

FOR STUDY STAFF USE
Date Dispensed:_____ AZD8186 # of 60 mg _____ # of 30 mg _____
Date Returned:_____ AZD8186 # of 60 mg _____ # of 30 mg _____
Discrepancy/Comments:
Reviewed By: _____ Date: _____ Signature of Study Staff

Cycle 1 of Part 2: Pharmacodynamic expansion cohort to include the lead-in dosing

Cycle Day	Date	# of 60 mg	# of 30 mg	Comments Time AM	PM	
-7						
-6						
-5						
-4						
-3						
-2						
-1						
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						

Completed by: _____ Date: _____
Signature of Participant

FOR STUDY STAFF USE
Date Dispensed:_____ AZD8186 # of 60 mg _____ # of 30 mg _____
Date Returned:_____ AZD8186 # of 60 mg _____ # of 30 mg _____
Discrepancy/Comments:
Reviewed By: _____ Date: _____ Signature of Study Staff

APPENDIX G COLLABORATIVE AGREEMENTS LANGUAGE

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:
Email: ncicteppubs@mail.nih.gov
The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX H - BIOSPECIMEN COLLECTION AND SHIPPING GUIDELINES

IMPORTANT NOTES:

- Before packing, please be sure to fill out and include the **Specimen Collection Log** (template provided in the last page) with each shipment and please keep paperwork dry and separate from specimens.
- Samples may be rejected for analysis if the samples are thawed, container is broken or leaking.

Overview of specimen types and shipment locations

Biospecimen Type	Specimen and Container Type		Shipment Temperature	Documents and information to be sent	Shipment Location
Frozen Tumor Tissue (PD cohort only)		Fresh Frozen or OCT, 1.5ml eppendorf tube	Dry Ice	- Email notification to PPBC - Print out of Specimen Collection Log with shipment (Appendix H) - Print out of Pathology Report with the shipment or email to PPBC - Print out of Batch Record (Appendix 1)	Precision Pathology Biobanking Center, PPBC Memorial Sloan Kettering Cancer (MSKCC)
FFPE Tumor Tissue	 	FFPE blocks in clear specimen bags, FFPE slides in slide box/cassette	Ambient	- Email notification to PPBC - Print out of Specimen Collection Log with the shipment (Appendix H) - Print out of Pathology Report with the shipment box	Precision Pathology Biobanking Center, PPBC Memorial Sloan Kettering Cancer (MSKCC)
Whole Blood		PAXgene™ blood tube (prefered) or EDTA purple top	Ambient	- Email notification to PPBC - Print out of Specimen Collection Log with the shipment	Precision Pathology Biobanking Center, PPBC Memorial Sloan Kettering Cancer (MSKCC)
Plasma blood for cell-free DNA (cfDNA)		Streck tube (x2)	Ambient	- Print out of Specimen Collection Log with the shipment	Department of Lab Medicine Memorial Sloan Kettering Cancer (MSKCC)

I. SUBMITTING FORMALIN-FIXED, PARAFFIN-EMBEDDED (FFPE) TUMOR TISSUES

A. Sample Requirements:

a. FFPE tumor block requirements
   i. Resection or core needle biopsy specimens preferred
   ii. >150 micron thickness in size
   iii. Contain >30% tumor content

b. FFPE unstained slides requirements
   i. Total of 22 slides: 2 unstained **charged** slides and 20 unstained uncharged (if uncharged slides not possible, all slides can be provided as charged). All 5 micron thickness.
   ii. Slides should be unbaked and without cover slips. Baked and cover slipped slides will not be accepted.
   iii. Contain >30% tumor content
   iv. 1 corresponding hematoxylin and eosin (H&E) slide should be provided, if available
   v. All sections must come from the same tissue block

Pathology Report corresponding to the submitted block should be either provided within the shipment box or emailed to PPBC (skibiobank@mskcc.org). Pathology report should contain below information:

i. Tissue fixative used and fixative time
ii. Specimen type (resection, core needle biopsy, fine needle aspirate etc)
iii. Tumor histiotype
iv. Anatomic site (primary, metastatic)
v. % tumor content and % necrosis

B. Format for Labeling the Specimen:

Label the FFPE tissue specimens with Patient ID, and original collection date (mm/dd/yyyy). This specimen may also be labeled with the pathology accession number and block identifier. Each tissue specimen should be accompanied by **pathology report**.

C. Shipping Instructions – Ambient

During the warmer months (June – August), it is advisable to ship the block(s) with a frozen gel ice-pack to prevent the melting of paraffin-embedded tissue blocks during the transit.

Please complete the forms/notifications below before the shipment:

1. Email notification to PPBC
2. Print out of Specimen Collection Log with shipment (Appendix H)
3. Print out of Pathology Report with the shipment or email to PPBC
4. Print out of Batch Record (Appendix 1)

All samples should be shipped to:
Memorial Sloan Kettering Cancer Center
Precision Pathology Biobanking Center (PPBC)
411 E 67th Street
Room C-573
New York, NY 10065
212-639-2296 / 6737

! Samples should be sent Monday through Thursday for priority overnight delivery. **Do not ship on Friday or before a Federal holiday**.

II. SUBMITTING FROZEN TUMOR TISSUES (FOR PD COHORT ONLY)

A. Format for Labeling the Specimen:

Label the tubes of the flash frozen tissue specimens with Patient ID, and original collection date (mm/dd/yyyy).

B. Shipping Instructions – Dry Ice

Frozen tumor tissues should be shipped in **dry Ice** in styrofoam box in an insulated cardboard box to avoid the loss of dry ice. Shipments in only styrofoam boxes will not be accepted.

Please complete the forms/notifications below before the shipment:

1. **Specimen Collection Log** (Appendix H, last page)
2. **Batch record** (Appendix 1)
3. **Shipping manifest** (Appendix 2)

Frozen Tumor Tissue samples should be shipped to:
Memorial Sloan Kettering Cancer Center
Precision Pathology Biobanking Center (PPBC)
411 E 67th Street
Room C-573
New York, NY 10065
212-639-2296 / 6737

! Samples should be sent Monday through **Wednesday** for priority overnight delivery. **Do not ship on Friday or before a Federal holiday**.

III. SUBMITTING WHOLE BLOODS

A. Instructions for Collecting and Submitting Whole Blood in PAXgene Blood DNA Tubes:

PAXgene™ Blood DNA Tubes (Qiagen Catalog No. 761115) are preferred for whole blood collections, which offer optimal collection, storage, and subsequent isolation of genomic DNA. An EDTA (purple top) tube is also acceptable.

1. Ensure that the tube is at room temperature (18-25^{o}C) prior to use and properly labeled with the appropriate Patient ID, and Collection Date information.
2. Collect approximately 8 ml of blood into the tube using your institution's recommended procedure for standard venipuncture technique. Note that PAXgene™ blood tube has an 8.5 ml draw volume.
3. Store the upright at room temperature until shipment

B. Shipping Instructions – Ambient

Whole blood specimens should be shipped at ambient temperature on the day the specimen is collected. If shipment is not possible immediately, whole blood specimens may be stored at room temperature until the shipment, which should be within the 48 hours of collection. Please complete the **Specimen Collection Log** (template provided in the last page) and include with each shipment.

All samples should be shipped ideally *on the same day of collection* to:
Memorial Sloan Kettering Cancer Center
Precision Pathology Biobanking Center (PPBC)
411 E 67th Street
Room C-573
New York, NY 10065
212-639-2296 / 6737

! Samples should be sent priority overnight delivery. When avoidable, do not ship on Friday.

! When shipping whole blood specimens, please be aware that your institution must comply with IATA standards (www.iata.org). To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., an cardboard or Styrofoam box), (2) a leak proof shipping bag with absorbent material*, (3) a puncture and pressure resistant envelop (e.g., Tyvek envelope), (4) and an Exempt Human Specimen Sticker.
! If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag.

IV. SUBMITTING PLASMAS

A. Purpose:

Plasma will be isolated from whole blood drawn into Streck tubes, and cell-free DNA (cfDNA) will be extracted from plasma and used for biomarker research.

B. Instructions for Collecting and Submitting Plasma Blood for Cell-Free DNA:

Plasma cell-free DNA should be collected using Streck Cell-Free DNA Blood Collection tubes (BCT) (Streck Catalog no. 218962). For each time point, two Streck Cell-Free DNA BCT tubes will be drawn (total 20 mL).

1. Ensure that the Cell-Free DNA BCT tubes is adjusted to room temperature (18-25^{o}C) rior to use and labeled with the appropriate Patient ID, and collection date.
2. Collect blood into the Cell-Free DNA BCT tube using your institution's recommended procedure for standard venipuncture technique. Fill the tube completely with blood.
3. Store the Cell-Free DNA BCT tubes upright at room temperature until ready for shipment.

C. Format for Labeling the Specimen:

Plasma should be labeled with the Patient ID, timepoint (e.g. cycle number), and collection date (mm/dd/yyyy).

D. Shipping Instructions – Ambient

All plasma blood specimens should be shipped at ambient temperature on the day of the specimen collection. Bloods collected on Fridays can be stored at ambient temperature and shipped on Monday. **Do not store the Streck tubes in fridge or freezer.**

Plasma blood samples should be shipped ideally *on the day of collection* to:
Memorial Sloan Kettering Cancer Center
Department of Laboratory Medicine
327 East 64th Street, Room # C2-004
New York, NY 10065
646-608-1034 / 1035

! Samples should be sent Monday through Thursday for priority overnight delivery. **Do not ship on Friday or before a Federal holiday**.

V. ORDERING INFORMATION

Cell-Free DNA BCT Streck tube
Company: STRECK https://www.streck.com/
Catalog Number: 218962 (100 pack of 10ml tubes)

PAXgene™ Blood DNA Tubes
Company: PreAnalytix http://www.preanalytix.com
Catalog Number: 761115 (100 pack of 8.5ml tubes)

VI. SHIPMENT EMAIL NOTIFICATION

For the sample shipments to PPBC (FFPE blocks/slides, frozen tissue and whole blood) please send an email notification to skibiobank@mskcc.org using the email template below. Do not send email notification to PPBC for STRECK-Blood for plasma cfDNA samples or for samples going to other tests.

Subject: NCI Protocol #:10131 shipment notification

Email body:

Site Name:
Patient Study ID:
Collection date (MM/DD/YYYY):
Specimen Type: *(select the ones that apply) FFPE block, FFPE slides, Frozen tissue. Whole blood (PAXgene)*
Number of samples/tubes:
Shipping Tracking Number:

VII. SPECIMEN COLLECTION LOG

Template **Specimen Collection Log** is provided in the following page for printing. Each sample/specimen should be listed in a separate row. Please provide the completed and printed collection log with the specimens in the shipment box.

MSKCC Biospecimen Collection Log

Please include the completed and printed Collection Log in the shipment box
For shipments to Precision Pathology Biobanking Center (PPBC) in MSKCC, please email shipment notifications and any questions to PPBC Study Coordinator Team
Email: skibiobank@mskcc.org ***Phone:*** *212-639-2296 / 6737*

→SECTION I. STUDY INFORMATION

Study details are pre-filled. Please fill in the Site Name/Code

Protocol/Study Title: A Phase 1 Study of AZD8186 in Combination with Docetaxel in patients with *PTEN* mutated or *PIK3CB* mutated advanced solid tumors, potentially amenable to docetaxel. NCI Protocol #:10131	**Principal Investigator:** Alison Schram, Early Drug Development Service (EDD), MSKCC	**IRB:** 18-237	**Site Name/Code:**

→SECTION II. PATIENT INFORMATION

For specimens from multiple patients please complete separate collection logs and include the print outs with the shipment

Patient Study ID	Patient Initials (FirstLast) e.g. JD (for John Doe)

→SECTION III. SPECIMEN INFORMATION

Please select **[x]** the specimen type being shipped (select multiple if applicable)

Specimen Type		Amount (# of blocks, slides or tubes)	Specimen Code / Pathology #	Specimen Collection Date (Day-Month-Year) e.g. 8 March 2018	Specimen Timepoint	Ship to
	☐ FFPE blocks				□ Pre-treatment/archival □ On-treatment □ Post-progression □ Unknown	**Memorial Sloan Kettering Cancer Center** **Precision Pathology Biobanking Center (PPBC)** **411 E 67th Street, Room C-573** **New York, NY 10065** **Phone: 212-639-2296 / 6737**
	☐ FFPE slides				□ Pre-treatment/archival □ On-treatment □ Post-progression □ Unknown	
	☐ Frozen Tissue* ***For Frozen tissues, also provide print outs of completed Appendix 1 and 2.**			**Date of Collection:** **Absolute Time of Collection:** **Absolute Time of Drug Dosing:**	□ Pre-treatment/archival □ On-treatment □ Post-progression □ Unknown	
	☐ Whole Blood (PAXgene/EDTA)					
	☐ STRECK-Blood (for plasma cfDNA)					**Memorial Sloan Kettering Cancer Center** **Department of Laboratory Medicine** **327 East 64th Street, Room # C2-004** **New York, NY 10065** **Phone: 646-608-1034 / 1035**

→SECTION IV. SHIPMENT INFORMATION

Shipment Prepared by	Contact Phone	Contact Email	Date of Shipment	Tracking Number

APPENDIX I TUMOR FROZEN NEEDLE BIOPSY SPECIMEN COLLECTION AND HANDLING

https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf

APPENDIX J SOP FOR PROCESSING NEEDLE BIOPSIES AT THE PADIS LAB

https://dctd.cancer.gov/ResearchResources/biomarkers/docs/met/SOP341201_METIA_Tumor_E xtraction.pdf