Clinical Study Protocol	
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A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

EudraCT: 2015-000886-30

VERSION HISTORY

Version 10.0, 05 September 2018 (Amendment 9)

Changes to the protocol are summarised below:

- Specified that patients still receiving AZD1775 after the primary data cut-off will have a Final Protocol Visit (FPV) occurring at their next scheduled visit focused on capturing safety information. Following the FPV, patients may continue to receive treatment with AZD1775 ± chemotherapy as deemed appropriate by the Investigator (see Table 2, footnote 'bb', Table 3, footnote 'cc', and Section 4.4). The end-of-study treatment visit is **not** required for patients continuing treatment after the FPV.
- Amended Section 5.6 to add clarification about optional tumour biopsies.
- Clarified that blood samples and optional tumour biopsies for exploratory biomarker research will be collected at treatment discontinuation due to disease progression for subjects that continue taking AZD1775 ± chemotherapy after the FPV (see Section 5.6).
- Clarified how SAEs will be reported after the FPV (see Section 6.4.1 and Section 6.5).
- Clarified that after the FPV pregnancies will be monitored while patients are on treatment and for 30 days after their final dose of AZD1775 ±chemotherapy (Section 6.7).
- Clarified that after the FPV, drug accountability information must continue to be collected until the patient discontinues treatment. In addition, patients must continue to be monitored for all SAEs, overdoses and pregnancies while receiving AZD1775 ± chemotherapy. SAEs and pregnancy test results will be collected for 30 days following the patient's last dose of AZD1775 ± chemotherapy (see Sections 4.4 and 9.3).
- Clarified that all safety data collected after the primary analysis and up to (and including) the last of the FPVs will be listed and/or summarised as appropriate (see Sections 8.6 and 9.3).
- Other miscellaneous minor changes throughout (corrections to typos, formatting, etc.).

Version 9.0, 14 February 2018 (Amendment 8)

Changes to the protocol are summarised below:

- Dose modification guidance for haematological events for patients receiving AZD1775 plus chemotherapy has been updated in Section 6.9.1, Table 2, and Table 3.
- Table 20, Table 21, and Table 22 have been replaced with the new Table 20 illustrating the new dose modification guidance.

Version 8.0, 19 June 2017 (Amendment 7)

Changes to the protocol are summarised below:

- Increased number of sites to reflect addition of 6 new sites to trial.
- Inclusion of allowable prior treatment regimens changed from 2 to 2-4.
- Updated text in Synopsis and Section 1.2 about enrolling 23 patients overall to Arm C.
- Deleted text in Synopsis about following patients 12 months after database lock.
- Clarified inclusion and exclusion criteria.
- Applicable sections of the protocol have been updated to reflect the current Investigator's Brochure (IB), 11 January 2017. Specifically:
  - updated the number of patients exposed to AZD1775 thus far
  - clarified language in the following sections: benefit/risk, non-haematologic toxicity dose modifications, diarrhoea, overdose
  - Addition of exclusion criteria*:* AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.
- Updated Objectives in Synopsis and Section 2 to include all chemotherapy regimens.
- Updated tumour response section language; removed text regarding 'Best Regimen'; updated CIs for PFS medians.
- Schedule of collection of cfDNA modified in Tables 2 and 3 and Section 5.6 for Arms B and C (Arms A and D closed to enrollment).
- In Appendix E, definition of 'total/true abstinence' has been expanded, in order to align with changes to UK protocol required by MHRA.
- Changed abbreviated version of Sarah Cannon Development Innovations to 'Innovations'.
- Other miscellaneous minor changes throughout (corrections to typos, formatting, etc.).

Version 7.0, 20 January 2017 (Amendment 6)

Changes to the protocol are summarised below:

- Due to emerging data, approximately 30 additional patients will be enroled in an expansion of Arm B (AZD1775 and paclitaxel). Patients will be enroled through selected sites.
- Approximately 12 additional patients will be treated within the expansion of AZD1775 and carboplatin (Arm C2) at selected sites.

Version 7.0, 20 January 2017 (Amendment 6)
• Mandatory AZD1775 pharmacokinetic samples will be collected from patients in AZD1775 and paclitaxel efficacy expansion and the AZD1775 and carboplatin expansion (see Table 14). • In addition to the collections described in the study plan table(s), another cfDNA sample will be collected from patients on Cycle 2 Day 1 (see Section 5.6). • An optional pharmacogenetic sample will be collection from all patients (see Section 5.5). • Triplicate ECGs will be obtained as described at baseline/screening. In addition, triplicate ECGs taken 2-5 minutes apart will be required prior to starting each new treatment cycle (see Section 5.2.3). • Applicable sections of the protocol have been updated to reflect the current Project Specific Safety Requirements (PSSR) 10 November 2016. Specifically, exclusion of Seville grapefruit and juices, triplicate ECGs prior to beginning each study treatment cycle, and guidelines for retaking missed doses of AZD1775. • Approximately 97 patients will be enrolled in the safety and efficacy portions of the study at completion. • Patient must be ≥18 years of age to be included in the study. This criterion was removed in error in the last protocol amendment. • In CSP Amendment 5, the Section 5.6.1 Plasma Pharmacogenetics was moved to Section 5.5. Amendment 5 incorrectly stated the section was expanded when it was moved and the content was reduced. • Clarifications for improved readability, references updated, and minor grammatical errors corrected.

Version 6.0, 17 August 2016 (Amendment 5)
Changes to the protocol are summarised below: • This Clinical Study Protocol (CSP) has been extensively modified as indicated in the redlined version, as the contents from the previous protocol have been placed into a new template. • Applicable sections of the protocol have been updated to reflect the current AZD1775 Investigator Brochure (IB) information throughout [updated safety information based on cut-off of November 11, 2015; updated information on contraception use and sperm freezing; language on nausea and diarrhoea]. • Section 5.5 has been expanded to describe the collection and use of data for pharmacogenetic research. • Additional areas have been updated to harmonise with the new template for consistency.

Version 6.0, 17 August 2016 (Amendment 5)
• Removed references to pegylated liposomal doxorubicin (PLD) expansion cohort of Arm D, which is not moving forward • Clarifications for improved readability, references updated, and minor grammatical errors corrected.

Version 5.0, 04 December 2015 (Amendment 4)
Primary reasons for amendment: • To stop enrolment into the following treatment arms: AZD1775 + paclitaxel and AZD1775 + gemcitabine, beyond the safety cohorts • To add an AZD1775 + Doxil treatment arm for evaluating safety and efficacy of this combination in advanced ovarian, fallopian tube, or primary peritoneal cancer patients • To update the study design by not performing the randomisation for enrolling patients in the treatment arms • *TP53* mutations are so prevalent in the eligible patient population, that requiring proof of these mutations prior to enrolment is no longer necessary in the amended protocol. However, mutational analysis of tumour samples will be performed for all patients, in a retrospective manner. • The study objectives have been updated to align with the updated study design • Correction of minor consistency errors and clarifications for readability.

Version 4.0, 29 June 2015 (Amendment 3)
Amendment 3 changed the restrictions and the inclusion criteria for the study. This amendment also identified corrections to the edition numbering to bring it back into alignment. • Clarified number of allowable prior treatment regimens, types of treatment and stage of disease; women of child bearing potential inclusion criteria updated • Included and clarified information presented in study plan • Clarified dosing instructions and harmonised them with other treatment schedules

Version 3.0, 18 May 2015 (Amendment 2)
Amendment 2 provided additional clarification and guidance for this study, including: • Allowing patients in that had received prior adjuvant therapy • Reducing starting dose of gemcitabine from 1000 mg/m^2 to 800 mg/m^2 • Adding windows for collection times • Providing better dose modification guidance, dose-limiting toxicity (DLT) clarification, tumour assessments clarification

Version 2.0, 06 October 2014 (Amendment 1)
Amendment 1 provided additional clarification and guidance for the conduct of this study. Additional dose-limiting criteria were included to part 1 of the study (grade 3 thrombocytopenia with bleeding as a haematologic DLT), the AZD1775 dosing schedule was changed to be administered concurrently with chemotherapy, the 48-hour gap or delay in administering AZD1775 was removed, and visit windows were clarified in the Study Plan tables.

Version 1.0, 12 August 2014 (Original Clinical Study Protocol)
Initial approved protocol.

This Clinical Study Protocol (CSP) has been subject to a peer review according to AstraZeneca Standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Principal Investigator:

Study site(s) and number of subjects planned

Approximately 97 patients will be enrolled at 32 global investigational sites.

Study period		Phase of development
Estimated date of first subject enrolled	Q4 2014	2
Estimated date of last subject completed	Q4 2018	2

Study design

The aim of this study is to evaluate the safety and tolerability of AZD1775 when combined with either gemcitabine, paclitaxel, carboplatin, or PLD in patients with platinum resistant ovarian cancer. The research hypothesis for the AZD1775 drug development programme is that administration of AZD1775 combined with chemotherapy in women with platinum-resistant ovarian, fallopian tube, or primary peritoneal carcinoma experience improved progression-free survival compared to women receiving chemotherapy alone. This study is being conducted to understand the dose level, dosing schedule, safety, and tolerability of AZD1775 combined with chemotherapy agents such that they can be subsequently studied for improvement in efficacy.

This is an open-label, four-arm lead-in safety and efficacy study in which AZD1775 will be combined in four separate treatment arms as follows: AZD1775 plus gemcitabine (Arm A); AZD1775 plus weekly paclitaxel (Arm B); AZD1775 plus carboplatin (Arm C); and

AZD1775 plus PLD (Arm D [See Figure 1]). A subset of patients will be evaluated for the safety assessment of each treatment arm (see Section 7.2.3.1).

The AZD1775 plus paclitaxel arm (Arm B) will enrol approximately 30 additional patients at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity.

The AZD1775 plus carboplatin arm (Arm C) will enrol approximately 23 patients overall at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity.

To further optimise the dosing schedule of AZD1775 in Arm C, a safety expansion arm (referred to as Arm C2) of approximately 12 additional patients will be enrolled at selected sites to receive carboplatin AUC 5 IV on Day 1 of a 21 day cycle in combination with AZD1775 BID for 2.5 days per dosing week (QW), on Weeks 1 (D1-3), 2 (D8-10) and 3 (D15-17), or on Weeks 1 (D1-3) and 2 (D8-10) (2 weeks on followed by 1 week off). These additional weeks of AZD1775 dosing are meant to explore emerging pre-clinical and clinical data that suggest that prolonged AZD1775 exposure may increase the clinical activity.

Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of 12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing may be modified to 2 weeks on followed by 1 week off. All decisions which include but are not limited to cohort dosing, dose escalation or de-escalation will be reviewed by the Safety Review Team (SRT).

Modified PK assessments will be obtained to harmonise and accommodate the investigation of alternative dose levels and/or schedules.

Objectives

Primary Objective:	Outcome Measure:
To evaluate the objective response rate (ORR) of AZD1775 in combination with gemcitabine, carboplatin, paclitaxel, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	The primary endpoint of this study is ORR for the arms included in the efficacy assessment, defined as the proportion of patients achieving a complete or partial tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (Eisenhauer et al 2009).

Secondary Objectives:	Outcome Measures:
To evaluate the duration of response (DoR) of AZD1775 in combination with gemcitabine, carboplatin, paclitaxel, or PLD	DoR, defined as the time from first documented tumour response until the date of documented progression or death from any cause.
To evaluate the safety and tolerability of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths; clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and abnormal vital signs.
To evaluate the disease control rate (DCR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	DCR, defined as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria.
To evaluate the Cancer Antigen-125 (CA-125) response of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Gynecologic Cancer Intergroup (GCIG) CA-125 response, defined as the proportion of patients achieving a 50% reduction in CA-125 levels from baseline, if baseline level is ≥2 x the upper limit of normal (ULN) within 2 weeks prior to starting treatment. Response must be confirmed and maintained for at least 28 days.
To characterise the pharmacokinetics (PK) of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD
To assess the drug interaction between AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD

Exploratory Objectives:	**Outcome Measures:**
To identify genetic alterations in breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) and other relevant genes, including *TP53,* from analysis of archived or fresh tumour tissue collected at baseline, and to determine if the presence of a genetic alteration is predictive of clinical outcomes.	Molecular analysis of tumour tissue samples will be reviewed and correlated with clinical data.
To analyse changes in plasma circulating free tumour DNA (cfDNA) over time, from baseline, to restaging, and at disease progression. (This exploratory analysis will be reported separately from the Clinical Study Report [CSR].)	Blood samples will be collected to analyse cfDNA concentrations and molecular alterations.
To obtain preliminary estimates of the overall survival (OS) and progression-free survival (PFS) of AZD1775 in combination with gemcitabine, paclitaxel, carboplatin, or PLD.	OS, defined as the time from first dose to death from any cause, and progression-free survival (PFS), defined as the time from first dose to the first documentation of disease progression (according to RECIST v1.1 criteria) as determined by the Investigator or death from any cause, whichever comes first.
To collect and store deoxyribonucleic acid (DNA) for future research into genes/genetic variations that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to the development of cancers.	Correlation of genetic polymorphisms with variation in PK, safety or response observed in subjects treated with AZD1775. Data generated may be reported separately and may also form part of a pooled analysis with other AZD1775 studies.

Target subject population

Target subject population consists of females aged 18 years or older with platinum-resistant, high-grade serous (HGS) epithelial ovarian, fallopian tube, or primary peritoneal cancer who progressed within 6 months of completing (but without progression during) at least 4 cycles of a first-line platinum-containing regimen for Stage III/IV disease, and had no more than 2-4 prior treatment regimens for Stage III/IV disease (investigational, chemotherapy, hormonal, biologic, or targeted therapy).

Duration of treatment

Patients will be allowed to continue on therapy as long as they have no limiting toxicity or disease progression, have not withdrawn from the study, and are considered by the Investigator to still be receiving clinical benefit.

Investigational product, dosage and mode of administration

AZD1775 is available as dry-filled capsules containing 25 or 100 mg of drug substance AZD1775 will be provided by AstraZeneca. Additional information about the investigational product (IP) may be found in the Investigator's Brochure (IB).

Commercially available **gemcitabine** 800 mg/m^2 IV will be infused over approximately 30 minutes or according to institutional standards. Refer to the gemcitabine package insert for additional information.

Commercially available **paclitaxel** will be administered as a 1-hour IV infusion (± 10 minutes) at a dose of 80 mg/m^2 according to institutional standards. Patients should be pre-medicated with corticosteroids, diphenhydramine and/or H_2 antagonists according to institutional standards (see Section 7.7). Refer to the paclitaxel package insert for additional information.

Carboplatin, at a dose calculated to produce an area under the curve (AUC) of 5 mg/mL min, will be administered by IV infusion according to institutional standards. The carboplatin dose will be calculated using the Calvert Formula based on the patient's glomerular filtration rate (GFR) which is estimated by using the creatinine clearance (CrCl). Refer to the carboplatin package insert for additional information.

Commercially available **pegylated liposomal doxorubicin (PLD)** (40 mg/m^2) will be administered by IV infusion on Day 1 of each 28-day Cycle. PLD should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, the rate of infusion can be increased to complete administration over 1 hour. A bolus injection or undiluted solution should not be administered. PLD should not be mixed with any other drug. Refer to the package insert for additional information.

Statistical methods

Sample size calculations for Arm C of the study are based upon testing a primary endpoint of ORR according to RECIST v1.1. In order to test the null hypothesis of an ORR of 10% versus an alternative hypothesis with an ORR of 30%, 23 patients are required in order to have 85% power to test the null hypothesis using a one-sided exact binomial test at the 0.10 significance level. The null hypothesis will be rejected if at least 5 responses are observed from 23 patients.

The Part C2 expansion will enrol approximately 12 patients to assess a weekly AZD1775 dosing regimen in combination with carboplatin in a 3 week cycle. Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of 12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing schedule will be shortened to 2 weeks on and 1 week off.

The AZD1775 plus paclitaxel arm (Arm B) will enrol approximately 30 additional patients. Historical response rates using weekly paclitaxel in platinum-resistant and refractory ovarian cancer are in the region of 20% to 40% (Pignata et al 2015, Lortholary et al 2011, McNeish et

al 2014). The following examples give an indication of the level of precision that will be achieved in the paclitaxel treated patients.

If the observed response rate is 30% (9/30), the 2-sided 80% confidence interval (CI) will be (18%, 43%). If the observed response rate is 50% (15/30), the 2-sided 80% CI will be (36%, 63%). For decision making, ORR will be considered in addition to the observed safety and tolerability data and the other efficacy endpoints.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.2)
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BRCA1/2	Breast cancer gene 1/2
CA-125	Cancer Antigen-125
CBC	Complete blood count
cfDNA	Circulating free tumour DNA
CI	Confidence interval
CR	Complete response
CrCl	Creatinine clearance
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group (Performance Status)
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FPV	Final protocol visit

Abbreviation or special term	Explanation
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GOG	Gynecologic Oncology Group
HGS	High-grade serous
IB	Investigator Brochure
ICH	International Conference on Harmonisation
Innovations	Sarah Cannon Development Innovations
IP	Investigational Product
MM	Medical monitor
MRI	Magnetic resonance imaging
MUGA	Multiple uptake gated acquisition scan
NCI	National Cancer Institute
NE	Non-evaluable
NSCLC	Non-small-cell-lung cancer
NTL	Non-target lesion
NYHA	New York Heart Association
OAE	Other significant adverse event (see definition in Section 8.4.2.3)
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PDx	Pharmacodynamics
PET	Positron-emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
PLD	Pegylated liposomal doxorubicin
PO	By mouth
PR	Partial response
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Response rate
SAE	Serious adverse event (see definition in Section 6.3)

Abbreviation or special term	Explanation
SD	Stable disease
SDV	Source data verification
SRT	Safety review team
TEAE	Treatment-emergent adverse events
TL	Target lesion
ULN	Upper limit of normal
WNL	Within normal limits
WoCBP	Women of childbearing potential

1. INTRODUCTION

Ovarian cancer accounts for 5% of cancer-related deaths among women in the United States according to the American Cancer Society. Diagnosis of 21,980 new cases and 14,270 deaths were estimated in 2014 (SEER Research Data). Although the death rate for ovarian cancer has been stable for the last 10 years it remains the cause of more cancer deaths of the female reproductive system than any other. Fallopian tube cancer and primary peritoneal cancer are grouped with ovarian cancer because of their similar prognostic features. Though less frequently diagnosed, these two female-reproductive cancers are known to respond to the same types of treatment and have similar histologic features as ovarian cancer (Bloss et al 1993; Schneider et al 2000).

Systemic chemotherapy with a platinum-based regimen (carboplatin or cisplatin with/without paclitaxel) following surgical debulking, has markedly improved the long-term survival of patients with advanced stage ovarian cancer. However, patients who experience disease recurrence within 6 months of completing treatment (defined as platinum-resistant) have a poorer prognosis than platinum-sensitive patients and require subsequent treatment options in order to extend survival and preserve quality of life. Platinum-resistant patients may benefit from retreatment with platinum-based therapy administered in a dose-dense fashion (Pignata et al 2015, Pinato et al 2013, Kavanagh et al 1995, and Bozas et al. 2007). It may be possible to overcome platinum resistance by combining platinum with other compounds. Carboplatin is approved by the Food and Drug Administration (FDA) for patients previously treated with cisplatin. The Gynecologic Oncology Group (GOG) conducted a series of studies in patients with platinum-resistant disease (Naumann and Coleman 2011). In one GOG study, a response rate (RR) of 21% was observed in 47 platinum- and paclitaxel-resistant ovarian cancer patients receiving weekly paclitaxel (80 mg/m^2/week) until disease progression. Previous treatment for this group of patients included standard paclitaxel once every three weeks (Markman et al 2006). Platinum-resistant ovarian malignancies are frequently treated with single agents such as topotecan, paclitaxel, oral etoposide or pegylated liposomal doxorubicin (PLD) with RRs ranging between 5% and 15%. Gemcitabine demonstrated activity in 8/51 patients with platinum and taxane refractory ovarian cancer. Four patients experienced significant cancer antigen-125 (CA-125) blood level declines (≥75%) and 4 patients achieved partial remissions of measureable disease. Three week on/1 week off cycles of single agent gemcitabine were administered. Ten patients received the initial starting dose of gemcitabine 1250 mg/m^2, 35 patients were initiated at a reduced dose of 1000 mg/m^2 and 6 patients were started at 800 mg/m^2 because of toxicity (Markman et al 2002). The median duration of response (DoR) was 4 months. Physician decision as to which agent to administer is usually based upon toxicity, tumour response and quality of life (Pignata et al 2015, Pinato et al 2013).

Gemcitabine is recognized for its ability to initiate cell death, and has been FDA approved for relapsed ovarian cancer when combined with carboplatin (refer to package insert). Two Phase II trials administering single-agent gemcitabine weekly for 3 weeks, followed by 1-week rest (1250 mg/m^2 – 1000 mg/m^2) to platinum/ paclitaxel-refractory or -resistant ovarian patients demonstrated RRs of 16% and 17%, respectively. These RRs were consistent with other Phase 2 study responses seen in platinum-resistant patients (Markman et al 2002 , D'Agostino et al 2003).

A recent report from a Phase II clinical trial indicated that patients receiving AZD1775 plus paclitaxel and carboplatin combination had greater progression-free survival (PFS) compared to patients receiving only paclitaxel and carboplatin (Oza et al 2015).

Another study report indicated that, AZD1775 in combination with carboplatin is well tolerated and shows promising anti-tumour activity in patients with p53 mutated ovarian cancer who are refractory or resistant to standard first line therapy (Leijen et al 2015).

Anti-tumour activity of doxorubicin against epithelial ovarian cancer has been subsequently proven in clinical trials (A'Hern and Gore 1995; Ozols et al 1980). Despite its potent antineoplastic activity, clinical use of doxorubicin has been limited by its associated side effects, in particular haematological toxicity and irreversible cardiac damage.

Recently there has been increasing attention on PLD (Gabizon 2001), which is a formulation of liposomal doxorubicin that is coated in polyethylene glycol (PEG). The PEG coating creates a hydrophilic barrier that protects the liposomes from detection by the reticuloendothelial system and increases the time that the active drug remains in circulation, which reduces the rate at which the active drug is broken down (Gabizon 2001) and makes it less toxic to heart muscle. The size of the liposomes prevents PLD from entering tissues with tight capillary junctions, such as the heart and gastrointestinal tract; therefore it causes less toxicity compared with non-modified doxorubicin, while leading to increased concentrations within the tumour (Waterhouse et al 2001). In 1999 it was first approved for platinum-refractory ovarian cancer and then received full approval for platinum-sensitive recurrent disease in 2005. The main toxicities associated with PLD are nausea, palmar-plantar erythema or hand-foot syndrome (HFS-redness and soreness of palms of hands and soles of feet), stomatitis and myelosuppression (Janssen-Cilag 2011).

Pegylated liposomal doxorubicin (PLD, e.g. Doxil® and Caelyx®) class of agents are approved for treating patients with ovarian cancer for whom the disease has progressed or recurred after treatment with platinum-based chemotherapy. In this study, the safety of PLD in combination with AZD1775 will be tested in some patients.

1.1 Background and rationale for conducting this study

1.1.1 The p53 signalling pathway

It is important to understand the molecular signature of tumours in order to improve therapeutic approaches and better manage refractory and recurrent ovarian cancer. One of the most important molecular aberrations in oncogenesis is related to protein 53 (p53) a tumour suppressor encoded by the *TP53* gene. In normal cells, wild-type p53 plays a pivotal role in DNA damage repair and cell cycle arrest as well as helping to trigger apoptosis in response to genotoxic stress (Vogelstein et al 2000). P53 deficiency leads to diminished DNA-repair capability; and germline *TP53* mutations are associated with early-onset cancers such as Li-Fraumeni and Li-Fraumeni-like syndromes (Hainaut and Hollstein 2000). Somatic *TP53* mutations are common in many forms of human cancer, as well. Aberrant p53 function and/or p53 deficiency is particularly important in ovarian cancer, where the overwhelming majority of patients demonstrate mutations in *TP53* (Vang et al 2009; Kurman and Shih 2010; TCGARN 2011). These mutations are heterogeneous, presenting a very complex scenario for an effective drug development strategy; and it is becoming increasingly apparent that tumour-associated mutations in the p53 signalling pathway can induce biological responses beyond that of simple loss of function. Mutant p53 proteins may acquire oncogenic properties that promote invasion, metastasis, proliferation, and cell survival.

Since p53 is a key regulator of the G1 cell-cycle check point, p53-deficient cells predominantly depend on the S or G2 checkpoint for the repair of damaged cells. Therefore, blocking the G2-checkpoint may selectively sensitize p53-deficient cells to DNA-damaging anticancer therapeutics while sparing normal tissue from toxicity. WEE1 is a protein tyrosine kinase that selectively phosphorylates the Tyr15 residue on cyclin-dependent kinase 1 (CDK1), inhibiting the transition from G2 into mitosis, preventing cells with damaged DNA from proliferating, so DNA repair can occur (Parker and Piwnica-Worms 1992; Igarashi et al 1991; Watanabe et al 1995; McGowan and Russell 1993).

Evaluation of tumour-associated mutations in the tumour suppressor *TP53* has indicated that while most mutations abrogate p53 protein function, a small fraction of these mutations are not predicted to abrogate it's function. Therefore, a list of *TP53* mutations has been generated that are known or predicted to have a deleterious impact on p53 function. This list represents approximately 87% of known *TP53* mutations in ovarian cancer, and will be used to determine retrospectively the *TP53* mutation status of the tumour tissue being collected for this clinical study.

1.1.2 AZD1775

AZD1775 is a highly selective, adenosine-triphosphate (ATP) competitive, small-molecule inhibitor of the WEE1 kinase that sensitises tumour cells to cytotoxic agents and is being developed for the treatment of advanced solid tumours and p53 pathway deficient

malignancies. Inhibition of the DNA damage checkpoint kinase WEE1 potentiates genotoxic chemotherapies by abrogating cell-cycle arrest and eliminating the opportunity for proper DNA repair to occur. From a therapeutic standpoint, inhibition of checkpoint kinases that mediate cell-cycle arrest may force tumour cells to continue cell division before chemically induced DNA damage is repaired, eventually causing apoptosis or mitotic catastrophe (Medema and Macurek 2012).

The primary objective of the clinical development of AZD1775 is to test it as a chemosensitising drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced solid tumours. In vitro experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. In studies with matched ovarian cell lines (p53 WT and shRNA p53 knockdown), AZD1775 enhanced cell death induction by gemcitabine in p53-deficient but not in p53 positive control cells. AZD1775 also demonstrates synergistic effects on cell death induction when used in combination with cisplatin and carboplatin in a p53-dependent manner. Cervical cancer cells with HPV induced inactivation of p53 demonstrated chemosensitisation to cisplatin and topotecan by AZD1775.

The ability of AZD1775 to affect tumour growth as monotherapy or to enhance the anti-tumour effects of gemcitabine, carboplatin, cisplatin, capecitabine, 5-fluorouracil, and gamma irradiation was evaluated in immunocompromised host animals bearing human xenograft tumours.

The anti-tumour effect of AZD1775 dosed as monotherapy was investigated in the A427 non-small-cell lung cancer (NSCLC) nude mouse xenograft model. Daily treatment with AZD1775 led to 51% tumour regression (n=10) and mean body weight loss did not exceed 5% over the course of the study. AZD1775 single agent treatment also led to tumour growth inhibition in additional xenograft models: 92% TGI (Day 28) in SKMES1 model of NSCLC, 13% regression (Day 11) in LoVo colorectal cancer model and 64% TGI (Day 19) in NCI-H2122 NSCLC.

The anti-tumour effect of AZD1775 in combination with gemcitabine was investigated in the WiDr (human colorectal adenocarcinoma) nude rat xenograft model. Several schedules of gemcitabine + AZD1775 were explored. A 10 mg/kg dose of AZD1775 significantly enhanced the anti-tumour effect of gemcitabine in WiDr tumours with % treated/control (T/C) = -2%.

The anti-tumour effect of AZD1775 in combination with carboplatin was investigated in the HeLa-luc (human cervical adenocarcinoma) nude rat xenograft model. AZD1775 dose-dependently enhanced the anti-tumour effect of carboplatin tumours with %T/C = 85, 39 and 28% at doses of 10, 20 and 30 mg/kg, respectively.

The anti-tumour effect of AZD1775 in combination with cisplatin was also investigated in the HeLa-luc model. These experiments showed dose-dependently enhanced the anti-tumour effect of cisplatin with %T/C = -5 and -16% at doses of 10 and 20 mg/kg respectively, compared to carboplatin (or cisplatin) alone (X% T/C).

AZD1775 enhanced the anti-tumour efficacy of 5-FU and capecitabine when used in combination with these agents, as well; and experiments with nude mouse xenograft models of A549 (p53 wild type) and Calu-6 (p53 null) NSCLC cell lines showed enhanced anti-tumour growth effect of radiotherapy preferentially in p53 mutant xenograft tumours. Please refer to the AZD1775 Investigator Brochure (IB) for more detailed information regarding these experiments and findings.

PLD is an anthracycline topoisomerase II inhibitor approved for treatment of patients with ovarian cancer who have failed on platinum-based chemotherapy. AZD1775 has been reported to potentiate cytotoxic effects of doxorubicin *in vitro* (Hirai et al 2010). This report supports the rationale of assessing the safety of doxorubicin in combination with AZD1775 as a potential therapeutic approach.

1.1.2.1 AZD1775 clinical experience

AZD1775 has been and is being evaluated in several clinical studies, including both phase I and phase II studies in a variety of combinations and tumour settings (AZD1775 (MK-1775) IB). These include:

- **PN001 (NCT 00648648) (except for Part 3):** a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours
- **PN005 (NCT 01047007)**: a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5-FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritization in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.
- **PN008 (NCT 01076400):** a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritization in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. Phase IIa was not initiated.

In Study PN001 (NCT 00648648), of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients (AZD1775 (MK-1775) IB). Nine patients received AZD1775 monotherapy. Single ascending doses of AZD1775 up to 1300 mg were well tolerated; the maximum tolerated dose (MTD) was not evaluated.

In Study PN005 (NCT 01047007), patients in Part 1 received single-cycle twice-daily (BID) dosing of AZD1775 for 5 days as monotherapy. A cohort of 3 patients was enrolled at the starting dose level of AZD1775 65 mg BID and no serious adverse events (SAEs) were experienced.

An ongoing study (NCT 01748825) sponsored by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program, in collaboration with AstraZeneca, is investigating AZD1775 monotherapy. The MTD for monotherapy treatment in patients with advanced refractory solid tumours was found to be 225 mg BID x 5 on Weeks 1 and 2 of a 3-week schedule. Paired biopsies were obtained from 5 patients on this dose and schedule. The biopsies showed that a decrease in pCDC2 was observed in the post-treatment biopsy in 3 of the biopsy pairs with an average of 80% reduction. The same biopsies were analysed for increases in γH2AX, an indicator of DNA damage. Three of the 5 biopsy pairs showed a post-treatment increase in γH2AX, with an average of 404% induction observed in these 4 biopsy pairs. This study is also evaluating a once daily (QD) schedule for monotherapy starting at a 200 mg dose. Twenty-five patients have been enrolled for the BID schedule and 3 for the QD schedule.

As of 11 November 2016, a total of approximately 551 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, 350 patients have also received AZD1775 as part of AstraZeneca's externally-sponsored scientific research. These patients have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 as a single-dose in combination with chemotherapy, and 325 mg BID in a multiple-dose regimen in combination with chemotherapy. Please refer to the current version of the AZD1775 IB.

The most common adverse events (AEs) observed in studies of AZD1775 combined with chemotherapy include blood and lymphatic disorders, (i.e., thrombocytopenia, neutropenia, leukopenia, anaemia, febrile neutropenia), gastrointestinal disorders (i.e., diarrhoea, vomiting, nausea, abdominal pain, and constipation), and blood investigations (haematology and serum chemistries). Other reported safety concerns include electrocardiogram (ECG) QT prolongation, fatigue, influenza like illness, malaise, mucosal inflammation, myalgia, palpitations, pruritus, pyrexia, rash, rash maculopapular, skin lesion, stomatitis, tachycardia, loss of weight.

The single-dose maximum tolerated dose (MTD) of AZD1775 was 200 mg in combination with gemcitabine and/or cisplatin. Dose-limiting toxicities (DLTs) tended to be haematological in nature in the gemcitabine group and constitutional in the cisplatin group. The single-dose MTD for the combination with carboplatin was 325 mg of AZD1775. DLTs in this group were related to serum chemistry.

Hematologic DLTs were most commonly observed in the multiple-dose AZD1775 combination treatment groups with gemcitabine and cisplatin. An MTD of AZD1775 in

combination with gemcitabine was established with an interim dose of 50 mg BID on Day 1, 25 mg BID on Day 2, and 25 mg on Day 3. An attenuated once daily for 2 day schedule in combination with gemcitabine continues under investigation. Two DLTs (grade 3 febrile neutropenia and grade 3 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increase) were observed at 200 mg once daily for 2 days with the regimen in combination with gemcitabine. The dose was adjusted to 175 mg once daily for 2 days, and one DLT has been reported to date. The MTD for combination with cisplatin has been exceeded at the 250 mg dose level, and tolerability of the MTD at 200 mg BID has been confirmed. DLTs observed in the multiple-dose carboplatin combination have been both haematological and constitutional in nature. The multiple-dose MTD in combination with carboplatin is AZD1775 225 mg BID.

The MTD for AZD1775 in combination with 5-FU was not reached due to early study termination. DLTs of encephalopathy and hyponatraemia were observed in the AZD1775 20 mg BID in combination with 1000 mg/m^2 5-FU treatment group.

Triplet-based therapy was administered in the study PN004, AZD1775, carboplatin, and paclitaxel. The starting dose of 225 mg AZD1775 (BID for 5 total doses) in Part 1 was generally well tolerated. One patient experienced a DLT in the first six patients treated and the dose remained at 225 mg BID 2.5 days. A total of 15 patients were treated, with 3 DLTs being reported (grade 3 and 4 febrile neutropenia and grade 4 thrombocytopenia). The study expanded to Part 2 and is ongoing. Other toxicities were generally blood and lymphatic system disorders and gastrointestinal.

For the combination of AZD1775 with topotecan plus cisplatin in study PN008, toxicities were generally haematological and gastrointestinal in nature. No unexpected toxicities were observed.

In study PN009 and the premarket formulation substudy to PN001 (both combining 2.5-day BID dosing of AZD1775 with carboplatin) there were no appreciable differences in toxicity from the ones observed in the carboplatin arm of study PN001. However, increased haematological toxicity was observed, which is considered to be a function of a drug-drug interaction with aprepitant (which was administered as anti-nausea medication in these studies).

Preliminary pharmacokinetic (PK) analyses revealed that co-administration of AZD1775 and aprepitant results in a ~60% increase of AZD1775 exposure.

Available preliminary efficacy data are encouraging, with confirmed PRs in patients participating in the two ovarian trials, as well as the phase I trial in solid tumours. Several studies are ongoing (AZD1775 (MK-1775) IB).

1.1.3 Rationale for conducting this study

The purpose of this study is to find a new alternative treatment for platinum-resistant *TP53*-mutated high-grade serous (HGS) ovarian cancer patients. AZD1775 has demonstrated efficacy in two ongoing ovarian carcinoma studies (PN004 and PN009) combined with either carboplatin alone or carboplatin and paclitaxel.

The platinum-resistant HGS ovarian patient presents unique treatment challenges. *TP53* mutations in HGS ovarian cancer occur in 80-96% of patients. In one report, *TP53* mutations were reported in 96% of 316 HGS ovarian cancer patients using high-throughput technology (TCGARN 2011). In the current study, archival tumour samples will be required to confirm *TP53* mutation status, in a retrospective manner.

The current study is an open-label, four-arm, lead-in safety and efficacy study of gemcitabine, paclitaxel, carboplatin or PLD in combination with AZD1775.

This study is intended to provide important safety and efficacy data for administering AZD1775 in combination with chemotherapy (gemcitabine, carboplatin, weekly paclitaxel, or PLD).

1.2 Rationale for study design, doses and control groups

The aim of this study is to evaluate the safety and tolerability of AZD1775 when combined with either gemcitabine, paclitaxel, carboplatin, or PLD in patients with platinum resistant ovarian cancer. The research hypothesis for the AZD1775 drug development programme is that administration of AZD1775 combined with chemotherapy in women with platinum-resistant *TP53* mutated ovarian, fallopian tube, or primary peritoneal carcinoma experience improved PFS compared to women receiving chemotherapy alone. This study is being conducted to understand the dose level, dosing schedule, safety, and tolerability of AZD1775 combined with chemotherapy agents such that they can be subsequently studied for improvement in efficacy.

This is an open-label, four-arm lead-in safety and efficacy study in which AZD1775 will be combined in four separate treatment arms as follows: AZD1775 plus gemcitabine (Arm A); AZD1775 plus weekly paclitaxel (Arm B); AZD1775 plus carboplatin (Arm C); and AZD1775 plus PLD (Arm D [See Figure 1]). A subset of patients will be evaluated for the safety assessment of each treatment arm (see Section 7.2.3.1). The dose/schedules for AZD1775 and paired chemotherapeutic agents that will be used in the lead in safety/expansion are presented below:

Arm A (AZD1775 175 mg PO daily days (D)1-2, 8-9, 15-16 + gemcitabine 1000 mg/m^2 IV D1, 8, 15 q28D);

Arm B (AZD1775 225 mg PO BID x 5 doses D1-3, 8-10, 15-17 + paclitaxel 80 mg/m^2 IV D1, 8, 15 q28D);

Arm C (AZD1775 225 mg PO BID x 5 doses D1-3 + carboplatin AUC 5 IV D1 q21D)

Arm D (AZD1775 175 or 225 mg PO BID x 5 doses D1-3 + PLD 40 mg/m2 IV D1 q28D)

The AZD1775 plus paclitaxel arm (Arm B) will enrol approximately 30 additional patients at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity.

The AZD1775 plus carboplatin arm (Arm C) will enrol approximately 23 patients overall at selected sites as part of a further efficacy evaluation based on emerging data that suggests clinical activity.

To further optimise the dosing schedule of AZD1775 in Arm C, a safety expansion arm (referred to as Arm C2) of approximately 12 additional patients will be enrolled at selected sites to receive carboplatin AUC 5 IV on Day 1 of a 21 day cycle in combination with AZD1775 BID for 2.5 days per dosing week (QW), on Weeks 1 (D1-3), 2 (D8-10) and 3 (D15-17), or on Weeks 1 (D1-3) and 2 (D8-10) (2 weeks on followed by 1 week off). These additional weeks of AZD1775 dosing are meant to explore emerging pre-clinical and clinical data that suggest that prolonged AZD1775 exposure may increase the clinical activity.

Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of 12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing may be modified to 2 weeks on followed by 1 week off. All decisions which include but are not limited to cohort dosing, dose escalation or de-escalation will be reviewed by the Safety Review Team (SRT).

Modified PK assessments will be obtained to harmonize and accommodate the investigation of alternative dose levels and/or schedules.

1.3 Benefit/risk and ethical assessment

The investigation of AZD1775 in this patient population appears acceptable based upon the non-clinical profile and emerging clinical data. The lead-in safety and efficacy phase of the study will be risk minimising with safety and medical monitoring, PK assessments, and Safety Review Team (SRT) involvement. Overall the benefit/risk assessment supports the administration of AZD1775 to patients with platinum-resistant ovarian, fallopian tube, or primary peritoneal carcinoma.

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies, adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhoea, nausea, and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. In addition, the following events are also considered expected during treatment with AZD1775 in combination with cytotoxic chemotherapy: febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, mucosal inflammation, and myalgia.

Based on information emerging during the clinical development programme of AZD1775, potential risks with AZD1775 monotherapy include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation. Gastrointestinal haemorrhage and sepsis are described in further detail in the current IB.

In addition, the following events are also considered potential risks for AZD1775 in combination with cytotoxic chemotherapy: tachycardia and pancytopenia.

Refer to the IB for AZD1775 for information on the potential benefits and assessment of potential and known risks.

1.4 Study Design

Figure 1 AZD1775 treatment arms and dosing schedules

Arm A – AZD1775 (2 Days On/5 Days Off) plus Gemcitabine

	Week 1							Week 2							Week 3							Week 4						
Cycle = 28 Days																												
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**26**	**27**	**28**
Arm A																												
AZD1775 PO Daily	X	X						X	X						X	X												
Gemcitabine	X							X							X													

Arm A (AZD1775 175 mg PO daily days (D)1-2, 8-9, 15-16 + gemcitabine 1000 mg/m2 IV D1, 8, 15 q28D)

Arm B – AZD1775 (2.5 Days/Weeks 1, 2 and 3) plus Paclitaxel

	Week 1							Week 2							Week 3							Week 4						
Cycle = 28 Days																												
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**26**	**27**	**28**
Arm B	**3/4 dosing (5 doses/2.5 days)**																											
AZD1775 PO BID	X	X	X					X	X	X					X	X	X											
Paclitaxel	X							X							X													

Arm B (AZD1775 225 mg PO BID x 5 doses D1-3, 8-10, 15-17 + paclitaxel 80 mg/m2 IV D1, 8, 15 q28D)

Arm C – AZD1775 (2.5 Days/Week 1) plus Carboplatin

	Week 1							Week 2							Week 3						
Cycle = 21 Days																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
	Day 1-3 (5 doses/2.5 days)																				
AZD1775 PO BID (5 doses)	X	X	X																		
Carboplatin	X																				

Arm C (AZD1775 225 mg PO BID x 5 doses D1-3 + carboplatin AUC 5 IV D1 q21D)

Arm C2 – AZD1775 (2.5 Days/Weeks 1, 2, and 3) plus Carboplatin

	Week 1							Week 2							Week 3						
Cycle = 21 Days																					
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**
Arm C2	**3/4 dosing (5 doses/2.5 days)**																				
AZD1775 PO BID (5 doses)	X	X	X					X	X	X					X	X	X				
Carboplatin	X																				

Arm C2 (AZD1775 on weeks 1 (D1-3), 2 (D8-10) and 3 (D15-17) over 2.5 days plus carboplatin AUC 5 IV on Day 1 or AZD1775 on weeks 1 (D1-3) and 2 (D8-10) over 2.5 days.)

Arm D – AZD1775 (2.5 Days/Week 1) plus PLD

	Week 1							Week 2							Week 3							Week 4						
Cycle = 28 Days																											
Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**26**	**27**	**28**
Arm D	**Day 1-3 (5 doses/2.5 days)**																											
AZD1775 PO BID (5 doses)	X	X	X																									
PLD	X																											

Arm D (AZD1775 175 or 225 mg PO BID x 5 doses D1-3 + PLD 40 mg/m2 IV D1 q28D)

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To evaluate the objective response rate (ORR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	The primary endpoint of this study is ORR for the arms included in the efficacy assessment, defined as the proportion of patients achieving a complete or partial tumour response according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (**Eisenhauer et al 2009**).

2.2 Secondary objectives

Secondary Objectives:	Outcome Measures:
To evaluate the DoR of AZD1775 in combination with gemcitabine, PLD, carboplatin or paclitaxel	DoR, defined as the time from first documented tumour response until the date of documented progression or death from any cause.
To evaluate the safety and tolerability of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and deaths; clinically significant changes in safety-related laboratory parameters according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03) and abnormal vital signs.
To evaluate the disease control rate (DCR) of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	DCR, defined as the proportion of patients achieving a complete response (CR), partial response (PR), or stable disease (SD) according to RECIST v1.1 criteria.
To evaluate the Cancer Antigen-125 (CA-125) response of AZD1775 in combination with carboplatin, paclitaxel, gemcitabine or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Gynaecologic Cancer Intergroup (GCIG) CA-125 response, defined as the proportion of patients achieving a 50% reduction in CA-125 levels from baseline, if baseline level is ≥2 x the upper limit of normal (ULN) within 2 weeks prior to starting treatment. Response must be confirmed and maintained for at least 28 days.
To characterise the PK of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus PLD, and AZD1775 plus gemcitabine
To assess the drug interaction between AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD	Plasma PK parameters of AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD

2.3 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
To identify genetic alterations in breast cancer genes 1 and 2 (*BRCA1* and *BRCA2*) and other relevant genes, including *TP53,* from analysis of archived or fresh tumour tissue collected at baseline, and to determine if the presence of a genetic alteration is predictive of clinical outcomes.	Molecular analysis of tumour tissue samples will be reviewed and correlated with clinical data.
To analyse changes in plasma circulating free tumour DNA (cfDNA) over time, from baseline, to restaging, and at disease progression. (This exploratory analysis will be reported separately from the Clinical Study Report [CSR].)	Blood samples will be collected to analyse cfDNA concentrations and molecular alterations.
To obtain preliminary estimates of the overall survival (OS) and progression-free survival (PFS) of AZD1775 in combination with gemcitabine, PLD, carboplatin or paclitaxel	OS, defined as the time from first dose to death from any cause, and progression-free survival (PFS), defined as the time from first dose to the first documentation of disease progression (according to RECIST v1.1 criteria) as determined by the Investigator or death from any cause, whichever comes first
To collect and store DNA for future research into genes/genetic variations that may influence PK or response to AZD1775 (i.e., absorption, distribution, metabolism, excretion, safety and efficacy) and/or susceptibility to the development of cancers.	Correlation of genetic polymorphisms with variation in PK, safety or response observed in subjects treated with AZD1775. Data generated may be reported separately and may also form part of a pooled analysis with other AZD1775 studies.

3. SUBJECT SELECTION, ENROLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1 Has read and understands the informed consent form (ICF) and has given written IC prior to any study specific procedures.

2 Histologic or cytologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer.

3 Progressed within 6 months of completing at least 4 cycles of a first-line platinum-containing regimen for Stage III/IV disease. Patients with refractory disease (progression during platinum-containing therapy) are ineligible.

4 No more than 2-4 prior treatment regimens for Stage III/IV disease defined as investigational, chemotherapy, hormonal, biologic, or targeted therapy.

5 Prior doxorubicin (or other anthracyclines) at a cumulative dose of ≤360 mg/m^2 or cumulative epirubicin dose of ≤ 720 mg/m^2 (calculated using doxorubicin equivalent doses: 1 mg doxorubicin = 1 mg PLD = 0.3 mg mitoxantrone = 0.25 mg idarubicin). Subjects without any prior anthracycline exposure can also be included (applies to Arm D only).

6 At least 1 measurable lesion according to RECIST v1.1.

7 Any prior palliative radiation therapy must be completed at least 7 days prior to start of study treatment and patients must have recovered from any acute adverse effects prior to start of study treatment.

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

9 Baseline laboratory values within 7 days of starting study drugs as follows:

- Absolute neutrophil count (ANC) ≥1500/μL
- Hemoglobin (Hgb) ≥9 g/dL with no blood transfusions in the past 28 days
- Platelets ≥100,000/μL
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN or ≤5 x ULN if known hepatic metastases.
- Serum bilirubin within normal limits (WNL) or ≤1.5 x the ULN in patients with liver metastases; or total bilirubin ≤3.0 x ULN with direct bilirubin WNL in patients with well documented Gilbert's Syndrome.
- Serum creatinine ≤1.5 x ULN OR measured creatinine clearance (CrCl) ≥45 mL/min as calculated by the Cockcroft-Gault method (confirmation of creatinine clearance is only required when creatinine is >1.5 x institutional ULN):

$$\text{CrCl (glomerular filtration rate [GFR])} = \frac{(140\text{-age}) \times (\text{weight/kg}) \times (0.85\ [\text{female}])}{(72 \times \text{serum creatinine mg/dL})}$$

10 Left ventricular ejection fraction (LVEF) WNL of the institution, as determined by multiple uptake gated acquisition (MUGA) or echocardiography (ECHO) (applies to Arm D only).

11 Female patients who are not of childbearing potential and fertile female patients of childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to start of study treatment (see Appendix E).

12 Predicted life expectancy ≥12 weeks.

13 Must be ≥18 years of age.

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

3.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2 Previous enrolment in the present study

3 Participation in another clinical study with an investigational product during the last 28 days

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

5 Major surgical procedures ≤28 days of beginning study treatment, or minor surgical procedures ≤7 days. No waiting required following port-a-cath placement, or any other central venous access placement.

6 No other (chemotherapy, immunotherapy, hormonal anti-cancer therapy, radiotherapy [except for palliative local radiotherapy]), biological therapy or other novel agent is to be permitted while the patient is receiving study medication

7 Grade >1 toxicity from prior therapy (except alopecia or anorexia).

8 Inability to swallow oral medication. Note: Patient may not have a percutaneous endoscopic gastrostomy (PEG) tube or be receiving total parenteral nutrition (TPN).

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

10 Patient has had prescription or non-prescription drugs or other products (i.e. grapefruit juice) known to be sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors or inducers of CYP3A4, which cannot be discontinued 2 weeks prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug. (See Appendix G).

11 Caution should be exercised when inhibitors or substrates of P-gP, substrates of CYP1A2 with a narrow therapeutic range, sensitive substrates of CYP2C19 or CYP2C19 substrates with a narrow therapeutic range are administered with AZD1775.

12 Transporter studies (*in vitro*) have shown that AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). Please refer to Appendix G for use of BCRP substrates.

13 Herbal medications should be discontinued 7 days prior to the first dose of study treatment. Please see Section 7.7.3 on prohibited concomitant medications and Appendix G for further details.

14 Any known hypersensitivity or contraindication to the components of study treatment (AZD1775, doxorubicin, paclitaxel, or carboplatin [and cisplatin]).

15 Any of the following cardiac diseases currently or within the last 6 months as defined by New York Heart Association (NYHA) ≥ Class 2

- Unstable angina pectoris
- Congestive heart failure
- Acute myocardial infarction
- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (patients with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).

16 AZD1775 should not be given to patients who have a history of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected. AZD1775 has not been studied in patients with ventricular arrhythmias or recent myocardial infarction.

17 Corrected QT interval (QTc) >470 msec at study entry or congenital long QT syndrome. QTc interval will be calculated using Fridericia's formula (per institutional standards) obtained from 3 ECGs performed 2-5 minutes apart at study entry.

18 Pregnant or lactating

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

20 Presence of other active cancers, or history of treatment for invasive cancer within the last 3 years. Patients with Stage I cancer who have received definitive local treatment within the last 3 years, and whom are considered unlikely to recur, are eligible. All patients with previously treated in-situ carcinoma (i.e., non-invasive) are eligible, as are patients with prior non-melanoma skin cancers.

21 Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

For procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

3.3 Subject enrolment

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1 Obtain signed informed consent from the potential patient before any study specific procedures are performed. Obtain study identifier according to the instructions provided in the Study Reference Manual.
2 Assign the patient a unique enrolment number/code.
3 Determine subject eligibility. See Sections 3.1 and 3.2.

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused.

3.3.1 Optional Pharmacogenetic (PGx) research

For inclusion in the optional exploratory PGx research, patients must provide informed consent for pharmacogenetic research.

Exclusion from this pharmacogenetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogenic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

If a patient declines to participate in the optional exploratory pharmacogenetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study.

3.4 Procedures for handling incorrectly enrolled subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is enrolled in error, or incorrectly started on treatment, the Investigator should inform the Medical Monitor (MM) immediately, and a discussion should occur between the MM and the Investigator regarding whether to continue or discontinue the patient from treatment. The MM must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

This is an open-label study and no randomisation details are required.

3.5.1 *TP53* testing

TP53 mutations are so prevalent in the eligible patient population that requiring proof of these mutations prior to enrolment is no longer necessary in the amended protocol. Retrospective *TP53* mutation assessments will be performed centrally from archival tumour tissue. A full report that includes all of the genes present on the gene panel will subsequently be made available to Investigators upon request.

Refer to the Laboratory Manual for complete instructions.

3.6 Methods to ensure blinding

The study is open-label; therefore, blinding procedures are not applicable.

3.7 Methods for unblinding

This is open-label; therefore, unblinding procedures are not applicable.

3.8 Restrictions

Please see Appendix G for information regarding concomitant medications that are prohibited or should be avoided while receiving AZD1775 and chemotherapy. Additional restrictions include the following:

- Women of childbearing potential (WoCBP) may be included only if acceptable contraception is in place for two weeks before study entry, for the duration of the study and for one month after the last dose of AZD1775 (see Appendix E for definitions of non-childbearing potential and acceptable contraceptive methods).
- WoCBP defined as: Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.
- WoCBP receiving paclitaxel chemotherapy may be included in the study only if acceptable contraception is in place for 2 weeks before study entry, for the duration of the study and for at least 6 months after the last dose of paclitaxel treatment.
- All WoCBP must have a negative pregnancy test within 3 days of starting study treatment and confirmed prior to the start of study treatment on the first day of dosing. WoCBP must have a negative pregnancy test prior to starting each new treatment cycle and at the end-of-treatment visit (EOT).

3.9 Discontinuation of investigational product

Subjects may be discontinued from investigational product (IP) in the following situations:

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Confirmed disease progression
- Pregnancy

- Patient is lost to follow-up
- Severe non-compliance with the study protocol
- Development of any study specific criteria for discontinuation
- Investigator decision.

3.9.1 Procedures for discontinuation of a subject from investigational product

At any time, subjects are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A subject that decides to discontinue investigational will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (see section 6), and all study drugs should be returned by the subject.

If a subject is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

Reasons for withdrawal from the study:

- Withdrawal of consent
- Death
- Incorrectly enrolled or treated patient
- AE
- Patient is lost to follow-up

If a patient wishes to withdraw her consent to both treatment and study assessments, they should be asked if they are willing to continue with survival follow-up (which can be conducted by telephone). If a patient wishes to withdraw her consent to further participation in the study entirely, including survival follow-up, this should be clearly documented in the patient medical record and in the electronic case report form (eCRF).

The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of analysis should be obtained by the site personnel by checking the patient’s medical record and hospital records, contacting the patient’s general practitioner, and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can still be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be enrolled. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (i.e., patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not enrolled patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then her enrolment code cannot be reused. Withdrawn patients will not be replaced unless they withdraw in Cycle 1 of the Part 1 lead-in safety cohort.

3.10.3 Lost to follow-up

Patients will be considered lost to follow-up only if contact was lost and could not be re-established by the time the study is completed, and there is insufficient information to determine the patient's status at that time. Note: Patients who refuse to continue participation in the study, including telephone contact, should be documented as 'withdrawal of consent' rather than 'lost to follow-up'. Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol. If a patient withdraws from participation in the study, then their patient number cannot be reused.

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the electronic case report form (eCRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Study Plan: Arm A (AZD1775 plus Gemcitabine)

	Screen[a]	AZD1775 and Chemotherapy (Cycle = 28-days)					Restage Every 2 Cycles[k] (±7 days)	End of Study Treatment Visit (30 Day FU)[l] (±2 days)	Follow-Up	
		Lead-In Safety Cycle 1			Cycles 2 and Beyond				PFS[m] (±7 days)	Survival FU[n] (±7 days)
Assessments	**Baseline**	**D1**	**D8**	**D15**	**D1 (±2 days)**	**D8/15 (±2 days)**				
Informed consent	X									
Archival tumour sample[b]	X									
Medical/surgical history	X									
Physical Examination	X	X			X			X		
ECOG performance status	X	X			X			X		
Vital signs[c]	X	X			X			X		
Hematology	X	X	X	X	X	X		X		
Clinical Chemistry[d]	X	X			X			X		
Coagulation (PT or INR with PTT)[e]	X									
Urinalysis	X									
Pregnancy test (urine or serum)[g]	X	X[g]			X[g]			X		
Triplicate 12-Lead ECG[f]	X				X[f]					
PK sample collection[p] (Lead-in)		X[p]			X[p]					
cfDNA[q] (Plasma sample)	X				X		X	X[q]	X[q]	
CA-125 (Serum sample)[r]	X[o]	X[o]			X[o]			X[o]		
Tumour assessments (RECIST v1.1)	X						X	X[w]	X[x]	
CT Scan/MRI of the Chest[i]	X						X[h,j,k]	X[w]	X[x]	
CT Scan/MRI of the Abdomen and Pelvis[i]	X						X[h,j,k]	X[w]	X[x]	
Optional tumour biopsy sample								X[v]	X[v]	
Concomitant medication review	X	X			X			X		
Adverse event assessment	X	X	X	X	X	X		X		
Survival status									X	X[n]
Dispense AZD1775[s] Review/Collect Dosing Diary[u]		X	X	X	X[s,u]	X				
Gemcitabine administration[t]		X	X	X	X	X				

a The physical examination, vital signs, medical history (capture previous treatment medications and response to each prior treatment regimen), concomitant medications (recorded ≤14 days prior to trial entry), ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, urinalysis, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if any of these initial examinations are required at Cycle 1 Day 1 and are obtained within 3 days prior to the initiation of treatment they do not have to be repeated. CA-125 should be done within 14 days prior to the initiation of treatment. Scans to document evaluable disease (i.e., tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

b All patients must provide a tumour sample (archival) for *TP53* testing and other exploratory biomarkers by a central laboratory (see Section 5.6).

c Vital signs (resting heart rate, blood pressure, temperature and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice.

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein, lactate dehydrogenase (LDH), phosphorus, and albumin.

e Coagulation performed at baseline only (PT or INR with PTT) should be done ≤7 days prior to initiation of treatment. Repeat at the beginning of every cycle if patient on Coumadin.

f QTc interval will be calculated using Fridericia's formula (as calculated per institutional standards) obtained from 3 ECGs 2-5 minutes apart at study entry (see Section 3.2). In addition, patients will have triplicate 12-lead ECGs performed 2-5 minutes apart at the beginning of each treatment cycle.

g Pregnancy tests will only be performed in women of childbearing potential (WoCBP) within 3 days of starting study treatment and confirmed prior to start of study treatment on the first day of dosing. WoCBP must have a negative pregnancy test prior to starting each new treatment cycle and at the end-of-treatment visit (see Section 3.8).

h Patients will be restaged after every 2 cycles (every 8 weeks [±7 days]). Patients with progressive disease (PD) or unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment.

i Computed tomography (CT) scans/magnetic resonance imaging (MRI) of the chest and abdomen and pelvis are required at baseline and every 2 cycles (8 weeks).

j The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment beyond 1 year may have the tumour imaging assessments expanded to every 3 cycles (12 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l The End of Study Treatment Visit will be performed 30 days after the last dose of study treatment or prior to the beginning of new therapy. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose (see Section 7.2.7). Tumour assessments will be repeated at the end of study treatment visit if they have not been performed within the past 2 cycles (3 cycles for patients on study for >1 year).

m Post follow-up for patients without disease progression at the time of study drug discontinuation should include repeat CT scan(s) and CA-125 (if applicable) until disease progression has been observed. The patient will be followed every 3 months (±1 week) from the date of the last tumour assessment and assessment of response, until death or until the study is terminated by the sponsor.

n Patients with documented disease progression will be followed every 3 months (±1 week) for survival status (e.g., date and cause of death). Patients may be contacted during outpatient visits or by telephone. All post study therapies and dates of administration will be collected.

o CA-125 serum sample collected at baseline (within 14 days prior to first study treatment), Day 1 of each cycle, and end-of-study treatment visit (see Section 5.2.4).

p The 6 patients in the lead-in safety group will have limited plasma PK samples collected pre-and post AZD1775 dosing (see Table 6 and Section 5.3.1). PK samples will be collected at the following time points: Cycle 1 Day 1 - 2 samples will be collected pre AZD1775 and gemcitabine administration (this collection may be done the previous day). Two samples will be collected at 30 minutes post AZD1775 morning dosing (once the gemcitabine infusion ends), and at 1, 2, and 4 hours. One sample will be collected at 6 hours and at the end of the first day, ideally around 8 hours post AZD1775 dosing. On Cycle 2 Day 1, samples will be collected at 2 hours and 3-4 hours after AZD1775 dosing. On Cycle 3 Day 1, 30 minutes to1 hour and 2 hours after AZD1775 dosing, Cycle 3 Day 2 after AZD1775 is dosed, and Cycle 4 Day 1 before AZD1775 dosing and 2 hours after dosing occurs. Refer to the Laboratory Manual.

q Collection of cfDNA to explore the genetic tumour markers in plasma correlation with markers in tumour samples and to monitor for the emergence of resistance is mandatory at baseline, restaging, end-of-treatment and progression for all patients. A baseline plasma sample will be required followed by subsequent single plasma samples at the time of each restaging, end-of-treatment and progression. Plasma samples will be collected in an EDTA tube and processed according to the Laboratory Manual. See Section 5.6 for more information.

r Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1. An additional sample will be collected for tumour response monitoring. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the upper limit of normal (ULN) and within 2 weeks prior to starting treatment (see Section 5.1).

s AZD1775 (175 mg by mouth [PO]) will be taken once a daily on Days 1-2, 8-9 and 15-16. AZD1775 should be taken approximately 2 hours before or 2 hours after food.

t Gemcitabine 800 mg/m^2 IV will be administered according to institutional standards on Days 1, 8, and 15 of each 28 day cycle.

u Review and document AZD1775 dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.

v Optional tumour biopsy samples will be requested from patients at the time of disease progression. Informed consent must be obtained from any patient who agrees to provide tissue for this optional testing.

w The end of study treatment visit tumour assessments do not need to be repeated if they were done during the previous 2 cycles (3 cycles if patient was on study for >1 year).

x Follow-up assessments start 12 weeks from the last date tumour and response assessments were performed.

Table 2 Study Plan: Arm B (AZD1775 plus Weekly Paclitaxel)

	Screen[a]	AZD1775 and Chemotherapy (Cycle = 28-days)					Restage Every 2 Cycles[k] (±7 days)	End of Study Treatment Visit (30 Day FU)[l] (±2 days)	Follow-Up		FPV[bb]
		Lead-In Safety Cycle 1			Cycles 2 and Beyond				PFS[m] (±7 days)	Survival FU[n] (±7 days)	
Assessments	Baseline	D1	D8	D15	D1 (±2 days)	D8/15 (±2 days)					
Informed consent	X										
Archival tumour sample[b]	X										
Medical/surgical history	X										
Physical Examination	X	X			X			X			X
ECOG performance status	X	X			X			X			X
Vital signs[c]	X	X			X			X			X
Haematology[aa]	X	X	X	X	X	X		X			X
Clinical Chemistry[d]	X	X	X	X	X	X		X			X
Coagulation (PT or INR with PTT)[e]	X										
Urinalysis	X										
Pregnancy test (urine or serum)[g]	X	X[g]			X[g]			X[g]			X[g]
Triplicate 12-Lead ECG[f]	X	X			X[f]						X[f]
PK sample collection[p]		X[p,q]			X[p]						
Sparse PK sample collection[q]		See Table 14			See Table 14						
Optional PGx blood sample[z]	X										
cfDNA[r] (Plasma sample)	X[r]				X[r]		X[r]	X[r]	X[r]		X[r]
CA-125 (Serum sample)[s]	X[o]	X[o]			X[o]			X[o]			X[o]
Tumour assessments (RECIST v1.1)	X[s]						X	X[x]	X[y]		
CT Scan/MRI of the Chest[i]	X						X[h,j,k]	X[x]	X[y]		
CT Scan/MRI of the Abdomen and Pelvis[i]	X						X[h,j,k]	X[x]	X[y]		
Optional tumour biopsy sample								X[w]	X[w]		X[w]
Concomitant medication review	X	X			X			X			X
Adverse event assessment	X	X	X	X	X	X		X			X
Survival status									X	X[n]	
Dispense AZD1775[t] Review/Collect Dosing Diary[v]		X	X	X	X[t,v]	X		X			X
Paclitaxel administration[u]		X	X	X	X	X					X

a The physical examination, vital signs, medical history, (capture previous treatment medications and response to each prior treatment regimen), concomitant medications (recorded ≤14 days prior to trial entry), ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, urinalysis, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if any of these initial examinations are required at Cycle 1 Day 1 and obtained within 3 days prior to the initiation of treatment they do not have to be repeated. CA-125 should be done within 14 days prior to initiation of treatment. Scans to document evaluable disease (i.e., tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

b All patients must provide a tumour sample (archival) for *TP53* testing and other exploratory biomarkers by a central laboratory (see Section 5.6).

c Vital signs (resting heart rate, blood pressure, temperature and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice at screening, on Day 1 of each cycle visit, at the end-of-study treatment visit, and the final protocol visit (FPV).

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, lactate dehydrogenase (LDH), phosphorus, and albumin.

e Coagulation performed at baseline only (PT or INR with PTT) should be done within ≤7 days prior to the initiation of treatment. Repeat at the beginning of every cycle if patient on Coumadin.

f QTc interval will be calculated using Fridericia's formula (as calculated per institutional standards) obtained from 3 ECGs 2-5 minutes apart at study entry (see Section 3.2). In addition, patients will have triplicate 12-lead ECGs performed 2-5 minutes apart at the beginning of each treatment cycle including the FPV.

g Pregnancy tests will only be performed in WoCBP within 3 days of starting study treatment and confirmed prior to start of study treatment on the first day of dosing. WoCBP must have a negative pregnancy test prior to starting each new treatment cycle and at the end-of-treatment visit (see Section 3.8), and at the FPV.

h Patients will be restaged after every 2 cycles (every 8 weeks [±7 days]). Patients with PD or unacceptable toxicity should be discontinued from study treatment; patients with SD or response to therapy will continue treatment.

i CT scans/MRIs of the chest and abdomen and pelvis are required at baseline and every 2 cycles (8 weeks).

j The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment beyond 1 year may have the tumour imaging assessments expanded to every 3 cycles (12 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l The End of Study Treatment Visit will be performed 30 days after the last dose of study treatment or prior to the beginning of new therapy. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose (see Section 7.2.7). Tumour assessments will be repeated at the end of study treatment visit if they have not been performed within the past 2 cycles (3 cycles for patients on study for >1 year). The end-of-study treatment visit is **not** required for patients continuing treatment after the FPV.

m Post follow-up for patients without disease progression at the time of study drug discontinuation should include repeat CT scan(s) and CA-125 (if applicable) until disease progression has been observed. The patient will be followed every 8 weeks (±1 week) from first dose (every 12 weeks for patients on study >1 year) until progression, death or until the study is terminated by the sponsor.

n Patients with documented disease progression will be followed every 3 months (±1 week) for survival status (e.g., date and cause of death). Patients may be contacted during outpatient visits or by telephone. All post study therapies and dates of administration will be collected.

o CA-125 serum sample collected at baseline (until 14 days prior to first study treatment), Day 1 of each cycle, at the end-of-study treatment visit, and the FPV (see Section 5.2.4).

p The 6 patients in the lead-in safety group will have limited plasma PK samples collected pre-and post AZD1775 dosing (see Table 7 and Section 5.3.1). PK samples will be collected at the following time points: Cycle 1 Day 1 - 2 samples will be collected at each of the following time points: before AZD1775 and paclitaxel administration (this collection may be done the day before), 1 sample at 30 minutes post AZD1775 morning dosing, 2 samples (once the paclitaxel infusion stops) at 1, 2, 4, and 6 hours post AZD1775 dosing and at the end of the first day, ideally around 8 hours from AZD1775 dosing. On Cycle 2 Day 1, samples will be collected at 2 hours and 3-4 hours after AZD1775 dosing. On Cycle 3 Day 1, 30 minutes to1 hour and 2 hours after AZD1775 dosing, Cycle 3 Day 2 after AZD1775 is dosed, and Cycle 4 Day 1 before AZD1775 dosing and 2 hours after dosing occurs. Refer to the Laboratory Manual.

q Efficacy Expansion: Mandatory sparse AZD1775 PKs will be collected from patients pre-dose, post-dose 1 hour and post-dose 2-4 hours to be collected on Day 3 or Day 10 or Day 17 on Cycle 1, 3, 5 and 7 (see Table 14). Paclitaxel ONLY PKs will be collected described in Table 7 during Cycle 1 (before paclitaxel administration (this collection may be done the day before), 1 samples (once the paclitaxel infusion stops) at 1, 2, 4, and 6 hours post AZD1775 dosing and at the end of the first day, ideally around 8 hours.

r Collection of cfDNA to explore the genetic tumour markers in plasma correlation with markers in tumour samples and to monitor for the emergence of resistance is mandatory at baseline, Cycle 2 Day 1, Day 1 of every odd-numbered cycle (Cycles 3, 5, etc.), end-of-treatment and progression for all patients. Patients continuing treatment after the FPV will have a cfDNA sample collected if the patient discontinues treatment due to disease progression. Plasma samples will be collected in an EDTA tube and processed according to the Laboratory Manual. See Section 5.6 for more information.

s Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1. An additional sample will be collected for tumour response monitoring. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the ULN and within 2 weeks prior to starting treatment (see Section 5.1).

t Five doses of AZD1775 (225 mg PO BID) will be taken in approximate 12 hour intervals over 2.5 days weekly (Days 1-3, 8-10 and 15-17). AZD1775 should be taken approximately 2 hours before or 2 hours after food. Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria.

u Weekly paclitaxel 80 mg/m^2 IV will be administered according to institutional standards on Days 1, 8 and 15 of each 28 day cycle. After the FPV, patients will continue to receive paclitaxel 80 mg/m2 IV until disease progression, or until they no longer derive clinical benefit, or until they fulfil any discontinuation criteria, in the opinion of the Investigator. Drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment.

v Review and document AZD1775 dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.

w Optional tumour biopsy samples will be requested from patients that discontinue treatment due to disease progression. Informed consent must be obtained from any patient who agrees to provide tissue for this optional testing, including patients that continue after the FPV.

x The end of study treatment visit tumour assessments do not need to be repeated if they were done during the previous 2 cycles (3 cycles if patient was on study for >1 year).

y Follow-up assessments every 8 weeks (±1 week) from first dose (every 12 weeks for patients on study >1 year) until progression, death, or until the study is terminated by the sponsor.

z An optional PGx sample will be collected from consenting patients. If not collected at Cycle 1 Day 1, the PGx sample may be collected at any visit until the last study visit (see Section 3.3).

aa Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment week and reviewed prior to dose administration. If haematologic toxicity occurs, treatment should be held and ANC and platelets should be monitored at least weekly. Patients should be managed as medically indicated. Treatment should not be resumed until recovery to Grade 1 (ANC ≥1.5 x 10^9/L or 1,500/µL; platelets ≥75,000/µL) (see Section 6.9.1 for further information).

bb The Final Protocol Visit (FPV) applies only to those patients who will be receiving AZD1775 ± chemotherapy after the time of primary data cut-off meant for the preparation of the CSR. The FPV should occur at the next scheduled visit following implementation of the Revised Protocol Edition 10. Beyond the FPV, patients may continue to receive AZD1775 ± chemotherapy if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment. After the FPV, SAEs, drug accountability, overdoses and pregnancy test results will be collected while the patient is receiving AZD1775 ± chemotherapy. The EOT visit is **not** required for patients continuing treatment after the FPV. SAEs and pregnancy test results will be collected for 30 days following the patient's last dose of AZD1775 ± chemotherapy.

Table 3 Study Plan: Arm C and C2 (AZD1775 plus Carboplatin)

	Screen[a]	AZD1775 and Chemotherapy (Cycle = 21-days)						Restage Every 2 Cycles[k] (±7 days)	End of Study Treatment Visit (30 Day FU)[l] (±2 days)	Follow-Up		FPV[cc]
		Lead-In Safety Cycle 1			Cycles 2 and Beyond					PFS[m] (±7 days)	Survival FU[n] (±7 days)	
Assessments	**Baseline**	**D1**	**D8**	**D15**	**D1 (±2 days)**	**D8 (±2 days)**	**D15 (±2 days)[y]**					
Informed consent	X											
Archival tumour sample[b]	X											
Medical/surgical history	X											
Physical Examination	X	X			X				X			X
ECOG performance status	X	X			X				X			X
Vital signs[c]	X	X			X				X			X
Hematology[bb]	X	X	X	X	X	X	X		X			X
Clinical Chemistry[d]	X	X	X	X	X	X	X		X			X
Coagulation (PT or INR with PTT)[e]	X											
Urinalysis	X											
Pregnancy test (urine or serum)[g]	X	X[g]			X[g]				X			X[g]
Triplicate 12-Lead ECG[f]	X	X			X[f]							X[f]
PK sample collection[p] (Lead-in)		X[p]										
Sparse PK collection[q]		See Table 14			See Table 14							
cfDNA[r] (Plasma sample)	X[r]				X[r]			X[r]	X[r]	X[r]		X[r]
Optional PGx blood sample	X[aa]											
CA-125 (Serum sample)[s]	X[o]	X[o]			X[o]				X[o]			X[o]
Tumour assessments (RECIST v1.1)	X							X	X[x]	X[y]		
CT Scan/MRI of the Chest[t]	X							X[h,j,k]	X[x]	X[y]		
CT Scan/MRI of the Abdomen and Pelvis[t]	X							X[h,j,k]	X[x]	X[y]		
Optional tumour biopsy sample									X[w]	X[w]		X
Concomitant medication review	X	X			X				X			X
Adverse event assessment	X	X	X	X	X	X	X		X			X
Survival status										X	X[n]	

	Screen[a]	AZD1775 and Chemotherapy (Cycle = 21-days)						Restage Every 2 Cycles[k] (±7 days)	End of Study Treatment Visit (30 Day FU)[l] (±2 days)	Follow-Up		FPV[cc]
		Lead-In Safety Cycle 1			Cycles 2 and Beyond					PFS[m] (±7 days)	Survival FU[n] (±7 days)	
Assessments	**Baseline**	**D1**	**D8**	**D15**	**D1 (±2 days)**	**D8 (±2 days)**	**D15 (±2 days)[y]**					
Dispense AZD1775[t] Review/Collect Dosing Diary[v]		X	X	X	X[s,u]	X	X		X			X
Carboplatin administration[u]		X			X							X

a The physical examination, vital signs, medical history (capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded ≤14 days prior to trial entry, ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, urinalysis, and 12-lead ECG should be done ≤7 days prior to initiation of treatment. However, if any of these initial examinations are required at Cycle 1 Day 1 and are obtained within 3 days prior to the initiation of treatment they do not have to be repeated. CA-125 should be done within 14 days prior to the initiation of treatment. Scans to document evaluable disease (i.e., tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

b All patients must provide a tumour sample (archival) for TP53 testing and other exploratory biomarkers by a central laboratory (see Section5.6).

c Vital signs (resting heart rate, blood pressure, temperature, and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice at screening, on Day 1 of each cycle visit, at the end-of-study treatment visit, and the final protocol visit (FPV).

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, lactate dehydrogenase (LDH), phosphorus, and magnesium.

e Coagulation performed at baseline only (PT or INR with PTT) should be done ≤7 days prior to initiation of treatment. Repeat at the beginning of every cycle if patient on Coumadin.

f QTc interval will be calculated using Fridericia's formula (as calculated per institutional standards) obtained from 3 ECGs 2-5 minutes apart at study entry (see Section 3.2). In addition, patients will have triplicate 12-lead ECGs performed 2-5 minutes apart at the beginning of each treatment cycle.

g Pregnancy tests will only be performed in WoCBP (within 3 days of starting study treatment and confirmed prior to start of study treatment on the first day of dosing. WoCBP must have a negative pregnancy test prior to starting each new treatment cycle and at the end-of-treatment visit (see Section 3.8), and at the FPV.

h Patients will be restaged after every 2 cycles (every 6 weeks [±7 days]). Patients with PD or unacceptable toxicity should be discontinued from study treatment; patients with SD or response to therapy will continue treatment.

i CT scans/MRIs of the chest and abdomen and pelvis are required at baseline and every 2 cycles (6 weeks).

j The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment beyond 1 year may have the tumour imaging assessments expanded to every 3 cycles (9 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l The End of Study Treatment Visit will be performed 30 days after the last dose of study treatment or prior to beginning a new therapy. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose (see Section 7.2.7). Tumour assessments will be repeated at the end of study treatment visit if they have not been performed within the past 2 cycles (3 cycles for patients on study for >1 year). The end-of-study treatment visit is **not** required for patients continuing treatment after the FPV.

m Post follow-up for patients without disease progression at the time of study drug discontinuation should include repeat CT scan(s) and CA-125 (if applicable) until disease progression has been observed. The patient will be followed every 6 weeks (±1 week) from first dose (every 9 weeks for patients on study >1 year) until progression, death or until the study is terminated by the sponsor.

n Patients with documented disease progression will be followed every 3 months (±1 week) for survival status (e.g., date and cause of death). Patients may be contacted during outpatient visits or by telephone. All post study therapies and dates of administration will be collected.

o CA-125 serum sample collected at baseline (within 14 days prior to first study treatment), Day 1 of each cycle, at the end-of-study treatment visit, and the FPV.

p The patients in the lead-in safety and expansion group will have limited plasma PK samples collected pre-and post AZD1775 dosing (see Table 8 and Section 5.3.1). These will not be collected during Part C2. PK samples will be collected at the following time points: Cycle 1 Day 1 - 2 samples will be collected at each of the following time points: before AZD1775 and carboplatin administration (this collection may be done the day before), 2 samples will be collected 30 minutes post AZD1775 dosing, once the carboplatin infusion stops 2 samples will be collected at 1, 2, 4, and 6 hours from AZD1775 dosing and at the end of the first day, ideally around 8 hours from AZD1775 dosing (Table 8). On Cycle 3 Day 3, **AZD1775 and carboplatin PK samples** will be collected before AZD1775 dosing (pre-dose). On Cycle 3 Day 3, another **carboplatin PK sample** will be collected 30 minutes after AZD1775 dosing (Table 9). Refer to the Laboratory Manual.

q Part C2 Safety Expansion: Mandatory sparse PKs will be collected from patients pre-dose, post-dose 1 hour and post-dose 2-4 hours to be collected on Day 3 or Day 10 or Day 17 on Cycle 1, 3, 5 and 7 (see Table 14). Refer to the Laboratory Manual.

r Collection of cfDNA to explore the genetic tumour markers in plasma correlation with markers in tumour samples and to monitor for the emergence of resistance is mandatory at baseline, Cycle 2 Day 1, Day 1 of every odd-numbered cycle (Cycles 3, 5, etc.), end-of-treatment and progression for all patients. Patients continuing treatment after the FPV will have a cfDNA sample collected at the time of disease progression. Plasma samples will be collected in an EDTA tube and processed according to the Laboratory Manual. See Section 5.6 for more information.

s Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1. An additional sample will be collected for tumour response monitoring. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the ULN and within 2 weeks prior to starting treatment (see Section 5.1).

t Five doses of AZD1775 (225 mg PO BID) will be taken in approximate 12 hour intervals over 2.5 days. AZD1775 should be taken approximately 2 hours before or 2 hours after food. See Table 15 for starting doses per arm, as well as dose level reductions for toxicity. Beyond the FPV, patients may continue to receive AZD1775 if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment.

u Carboplatin area under the curve (AUC) 5 mg/mL min IV will be administered according to institutional standards on Day 1 of each 21-day cycle. After the FPV, patients will continue to receive carboplatin area under the curve (AUC) 5 mg/mL min IV until disease progression, or until they no longer derive clinical benefit, or until they fulfil any discontinuation criteria, in the opinion of the Investigator. Drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment.

v Review AZD1775 dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.

w Optional tumour biopsy samples will be requested from patients that discontinue treatment due to disease progression. Informed consent must be obtained from any patient who agrees to provide tissue for this optional testing, including patients that continue after the FPV.

x The end of study treatment visit tumour assessments do not need to be repeated if they were done during the previous 2 cycles (3 cycles if patient was on study for >1 year).

y Follow-up assessments every 6 weeks (±1 week) from first dose (every 9 weeks for patients on study >1 year), until progression, death, or until the study is terminated by the sponsor.

z Patients receiving AZD1775 weekly as part of the safety expansion will need to return to the clinic on Days 1, 8 and 15 for the first 2 cycles. After completing Cycle 2 patients will not be required to return to the clinic on Day 15 of each subsequent cycle unless instructed by the Study Doctor.

aa An optional PGx sample will be collected from consenting patients. If not collected at Cycle 1 Day 1, the PGx sample may be collected at any visit until the last study visit (see Section 3.3).

bb Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment week and reviewed prior to dose administration. If haematologic toxicity occurs, treatment should be held and ANC and platelets should be monitored at least weekly. Patients should be managed as medically indicated. Treatment should not be resumed until recovery to Grade 1 (ANC $\geq$1.5 x 10^9/L or 1,500/µL; platelets $\geq$75,000/µL) (see Section 6.9.1 for further information).

cc The Final Protocol Visit (FPV) applies only to those patients who will be receiving AZD1775 ± chemotherapy after the time of primary data cut-off meant for the preparation of the CSR. The FPV should occur at the next scheduled visit following implementation of the Revised Protocol Edition 10. Beyond the FPV, patients may continue to receive AZD1775 ± chemotherapy if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Drug accountability information must continue to be collected in patient source documents until the patient discontinues the treatment. After the FPV, SAEs, drug accountability, overdoses and pregnancy test results will be collected while the patient is receiving AZD1775 ± chemotherapy. The EOT visit is **not** required for patients continuing treatment after the FPV. SAEs and pregnancy test results will be collected for 30 days following the patient's last dose of AZD1775 ± chemotherapy.

Table 4 Study Plan: Arm D (AZD1775 plus PLD)

	Screen[a]	AZD1775 and Chemotherapy (Cycle = 28-days)					Restage Every 2 Cycles[k] (±7 days)	End of Study Treatment Visit (30 Day FU)[l] (±2 days)	Follow-Up	
		Lead-In Safety Cycle 1			Cycles 2 and Beyond				PFS[m] (±7 days)	Survival FU[n] (±7 days)
Assessments	**Baseline**	**D1**	**D 8**	**D15**	**D1 (±2 days)**	**D8/15 (±2 days)**				
Informed consent	X									
Archival tumour sample[b]	X									
Medical/surgical history	X									
Physical Examination	X	X			X			X		
ECOG performance status	X	X			X			X		
Vital signs[c]	X	X			X			X		
Haematology	X	X	X	X	X	X		X		
Clinical Chemistry[d]	X	X			X			X		
Coagulation (PT or INR with PTT)[e]	X									
Urinalysis	X									
Pregnancy test (urine or serum)[g]	X	X[g]			X[g]			X[g]		
12-Lead ECG[f]	X	X			X[f]					
ECHO or MUGA[p]	X							X[p]		
PK sample collection[q] (Lead-in)		X[q]			X[q]					
cfDNA[r] (Plasma sample)	X						X	X[r]	X[r]	
CA-125 (Serum sample)[o,s]	X[o,s]	X[o,s]			X[o,s]			X[s]		
Tumour assessments (RECIST v1.1)	X						X	X[w]	X[x]	
CT Scan/MRI of the Chest[i]	X						X[h,j,k]	X[x]	X[y]	
CT Scan/MRI of the Abdomen and Pelvis[i]	X						X[h,j,k]	X[x]	X[y]	
Optional tumour biopsy sample[w]								X[w]	X[w]	
Concomitant medication review	X	X			X			X		
Adverse event assessment	X	X	X	X	X	X		X		
Survival status									X	X[n]
Dispense AZD1775[t] Review/Collect Dosing Diary[u]		X	X	X	X[t,u]	X		X		
PLD administration[v]		X			X					

a The physical examination, vital signs, medical history (capture previous treatment medications and response to each prior treatment regimen), concomitant medications (recorded ≤14 days prior to trial entry), ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, urinalysis, and 12-lead triplicate ECG should be done ≤7 days prior to initiation of treatment. However, if any of these initial examinations are required at Cycle 1 Day 1 and are obtained within 3 days prior to the initiation of treatment they do not have to be repeated. If an ECG is done ≤7 days prior to initiation of treatment, then it does not need to be repeated pre-dose on C1D1. CA-125 should be done within 14 days prior to the initiation of treatment. Scans to document evaluable disease (i.e., tumour measurement) should be performed ≤28 days prior to initiation of treatment and should be performed as close to the start of treatment as possible.

b All patients must provide an archival tumour for *TP53* testing and other exploratory biomarkers by a central laboratory(see Section 5.6).

c Vital signs (resting heart rate, blood pressure, temperature and weight) at the Screening visit will include height. After Screening, height will not be measured. Vital signs and weight will be obtained prior to chemotherapy administration according to institutional practice.

d Clinical chemistry will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO_2, ALP, AST, ALT, total bilirubin, total protein, lactate dehydrogenase (LDH), phosphorus, and albumin.

e Coagulation performed at baseline only (PT or INR with PTT) should be done ≤7 days prior to initiation of treatment. Repeat at the beginning of every cycle if patient on Coumadin.

f QTc interval will be calculated using Fridericia's formula (as calculated per institutional standards) obtained from 3 ECGs 2-5 minutes apart at study entry (see Section 3.2). An ECG will be collected at baseline to calculate the QTc interval and confirm eligibility (see Section 3.2). Thereafter, patients will have triplicate ECG on C1D1 (pre-dose, 2 and 4 hr post-dose) and C1D3 (pre-dose, and 2 hours and 4 hours post-dose) and on C3D3 (pre-dose only). In addition, patients will have triplicate 12-lead ECGs performed 2-5 minutes apart at the beginning of each treatment cycle.

g Pregnancy tests will only be performed in WoCBP within 3 days of starting study treatment and confirmed prior to start of study treatment on the first day of dosing. WoCBP must have a negative pregnancy test prior to starting each new treatment cycle and at the end-of-treatment visit (see Section 3.8).

h Patients will be restaged after every 2 cycles (every 8 weeks [±7 days]). Patients with PD or unacceptable toxicity should be discontinued from the study; patients with SD or response to therapy will continue treatment.

i CT scans/MRIs of the chest and abdomen and pelvis are required at baseline and every 2 cycles (8 weeks).

j The same method of assessment and the same technique must be used to characterise each identified and reported lesion at baseline and during subsequent imaging procedures. Patients continuing study treatment beyond 1 year may have the tumour imaging assessments expanded to every 3 cycles (12 weeks [±7 days]).

k Patients without evidence of undue toxicity may continue treatment with study drugs until disease progression occurs as long as they are achieving clinical benefit and desire to continue therapy.

l The End of Study Treatment Visit will be performed 30 days after the last dose of study treatment or prior to the beginning of new therapy. Reassessments for toxicity, disease progression, and survival will be performed 30 days from last treatment dose (see Section 7.2.7). Tumour assessments will be repeated at the end of study treatment visit if they have not been performed within the past 2 cycles (3 cycles for patients on study for >1 year).

m Post follow-up for patients without disease progression at the time of study drug discontinuation should include repeat CT scan(s) and CA-125 (if applicable) until disease progression has been observed. The patient will be followed every 3 months (±1 week) from the date of the last tumour assessment and assessment of response, until death or until the study is terminated by the sponsor.

n Patients with documented disease progression will be followed every 3 months (±1 week) for survival status (e.g., date and cause of death). Patients may be contacted during outpatient visits or by telephone. All post study therapies and dates of administration will be collected.

o CA-125 serum sample collected at baseline (within 14 days prior to first study treatment), Day 1 of each cycle, and end-of-study treatment visit (see Section 5.1).

p Left ventricular cardiac function (e.g. MUGA or echocardiogram [ECHO]) will be assessed at baseline, every 6 cycles or as clinically indicated based on prior anthracycline exposure and clinical symptoms. End of treatment assessment should be done for patients who receive at least 3 cycles of treatment and have not had an ECHO done in the past three months.

q All patients will have limited plasma PK analysis. Samples will be collected as follows:
PK samples for PLD will be collected on Cycle 1, Day 1: 0 (pre-dose), and 0.5, 1, 2, 6, 24 h, 48 h, 7d and 14d after infusion start (Table 10 and Table 11);
Additional **PK samples for PLD** will be collected pre-dose & 1 hour post-dose time point on Day 1 of alternate cycles, starting from Cycle 3 (Cycles 3, 5, 7 etc.) (Table 13). **PK samples for AZD1775** will be collected on Cycle 1 Day 3 (0, 1, 2, 4, 6, and approximately 8 hrs post-dose) (Table 12)
Additional **PK samples for AZD1775** will be collected pre-dose on Day 3 on alternate cycles, starting from Cycle 3 (Cycles 3, 5, 7 etc.) (Table 13).

r Collection of cfDNA to explore the genetic tumour markers in plasma correlation with markers in tumour samples and to monitor for the emergence of resistance is mandatory at baseline, Cycle 2 Day 1, restaging, end-of-treatment and progression for all patients. Plasma samples will be collected in an EDTA tube and processed according to the Laboratory Manual. See Section 5.6 for more information.

s Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1. An additional sample will be collected for tumour response monitoring. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the ULN and within 2 weeks prior to starting treatment (see Section 5.1

t Five doses of AZD1775 (175 mg or 225 mg PO) will be taken within 3 consecutive days (at least 12 hours apart). AZD1775 should be taken approximately 2 hours before or 2 hours after food.

u Review and document AZD1775 dosing compliance with the patient at the beginning of each new treatment cycle when study drug is dispensed.

v PLD 40 mg/m^2 IV will be administered according to institutional standards on Days 1 of each 28 day cycle.

w Optional tumour biopsy samples will be requested from patients at the time of disease progression. Informed consent must be obtained from any patient who agrees to provide tissue for this optional testing.

x The end of study treatment visit tumour assessments do not need to be repeated if they were done during the previous 2 cycles (3 cycles if patient was on study for >1 year).

y Follow-up assessments start 12 weeks from the last date tumour and response assessments were performed.

4.1 Screening period

Procedures will be performed according to the Study Plan. At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study.

4.2 Treatment period

A patient is defined as being on-study if they are continuing to have any study data collected, if the patient is receiving study specific treatment, is being followed for efficacy after discontinuation of protocol specific treatment, or is in follow-up. Descriptions of the procedures for this period are included in the Study Plan.

4.3 Follow-up period

Patients discontinuing study treatment should be scheduled for an end-of-treatment (EOT) visit, approximately 30 days after the study drug is permanently discontinued unless the patient withdraws consent.

Approximately 30 days after the last treatment, patients will return to the clinic for a follow-up assessment. The primary purpose of this visit is to follow-up any AEs ongoing at the time of discontinuation and to assess any new AEs that may have occurred since discontinuation. Any AE, SAE, abnormal laboratory findings that are ongoing at the time of study treatment discontinuation or any new events within 30 days of last study treatment, must be followed up to resolution or until the event becomes stable (or returns to baseline) or is unlikely to resolve further in the opinion of the Investigator.

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 8 weeks (±1 week) from first dose (every 12 weeks for patients on study >1 year), until progression, death, or until study is terminated by sponsor. The exception is for Arm C, which will be followed every 6 weeks (±1 week) from first dose (every 9 weeks for patients on study >1 year), until progression, death, or until the study is terminated by the sponsor.

Patients with documented disease progression will be followed every 3 months for survival status (e.g., date and cause of death) for up to 2 years, death, or until time of final data collection for the progression-free survival analysis, whichever comes first. Patients may be contacted during outpatient visits or by telephone. Information pertaining to the type and dates of administration of post-study therapy will be collected when available.

4.4 Final Protocol Visit and Beyond

The Final Protocol Visit (FPV) requirement applies only to those patients who will be receiving AZD1775 ± chemotherapy after the time of primary data cut-off meant for the preparation of the CSR.

Any patients receiving AZD1775 ± chemotherapy at the time of the primary data cut-off will complete a FPV, which should occur at the next scheduled visit following implementation of the Revised Protocol Edition 10.

Beyond the FPV, patients may continue to receive AZD1775 ± chemotherapy if they are deriving clinical benefit, in the opinion of the Investigator, and not fulfilling any of the discontinuation criteria. Combining AZD1775 with a different anti-cancer therapy is not allowed. Such patients are to be treated as deemed appropriate by the Investigator to ensure continued safety monitoring of the patient while receiving the investigational product. It is recommended to continue observing ongoing patients at the frequency indicated within the study plans as described in Table 2, Table 3 and Table 4. Restrictions regarding concomitant medications (refer to Section 7.7.2) will be followed while the patient is receiving AZD1775 ± chemotherapy. A change in AZD1775 ± chemotherapy dose/schedule should only occur for safety reasons, based on the Investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. After the FPV, SAEs, drug accountability, overdoses and pregnancy test results will be collected while the patient is receiving AZD1775 ± chemotherapy.

If a patient is no longer receiving benefit from AZD1775 ± chemotherapy beyond the FPV in the opinion of the treating physician, then the study drug should be stopped. The Investigator will inform AstraZeneca when a patient discontinues the study drug. Patients must return unused medication when they discontinue treatment. In addition, provided that a patient gives proper informed consent, a plasma isolation (cfDNA) blood sample and optional tumour biopsy for future biomedical research should be obtained at the time of AZD1775 ± chemotherapy discontinuation, if due to disease progression. SAEs and pregnancy test results will be collected for 30 days following the patient's last dose of AZD1775 ± chemotherapy.

5. STUDY ASSESSMENTS

The Sarah Cannon Development Innovations, LLC (Innovations) Trial Master electronic data capture (EDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator must ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement

(CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Efficacy assessments

Tumour assessments

RECIST v1.1 criteria will be used to assess patient response to treatment by PFS, ORR and DCR. The RECIST v1.1 guidelines for measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumour response criteria (CR, PR, SD or progression of disease) are presented in Appendix E.

The same method of assessment of tumour burden used at baseline (CT scans or magnetic resonance imaging [MRI] of the chest and abdomen/pelvis) must be used at each subsequent follow-up assessment (see Table 1 – Table 4). CT scan or MRI of chest and abdomen/pelvis are mandatory and must be repeated every 2 cycles. Patients will be assessed for biochemical response (CA-125) at baseline, Day 1 of each cycle, at the end of study treatment visit and the FPV.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments after start of treatment until objective disease progression as defined by RECIST v1.1 or withdrawal from study. For patients in Arm C, objective tumour assessments will be done every 6 weeks (± 1 week) (2 cycles). For patients in Arms A, B, and D, objective tumour assessments will be done every 8 weeks (±1 week) (2 cycles).

Categorisation of objective tumour response assessment will be based on the RECIST v1.1 criteria of response: CR (complete response), PR (partial response), SD (stable disease) and PD (progression of disease). Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (i.e. smallest sum of longest diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with regard to NTLs or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated, and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit

discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to quality for unequivocal progression status.

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Table 1, Table 2, Table 3, or Table 4. Patients will be assessed by standard criteria. For the purposes of this study, patients should be evaluated for radiographic tumour response every six or eight weeks (±1 week [cycle length dependent]). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and throughout the study. Overall tumour response and progression will be calculated according to RECIST 1.1 (see Appendix E), at the designated time points. Patients continuing study treatment beyond one year may have tumour assessments expanded to be repeated every 9 or 12 weeks instead of every 6 or 8 weeks.

Tumour status will be compared to baseline and confirmation of response will be evaluated by physical examination, anatomic imaging measurement, and performance status.

Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1.

GCIG Criteria

The GCIG has agreed criteria for defining response and progression of ovarian carcinoma which use the serum marker CA-125 and the situations where these criteria should be used. The GCIG recommends that for trials of relapsed ovarian cancer the following definition for response according to CA-125 be used in addition to RECIST v1.1 response criteria (Rustin et al 2011).

Evaluation of Response according to CA-125

Definition of response: A response according to CA-125 has occurred if there is at least a 50% reduction in CA-125 levels from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pre-treatment sample that is at least twice the ULN and within 2 weeks prior to starting treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.
- Variations within the normal range of CA-125 levels will not interfere with the response definition.
- For each patient, it is preferred that the same assay method be used, and the assay must be tested in a quality-control scheme.

– Patients are not evaluable (NE) by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by HAMA [1, 2]) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. If assessing therapy that includes two treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatments modalities. CA-125 cannot distinguish between the effects of the two treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate RRs, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the ULN as eligible and evaluable. In addition, as a separate analysis, those patients who have both a CA-125 response and whose CA-125 level falls to within the normal range, can be classified as CA-125 complete responders. Patients who have a fall of CA-125 to within the normal range but whose initial CA-125 was less than twice the ULN, have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

5.2 Safety assessments

A physical examination, medical history (to capture previous treatment medications and response to each prior treatment regimen), concomitant medications recorded (including ≤14 days prior to trial entry), ECOG PS, complete blood count (CBC) with differential and platelets, clinical chemistry, and 12-lead ECG should be done at screening, at the beginning of each treatment cycle, and at the FPV according to the study plan. Assessments at other time points are indicated in the study plan.

Vital signs (resting heart rate, blood pressure, temperature) and weight will be recorded at screening and at times shown in the study plan.

The following are AZD1775 project related assessments that should be carried out in addition to any standard protocol monitoring such as routine haematology/biochemistry, vital signs, and physical examinations.

5.2.1 Laboratory safety assessments

Blood samples for determination of clinical chemistry, haematology, coagulation, and PK will be performed at the times indicated in the Study Plan (Table 1-Table 4) and PK assessment schedule (Table 6-Table 13).

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

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

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

Table 5 Laboratory Safety Variables

Clinical chemistry	**Haematology**
Serum (S)/Plasma (P)-Albumin	Blood (B)-Haemoglobin
S/P-ALT	B-Leukocyte count
S/P-AST	B-Absolute leukocyte differential count:
S/P-Alkaline phosphatase (ALP)	Neutrophils
S/P-Bilirubin, total	Lymphocytes
S/P-Calcium	Monocytes
S/P-Creatinine	Basophils
S/P-Glucose	Eosinophils
S/P-CO_2	B-Platelet count
S/P-Phosphorus	
S/P-Potassium	**Coagulation**
S/P-Sodium	PT/INR/PTT
S/P-Chloride	
S/P-Total protein	**Serum or Urine Pregnancy Test**
S/P-BUN	**Urinalysis**
S-Lactate dehydrogenase (LDH)	Urine dipstick (pH, specific gravity, blood, protein and glucose)

Pre-menopausal women of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to starting study treatment on Day 1, and a confirmatory test will be performed before treatment at the start of each cycle, at the EOT visit, and the FPV. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For

information on how AEs based on laboratory tests should be recorded and reported, see Section 6.4.

NB. In case a subject shows an AST **or** ALT ≥3xULN **AND** total bilirubin ≥ 2xULN please refer to Appendix C, 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

5.2.2 Physical examination

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

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (Section 6.4). Performance status will be assessed using the ECOG performance status criteria.

5.2.3 ECG

An ECG will be performed at baseline as indicated in the Study Plans. QTc interval will be calculated using Fridericia's formula (per institutional standards) obtained from 3 ECGs performed 2-5 minutes apart at study entry. Thereafter, triplicate 12-lead ECGs will be performed 2-5 minutes apart prior dosing on Day 1 of each treatment cycle and the FPV.

Attention should be paid to any detected increases in QTc interval. Patients who develop a single resting value of QTc interval of >470 msec/female or a shift from baseline of 60 ms should stop taking AZD1775. Dosing can be resumed at a reduced dose (see Section 6.9.2) after return of the resting QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made.

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

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

5.2.4 CA-125 tumour markers

Serum samples will be collected for CA-125 tumour markers on all patients at baseline (within 14 days prior to Cycle 1 Day 1), Day 1 of each cycle, end-of-study treatment visit, and the FPV. The CA-125 analysis will be performed by a local laboratory. Patients with elevated CA-125 levels that can be monitored for response will be assessed according to the GCIG CA-125 response criteria in addition to RECIST v1.1.

5.2.5 Other safety assessments – ECHO or MUGA

For patients participating in the AZD1775 and PLD combination cohort (Arm D), left ventricular cardiac function (ECHO or MUGA) will be assessed at baseline, every 6 cycles or as clinically indicated based on prior anthracycline exposure and clinical symptoms. End of treatment assessment should be done for patients who receive at least 3 cycles of treatment and have not had an ECHO done in the past three months.

5.3 Pharmacokinetics

5.3.1 Collection of samples

All patients in each treatment arm will have PK plasma samples collected according to Table 6–Table 14.

Objectives for the collection of PKs from the lead-in safety and expansion group patients are:

- To characterise the exposure of all analytes in the lead-in safety group to confirm no change in exposure
- To characterise the exposure of all analytes to help determine the cause of any adverse effects observed in the safety cohort
- To assess the drug interaction between AZD1775 plus carboplatin, AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, and AZD1775 plus PLD
- To provide exposure data for AZD1775 which can be included with that from other studies for overall population PK (POPPK) analysis to help understand the PKs of the compound and identify covariates.

During Cycle 1, the PK collection schedule will vary with the treatment arm reflecting the different PKs of the 4 chemotherapeutic agents (see Table 6, Table 7, Table 8, Table 10, Table 11, Table 12, and Table 13). AZD1775 will be given at the start of each cycle, which also defines the start of PK sampling for all analytes. The chemotherapeutic agent infusion will start at the same time AZD1775 is dosed. PK collections for additional cycles are presented in Table 9 and Table 13).

The following information will be recorded each time a PK sample is collected:

- Date and actual time of the PK sample collection
- Date and time of the AZD1775 dose preceding PK collection
- Date and time of the start and end of infusion of the relevant chemotherapeutic agent
- Time and date of last meal

If a patient's dosing regimen is altered, the PK sampling regimen will be appropriately amended to characterise PK profiles. Equivalent PK samples will be required if an additional lead-in safety/expansion cohort is necessary.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.3.2 Determination of drug concentration

Samples for determination of AZD1775 concentrations in plasma will be analysed by Covance on behalf of AstraZeneca using an appropriate bioanalytical method. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites. Full details of the analytical method used will be described in a separate bioanalytical report. The data may be compared by visual inspection to broadly compare exposure to historic monotherapy or other data. The analysis of the PK samples may be expedited if tolerance, safety or other issues are suspected to be related to, or have caused changes in the exposure of AZD1775. From a PK modelling perspective, this data will be used for pooling with PK data collected from other AZD1775 studies in order to perform a population PK analysis using non-linear mixed effects modelling. This data together with safety and pharmacodynamics (PDx) data may be used as part of a future exploratory PK/PDx analysis which will be reported separately from the CSR.

Plasma concentrations of gemcitabine (and 2'Difluoro-2'2'-deoxyuridine), paclitaxel, total platinum, and total doxorubicin will be analysed by Covance on behalf of AstraZeneca and used to compare exposure and PKs to published data. Other drug related components may be measured if required.

Table 6 Lead-in PKs: Arm A gemcitabine and AZD1775 cycle 1

Time (h) post AZD1775 dose	0[a]	0.5[c]	1[c]	2[d]	4[d]	6[d]	end of day[b,d]
Swallow AZD1775	X						
Start gemcitabine IV	X						
Stop gemcitabine IV		X					
PK sample for gemcitabine	X	X	X	X	X		
PK sample for AZD1775	X	X	X	X	X	X	X

h = hour, IV = intravenous infusion

[a] PK sample may be collected the day before dosing.

[b] Collection time optional, collect as late as possible at the end of the first day, ideally around 8 hours post dose.

[c] ±5 minutes.

[d] ±15 minutes.

Table 7 Lead-in PKs: Arm B paclitaxel and AZD1775 cycle 1

Time (h) post AZD1775 dose	0[a]	0.5[c]	1[c]	2[d]	4[d]	6[d]	end of day[b, d]
Swallow AZD1775	X						
Start paclitaxel IV	X						
Stop paclitaxel IV			X				
PK sample for **paclitaxel**[e]	X		X	X	X	X	X
PK sample for **AZD1775**	X	X	X	X	X	X	X

h = hour, IV = intravenous infusion

[a] PK sample may be collected the day before dosing.

[b] Collection time optional, collect as late as possible at the end of the first day, ideally around 8 hours post dose.

[c] ±5 minutes.

[d] ±15 minutes.

[e] Efficacy expansion: PKs will be collected only for paclitaxel according to this schedule. AZD1775 PKs will not be collected according to this schedule but will follow the sparse collections described in Table 14.

Table 8 Lead-in and Expansion PKs: Arm C carboplatin and AZD1775 Cycle 1, Day 1

Time (h) post AZD1775 dose	0[a]	0.5[c]	1[c]	2[d]	4[d]	6[d]	end of day[b d,]
Swallow AZD1775	X						
Start Carboplatin IV	X						
Stop Carboplatin IV		X					
PK sample for total platinum	X	X	X	X	X	X	X
PK sample for AZD1775	X	X	X	X	X	X	X

h = hour, IV = intravenous infusion

[a] PK sample may be collected the day before dosing.

[b] Collection time optional, collect as late as possible at the end of the first day, ideally around 8 hours post dose.

[c] ±5 minutes.

[d] ±15 minutes.

Table 9 Lead-in and Expansion PKs: Arm C Carboplatin and AZD1775, Cycle 3, Day 3

Time (h) pre-dose	Cycle 3[+] Day 3[a, b]	Cycle 3[+ a, b] Day 3[a, b]
	Pre-dose	0.5h
PK samples for AZD1775	X	

[a] Alternate cycles, starting with Cycle 3 (e.g. Cycles 3, 5, 7 etc.)
[b] ±15 minutes.

Table 10 Lead-in PKs: Arm D PLD and AZD1775 (PK for PLD only), Cycle 1, Day 1

Time (h) post infusion	0[a]	0.5[b]	1[b]	2	6
Swallow AZD1775	X				
Start PLD IV	X				
PK sample for PLD	X	X	X	X	X

[a] ±5 minutes.
[b] ±15 minutes.

Table 11 Lead-in PKs: Arm D PLD and AZD1775 (PKs for PLD only), Additional Cycle 1 time points

Time (h) post infusion	Cycle 1 Day 2[a, b]	Cycle 1 Day 3[a, c]	Cycle 1 Day 8[a, d]	Cycle 1 Day 15[a, e]
PK sample for PLD	X	X	X	X

[a] ± 1 hour
[b] 24 hours post-infusion
[c] 48 hours post-infusion
[d] 7 days post-infusion
[e] 14 days post-infusion

Table 12 Lead-in PKs: Arm D PLD and AZD1775 (PKs for AZD1775), Cycle 1 Day 3

Time (h) post	0[a]	1[c]	2[c]	4[d]	6[d]	end of day[b,d]
Swallow AZD1775						
PK sample for AZD1775	X	X	X	X	X	X

[a] PK sample may be collected the day before dosing.
[b] Collection time optional, collect as late as possible at the end of the first day, ideally around 8 hours post dose.
[c] ±5 minutes.
[d] ±15 minutes.

Table 13 Lead-in PKs: Arm D PLD and AZD1775, Alternate cycles starting from Cycle 3

Time (h) pre-dose	Cycle 3+ Day 1[a, b]	Cycle 3+ [a, b] Day 1 [a, b]	Cycle 3+ Day 3[a, b]
	Pre-dose	1h	Pre-dose
PK sample for PLD	X	X	
PK samples for AZD1775			X

[a] Alternate cycles, starting with Cycle 3 (e.g. Cycles 3,5,7 etc.)
[b] ±15 minutes.

Table 14 AZD1775 Sparse PKs for Arm B Efficacy and Arm C2 Safety Expansions

	Cycle 1	Cycle 3	Cycle 5	Cycle 7
Day	**Day 3 or 10 or 17**	**Day 3 or 10 or 17**	**Day 3 or 10 or 17**	**Day 3 or 10 or 17**
AZD1775 Pre-dose	X	X	X	X
AZD1775 1-hour post-dose	X	X	X	X
AZD1775 2-4 hours post-dose	X	X	X	X

Sparse PKs will be collected from all patients in the Arm B efficacy expansion and Arm C2 safety expansion as described below. The collection of these PKs is mandatory.

5.3.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses. Any pharmacokinetic sample remaining after analysis for AZD1775 may be used for exploratory drug-drug interaction (DDI), metabolite, or biomarker analyses. Any results from such analyses may be reported separately from the CSR.

Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Any residual back-up PK samples will be disposed of after the CSR is finalized.

5.4 Pharmacodynamics

5.4.1 Collection of samples

Pharmacodynamic samples will not be taken during the study.

5.5 Pharmacogenetics

5.5.1 Background and rationale

AstraZeneca intends to perform genetic research in the AZD1775 clinical development programme to explore how genetic variations may affect the clinical parameters associated with AZD1775 when combined with chemotherapy. Collection of DNA samples from populations with well-described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies. Future research may suggest other genes or gene categories as candidates for influencing not only response to AZD1775 but also susceptibility to or evolution of ovarian cancer/cancer studies, for which AZD1775 is being evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility to or evolution of ovarian cancer/cancer studies, and drug action.

5.5.2 Pharmacogenetic research objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (e.g., distribution, metabolism, safety, tolerability and efficacy) to AZD1775, as well as susceptibility to disease evolution of ovarian cancer studies and drug action.

The benefits of being able to explore associations between genes and clinical outcomes within the AZD1775 programme are potentially many, and include:

- Analysis of genes that may affect efficacy, safety, and tolerability of AZD1775 when combined with chemotherapy (for example, but not limited to, drug metabolising enzymes and drug transporters).
- Genetic research into genes that may contribute to the development or evolution of, or susceptibility to ovarian cancer/cancer studies.

5.5.3 Genetic Research Plan and Procedures

Selection of genetic research population

Patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any other aspect of the main study.

5.5.4 Discontinuation of patients from this genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

5.5.5 Collection of pharmacogenetic samples

The patient's consent to participate in the pharmacogenetic research components of the study is optional; however, for inclusion in this optional research, patients must provide informed consent.

The blood sample (approximately 10 mL) for genetic research will be obtained from the patients at screening, prior to their first dose of study drug. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE); such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn prior to the first dose of study drug, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetic research during the study.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

5.5.6 Storage, re-use and destruction of pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses

will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication.

For all samples the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the patient has requested disposal/destruction of collected samples not yet analysed.

5.5.7 Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10.

5.5.8 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the originals filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

5.5.9 Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of

a medical emergency, an AstraZeneca Physician or an investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

5.5.10 Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse the samples.

The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

5.5.11 Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

5.6 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Biological samples (e.g., archived tumour samples and cfDNA) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of study drug, clinical outcomes and toxicity.

5.6.1 Circulating free tumour DNA samples

Collection of cfDNA is mandatory at baseline, Cycle 2 Day 1, Day 1 of every odd-numbered cycle (Cycles 3, 5, etc.), end-of-study treatment visit, and at treatment discontinuation due to progression for all patients continuing treatment after the FPV in order to explore the genetic tumour markers in plasma, correlate with markers in tumour samples and to monitor for the emergence of resistance. A baseline plasma sample will be required and subsequent plasma samples collected as described in the Laboratory Manual. This exploratory analysis will be reported separately from the Clinical Study Report (CSR).

5.6.2 Optional tumour biopsies

Optional tumour biopsies during this study will be requested from consenting patients with easily accessible tumours who discontinue treatment due to disease progression including from consenting patients that continue treatment after the FPV.

The tumour biopsy procedure will be performed by core needle, under radiological guidance, or surgically if the site of disease is superficial and palpable or visible. It is mandated that the core biopsy be removed directly from the tumour *in situ* and not cored from a surgically removed tumour. This is to ensure the best possible quality of the biopsy, as the blood/nutrient supply to the tumour is not disrupted prior to biopsy collection.

All tumour biopsies will be collected, stored, and shipped as detailed in the Laboratory Manual.

Any residual samples remaining after analysis will be retained for any potential subsequent retrospective analysis of other response related and/or cancer related biomarkers. It is not intended that data derived from residual sample analysis will be reported in the CSR.

Informed consent must be obtained from any patient who agrees to provide tissue for tumour tissue sample testing.

5.6.3 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

5.6.4 Labelling and shipment of biological samples

The Principal Investigator (PI) ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria) (see Appendix B, 'IATA 6.2 Guidance Document').

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.6.5 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The PI at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

5.6.6 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of some of the biological samples is an optional part of the study, then the subject may continue in the study.

The PI:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Data collection of safety-related study variables

6.1.1 Adverse events of special interest related to AZD1775

There are no AESI for AZD1775 which require additional data collection.

6.2 Definition of adverse events

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

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

6.3 Definitions of serious adverse event

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

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

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol (CSP).

6.4 Recording of adverse events

6.4.1 Time period for collection of adverse events

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

SAEs will be recorded from the time of informed consent and should be reported to the Innovations Safety Department as described in Section 6.5. After the FPV, patients will continue to be monitored for all SAEs, overdoses and pregnancies while receiving AZD1775 ± chemotherapy and for 30 days after the last dose of AZD1775 ± chemotherapy.

Following discontinuation of study treatment, SAEs considered related to study procedures should continue to be collected while patients are followed-up for disease progression.

For each patient who discontinues study treatment for a reason other than disease progression:

- Follow-up information on all ongoing AEs should continue to be collected until the survival follow-up.
- SAEs considered related to study procedures must continue to be collected and reported using standard SAE timelines and process until the end of progression follow-up (i.e., disease progression).
- All deaths must continue to be collected after progression and during the survival follow-up.

6.4.2 Follow-up of unresolved adverse events

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

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s) at the end of the study, if judged necessary.

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

6.4.3 Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Outcome.

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason AE is serious
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to other medication
- Causality assessment in relation to module-specific combination treatments
- Description of AE.

The grading scales found in the revised NCI CTCAE v4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria should be utilized that converts mild, moderate and severe events. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

6.4.4 Causality collection

The Investigator will assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question '*Do you consider that there is a reasonable possibility that the event may have been caused by the IP?*'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the CSP.

6.4.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient, reported in response to an open question from the study personnel or revealed by observation will be collected and recorded in the eCRF.

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

They do not include metastases of the original cancer.

6.4.6 Adverse events based on examinations and tests

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

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value which is unequivocally due to disease progression should not be reported as an AE/SAE.

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

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

6.4.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3 x ULN and total bilirubin $\geq$ 2 x ULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4.8 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing, metastasis to the primary cancer under study should be considered as disease progression and not an AE.

Events which are unequivocally due to disease progression should not be reported as an AE during the study.

Events including diagnosis or signs and symptoms or the abnormal results of an investigation including those leading to hospitalization, which constitute or result from:

(a) 'unequivocal progression' (i.e., representative of overall disease status change, not a single lesion increase) of non-measurable/non-target disease,

or

(b) progression of malignancy under study (target disease)as determined per RECIST 1.1 criteria, should not be reported as AEs or SAEs.

Progression of the malignancy under study, including signs and symptoms of progression, should not be reported as a serious adverse events. Hospitalizations due to signs and symptoms of disease progression should not be reported as serious adverse events.

6.4.9 New cancers

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

6.4.10 Handling of deaths

All deaths that occur during the study or within the follow-up period after the administration of the last dose of study treatment must be reported as follows:

- Death which is unequivocally due to disease progression should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to progression of the disease under study the AE causing the death should be reported by entering into the WBDC system as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Death with an unknown cause should always be reported as an SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.5 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF. For patients continuing after the

FPV (see Section 4.4), SAEs should be determined per protocol and must continue to be reported via the standard pharmacovigilance process (on paper) as stated below. For medical emergencies, see below.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Innovations Safety Department, the AstraZeneca representative within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Innovations representative works with the Investigator to ensure that all the necessary information is provided within 24 hours of investigator awareness.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Innovations representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

SAE information will be sent via secure e-mail connection or via fax. The Innovations Safety Department standard paper SAE Report with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be attached and sent via:

- Secure email (Innovations SAE mailbox: PPD
- or by
- Fax (Innovations safety fax number: PPD

Transmission of the SAE Report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Innovations Safety Department as soon as it is available; these reports should be submitted using the Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the trial reference manual.

The appointed study Medical Monitor works with the Investigator to ensure that all necessary information is provided to the Innovations Safety Department **within 24 hours of Investigator awareness**.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of each responsible IRB. For fatal or life-

threatening AEs for which important or relevant information is missing, active follow-up is undertaken immediately.

AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees (ECs), IRBs and PIs with clinical safety updates/reports according to local requirements.

6.6 Overdose

A dose of AZD1775 in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to AZD1775, and the treatment of overdose should be supportive for the underlying symptoms. To date, there has been one patient who has experienced an overdose with AZD1775 which was associated with adverse events.

Overdoses with non-AZ products used in combination or comparative studies should be managed according to the product label.

Such overdoses should be recorded as follows:

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose of AZD1775 occurs in the course of the study, then the Investigator or other site personnel will inform the Innovations Safety Department immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The Innovations Safety Department representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.5. For other overdoses, reporting must occur within 24 hours.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the Innovations Safety Department. After the FPV, pregnancies will be monitored while patients are on treatment and for 30 days after their final dose of AZD1775 ± chemotherapy.

6.7.1 Maternal exposure

If a subject becomes pregnant during the course of the study, IP should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and

handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Innovations Safety Department representatives within 1 day (i.e., immediately but **no later than 24 hours**) of when he or she becomes aware of it.

- The designated Innovations Safety Department representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.8 Medication error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for the study drug(s) that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error has:

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were identified that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong patient received the medication

- Wrong drug administered to patient

Examples of events that do not require reporting as medication errors in clinical studies:

- Patient accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the Innovations representatives within 1 day, i.e., immediately but no later than 24 hours of when he or she becomes aware of it. The Innovations representative works with the Investigator to ensure that all relevant information is completed within 1 to 5 calendar days if there is an SAE associated with the medication error (see Section 6.3) and within 30 days for all other medication errors.

6.9 Management of IP related toxicities / Dose Reductions

Toxicity will be assessed utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), unless otherwise specified.

The DLT evaluations (see Section 7.2.4) will be used to assess the first 6 patients during Cycle 1. Toxicity occurring in patients beyond Cycle 1 of the Part 1 lead-in safety phase will be graded and the appropriate dose modification or supportive care will be administered to decrease the signs and symptoms thereof according to this section.

Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. A maximum of 2 dose reductions for the AZD1775 and chemotherapy will be allowed. For patients experiencing toxicity while taking AZD1775 over 2.5 days weekly the Investigator should contact the Medical Monitor to discuss alternative dosing frequencies. Patients requiring >2 dose reductions of these drugs will be discontinued from the study drug and chemotherapy.

Brief treatment or visit delays (±7 days) for public holidays or weather conditions do not constitute a protocol violation but should be recorded in the eCRF.

Any patient requiring a toxicity-related dose delay of more than 28 days from the intended day of the next scheduled dose must be discontinued from the study unless there is approval from the MM for the patient to continue.

The AZD1775 and chemotherapy dose level reductions for Arms A, B, C and D are presented in Table 15, Table 16, Table 17, Table 18, and Table 19.

Table 15 AZD1775 Dose Level Reductions for Toxicity

Arm	AZD1775 Starting Dose	AZD1775 -1 level	AZD1775 -2 level
Arm A[a,]	175 mg QD	125 mg QD	100 mg QD
	(2 doses over 2 consecutive days)	(2 doses over 2 consecutive days)	(2 doses over 2 consecutive days)
Arm B[b], C[c], and D[d,e]	225 mg BID (5 doses over 2.5 days)	175 mg BID (5 doses over 2.5 days)	125 mg BID (5 doses over 2.5 days)
Arm C2[f]	225 mg BID (5 doses over 2.5 days) weekly	175 mg BID (5 doses over 2.5 days) weekly	125 mg BID (5 doses over 2.5 days weekly)

[a] AZD1775 once daily for 2 days on Days 1-2, 8-9, and 15-16.
[b] AZD1775 twice daily taken in 12 hour intervals over 2.5 days on Days 1-3, 8-10, and 15-17 of each 28-Day cycle.
[c] AZD1775 twice daily taken in 12 hour intervals over 2.5 days on Days 1-3 of each 21-day cycle.
[d] AZD1775 twice daily taken in 12 hour intervals over 2.5 days on Days 1-3 of each 28-Day cycle
[e] If DLTs are encountered during the lead-in safety portion the SRT may decrease AZD1775 to the next lowest dose level and new -1 and -2 dose levels would be: Arm A (100 mg and 75 mg) and Arms B and C (125 mg and 100 mg) respectively. A formal protocol amendment will be generated should the dose levels change.
[f] AZD1775 twice daily taken in 12-hour intervals over 2.5 days on Days 1-3, 8-10, and 15-17. If the initial dose reduction from 225 mg BID to 175 mg BID is intolerable, patient may further dose reduce to 125 mg BID over 2.5 days weekly or reduce frequency of dosing e.g., Days 1-3 and 8-10 of each 21 day cycle or Days 1-3 only of each 21 day cycle after discussion with Medical Monitor.

Dose level reductions for gemcitabine are shown below.

Table 16 Gemcitabine Dose Level Reductions for Toxicity

	Gemcitabine[a] Starting Dose	Gemcitabine -1 level	Gemcitabine -2 level
	800 mg/m^2	600 mg/m^2	400 mg/m^2

[a] Gemcitabine is administered on Days 1, 8 and 15 of each 28-day cycle.

Dose level reductions for weekly paclitaxel, 28-day schedule are shown in Table 17.

Table 17 Weekly Paclitaxel (28-Day Cycle) Dose Level Reductions for Toxicity

	Paclitaxel[a] Starting Dose	Paclitaxel -1 level	Paclitaxel -2 level
	80 mg/m^2	60 mg/m^2	50 mg/m^2

[a] Paclitaxel is administered on Days 1, 8 and 15 of each 28-day cycle.

Table 18 Carboplatin Dose Level Reductions for Toxicity

	Carboplatin[a] Starting Dose	Carboplatin -1 level	Carboplatin -2 level
Safety and efficacy	AUC 5	AUC 4	AUC 3

[a] Carboplatin is administered on Day 1 of each 21-day cycle.

Table 19 PLD Dose Level Reductions for Toxicity

Arm	PLD[a] Starting Dose	PLD -1 Dose Level
D	40 mg/m^2	30 mg/m^2

[a] PLD is administered on Day 1 of each 28-day cycle.

6.9.1 Dose modifications due to haematologic toxicity

Complete blood counts (CBC) will be obtained for all patients at the beginning of each treatment week and reviewed prior to dose administration. If hematologic toxicity occurs (see Table 20), treatment should be held and ANC and platelets should be monitored at least weekly. Patients should be managed as medically indicated.

Treatment should not be resumed until recovery to Grade 1 (ANC ≥1.5 x 10^9/L or 1,500/µL; platelets ≥75,000/µL).

Table 20 Management of haematological toxicity in patients receiving AZD1775 plus chemotherapy

Blood Neutrophil and Platelet Counts and AZD1775/Chemotherapy Action								
Neutrophil count	**Action AZD1775**	**Action chemo**	**2nd event**	**Action AZD1775**	**Action chemo**	**3rd event**	**Action AZD1775**	**Action chemo**
Grade 2 <1.5-1.0 x 10^9/L	Hold Resume at same dose	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1
Grade 3 <1.0-0.5 x 10^9/L	Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2

Blood Neutrophil and Platelet Counts and AZD1775/Chemotherapy Action								
Grade 3 <1.0-0.5 x 10^9/L with documented infection and/or fever	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Hold Contact Medical Monitor	Hold Contact Medical Monitor
Grade 4 <0.5 x 10^9/L	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Discontinue and follow for disease progression	Discontinue and follow for disease progression
Grade 4 Febrile neutropenia or Grade 4 Infection with neutropenia	Discontinue and follow for disease progression	Discontinue and follow for disease progression						

Platelet count	Action AZD1775	Action chemo	2nd event	Action AZD1775	Action chemo	3rd event	Action AZD1775	Action chemo
Grade 2 75,000-50,000/µL	Hold Resume at same dose	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-1	Hold Resume at DL-1
Grade 3 50,000-25,000/µL	Hold Resume at DL-1	Hold Resume at same dose		Hold Resume at DL-2	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2
Grade 4 <25,000/µL without any evidence of bleeding	Hold Resume at DL-1	Hold Resume at DL-1		Hold Resume at DL-2	Hold Resume at DL-2		Discontinue and follow for disease progression	Discontinue and follow for disease progression
Thrombocytopenic haemorrhage (gross occult bleeding) associated with platelet count <50,000/µL (≥ Grade 3)	Discontinue	Discontinue						

Please consider using G-CSF in the event of severe neutropenia or febrile neutropenia according to institutional standards.

No more than two dose reductions will be allowed for any patient. Patients requiring further dose reduction due to toxicity must discontinue study treatment. Dose re-escalation is not allowed. If the patient has concurrent neutropenia and thrombocytopenia, please follow the most conservative guidance in Table 20 and discuss with the MM as needed.

If haematologic parameters do not recover within 28 days, the patient should be removed from the study treatment.

6.9.2 Non-haematologic toxicity dose modifications

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

Dose reductions of AZD1775 should be considered if the toxicity is considered to be related to AZD1775 (i.e. in monotherapy studies or in combination studies) if the relationship cannot be wholly attributed to the combination agent (each combination agent should be considered on an individual basis). Dose re-escalation is not permitted.

In general, if a patient experiences a Grade 1/Grade 2 non-haematological toxicity, no dose modification is required (except QTc prolongation; see table below). If a patient experiences a Grade 3 or Grade 4 toxicity which is not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and/or the dose reduced, and supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-haematologic toxicity (during the lead-in safety and efficacy portion after completing Cycle 1) that does not resolve to ≤ Grade 1 within 21 days should be removed from the study treatment, unless approved by the Medical Monitor. However, if the Investigator determines that the non-haematologic toxicity was due to one study drug and not the other, treatment with the remaining study drug may continue as clinically appropriate.

Table 21 AZD1775 dose modifications for QTc interval prolongation

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

Based upon the maximum non-haematologic toxicities experienced during the previous cycle, dose adjustments for subsequent cycles are to be made according to the criteria defined in Table 15-19, unless specified per unique toxicities noted below:

Table 22 Non-Haematologic Toxicity Dose Modification and Management

CTCAE v4.03	**Gemcitabine**	**Paclitaxel**	**Carboplatin**	**PLD**	**AZD1775**
Grade 0 - 2	No dose modification	No dose modification	No dose modification	No dose modification	No dose modification
Grade 3[b,c,d]	Hold[a]	Hold[a]	Hold[a]	Hold[a]	Hold[a]
Grade 4[b]	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction

CTCAE v4.03	Gemcitabine	Paclitaxel	Carboplatin	PLD	AZD1775
Second repeat incidence of Grade 3 or 4 toxicity (except nausea, vomiting, fatigue, malaise, lethargy, anorexia, alopecia)	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment
Hepatic					
Grade 1-2	No dose modification	No dose modification	No dose modification	No dose modification	No dose modification
Grade 3 or 4 (manifested as elevations in ALT, AST, ALP or bilirubin)	Hold until resolves to Grade ≤1 or baseline, then resume gemcitabine with a 1 level dose reduction. If not resolved within 28 days discontinue gemcitabine.	Hold until resolves to Grade ≤1 or baseline, then resume paclitaxel with a 1 level dose reduction. If not resolved within 28 days discontinue paclitaxel.	Hold until resolves to Grade ≤1 or baseline, then resume carboplatin with a 1 level dose reduction. If not resolved within 28 days discontinue carboplatin.	Hold until resolves to Grade ≤1 or baseline, then resume PLD with a 1 level dose reduction. If not resolved within 28 days discontinue PLD.	Hold until resolves to Grade ≤1 or baseline, then resume study drug with a 1 level dose reduction. If not resolved within 28 days discontinue study drug.
Diarrhea or Mucositis					
Grade 3 or 4 (or requiring hospitalization)	Hold[a]	Hold[a]	Hold[a]	Hold[a]	Hold[a]
Renal					

CTCAE v4.03	Gemcitabine	Paclitaxel	Carboplatin	PLD	AZD1775
Grade ≥ 2	Hold[a]	Hold until resolves to Grade ≤1 or baseline, then resume paclitaxel with a 1 level dose reduction. If not resolved within 28 days discontinue paclitaxel or reduce 1 dose level. If AE reoccurs after 1 dose level reduction, reduce a second dose level once AE recovers to Grade ≤1.	Hold until resolves to Grade ≤1 or baseline, then resume carboplatin with a 1 level dose reduction. If not resolved within 28 days discontinue carboplatin.	Hold[a]	Hold[a]
Neurotoxicity					
Grade 1	No dose modification	No dose modification	No dose modification	No dose modification	No dose modification
Grade 2	No dose modification	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction.	Hold until toxicity resolves to Grade ≤1. Resume with 1 dose level reduction.	No dose modification	No dose modification
Grade 3 or 4	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

[a] Hold until toxicity resolves to ≤ Grade 1, and then resumed at the same dose with no modification.
[b] Dose reduction for nausea and vomiting should be made only if Grade 3 or Grade 4 toxicity occurs in spite of maximum anti-emetics.
[c] For a Grade 3 pulmonary embolism, the dose should be held but the subsequent doses do not have to be reduced 1 dose level, at the Investigator's discretion.
[d] Grade 3 electrolyte value(s) (i.e., hypokalaemia), do not require a dose reduction once the electrolyte is ≤ Grade 1.

Table 23 Additional Non-Haematologic Toxicity Dose Modification and Management for PLD (arm D only)

Toxicity	Dose Adjustment
Hand-Foot Syndrome (HFS)	
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities	If no previous Grade 3 or 4 HFS: no dose adjustment. If previous Grade 3 or 4 HFS: delay dose up to 2 weeks, then decrease dose by 25%.
Grade 2: Erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Discontinue PLD if no resolution after 2 weeks. If resolved to Grade 0-1 within 2 weeks: ° And no previous Grade 3 or 4 HFS: continue treatment at previous dose. ° And previous Grade 3 or 4 toxicity: decrease dose by 25%.
Grade 3: Blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing	**Delay dosing up to 2 weeks or until resolved to Grade 0-1,** then decrease dose by 25%. Discontinue PLD if no resolution after 2 weeks.
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization	**Delay dosing up to 2 weeks or until resolved to Grade 0-1,** then decrease dose by 25%. Discontinue PLD if no resolution after 2 weeks.
Stomatitis	
Grade 1: Painless ulcers, erythema, or mild soreness	If no previous Grade 3 or 4 toxicity: no dose adjustment. If previous Grade 3 or 4 toxicity: delay up to 2 weeks then decrease dose by 25%.
Grade 2: Painful erythema, edema, or ulcers, but can eat	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Discontinue PLD if there is no resolution after 2 weeks. If resolved to Grade 0-1 within 2 weeks: -And no previous Grade 3 or 4 stomatitis: resume treatment at previous dose. -And previous Grade 3 or 4 toxicity: decrease dose by 25%.

Toxicity	Dose Adjustment
Grade 3: Painful erythema, edema, or ulcers, and cannot eat	**Delay dosing up to 2 weeks or until resolved to Grade 0-1**. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, discontinue PLD.
Grade 4: Requires parenteral or enteral support	**Delay dosing up to 2 weeks or until resolved to Grade 0-1**. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, discontinue PLD.

6.9.3 Non-haematologic toxicity management guidelines

6.9.3.1 Diarrhoea

Due to frequent reports of diarrhoea with AZD1775 administration, vigorous anti-diarrhoeal treatment loperamide (lmodium) is required at the first onset of diarrhoea according to American Society of Clinical Oncology (ASCO) guidelines. Patients should be instructed to take oral loperamide (Imodium) 4 mg at the first onset of diarrhoea and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide (Imodium) or other prescribed anti-diarrhoeal medications.

If diarrhoea is severe (i.e., requiring IV rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patient with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalized for IV hydration and correction of electrolyte imbalances.

6.9.3.2 Nausea and vomiting

All patients receiving oral AZD1775 are required to receive premedication for preventing nausea and vomiting prior to each AZD1775 dose regardless of the protocol schedule or dose. The regimen described below should be instituted immediately for these symptoms:

- All patients must receive a 5-HT3 antagonist, e.g., ondansetron (Zofran) 8 mg PO BID or granisetron (Kytril) 1 mg PO BID prior to each dose of AZD1775. Additional doses of 5-HT3 antagonist may be used if needed. In addition, dexamethasone 4 mg PO will be given as a minimum with each AZD1775 dose, on the first day of every 3-5 day dosing

period, unless contraindicated or not well tolerated. Dexamethasone may be continued on further days of dosing, potentially at a lower dose. Dexamethasone or the 5-HT3 antagonist may be given by IV, as needed.

- Aprepitant (Emend) and fosaprepitant are not permitted due to known drug-drug interactions.
- Promethazine (Phenergan], prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.
- Patients should be strongly encouraged to maintain liberal oral fluid intake.
- Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

6.9.3.3 Febrile neutropenia

Patients experiencing febrile neutropenia with significant symptoms should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Patients with febrile neutropenia without symptoms should be managed according to standard guidelines.

6.9.3.4 Motor neuropathy or muscle weakness

Any onset of > Grade 2 motor neuropathy or > Grade 2 muscle weakness should be evaluated by an electromyogram to rule out the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP). With a diagnosis of CIDP the patient should be discontinued from study treatment.

6.9.3.5 Dose modifications for infusion reactions

Infusion reactions (e.g. rash, urticaria, erythema, pruritus, bronchospasm, and hypotension) can occur with the agents used in this study. There is increased risk of a reaction with carboplatin, paclitaxel and PLD. Carboplatin and PLD must be discontinued in patients experiencing a Grade 3 or 4 infusion reaction during treatment.

To identify the grade of a reaction, refer to the list below adapted for the General Disorders and Administration Site Conditions section of the NCI CTCAE v4.03:

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, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids indicated for ≤24 hours).

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic mediation 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.

6.10 Study governance and oversight

A Safety Review Team (SRT) will be established by Innovations for this study. Reviewers may include the study PI, MM, Principal Biostatistician, Safety Director, Safety Lead, Clinical Data Analyst, Clinical Project Manager, and Sponsor representatives. The roles and responsibilities of the SRT and the MM are described in the Dose Escalation Plan.

The SRT will review all available safety data on the first 6 evaluable lead-in safety patients completing Cycle 1 DLT evaluation from each Part 1 treatment arm. The SRT will review the frequency and severity of AEs of the 6 lead-in safety patients and will compare to published data for similar regimens administered in this setting. The frequency of additional safety reviews will be determined by the SRT based on the early safety reviews. Accrual will not be halted while the review is being conducted unless 2 patients experience a DLT in a treatment arm. If safety signals arise from this review, the SRT may recommend discontinuation of enrolment to a treatment arm or a change to the dose and/or schedule of AZD1775. If fewer than 2 of the 6 evaluable patients experience a DLT in a treatment arm then enrolment to that arm will continue for evaluation of efficacy.

The MM will monitor the safety of individual patients during the entire AE reporting period (i.e., from the first administration of AZD1775 through 30 days after completion of study treatment). In addition, the MM will conduct the safety review to preserve the integrity of the study. MM duties may include, but not limited to the following:

- Perform periodic reviews of all safety data for individual patients. These listings will include: demographic characteristics, general medical history (including concurrent illnesses), disease history, clinical laboratory data (serum chemistry, haematology), any AEs requiring study drug interruption or discontinuation, and AEs (all grades).
- Perform continued monitoring of Grade 3 and higher adverse events and SAEs on an ongoing basis for all patients.

Please refer to the Dose Escalation Plan for additional details.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply AZD1775 capsules for oral use. The capsules will be supplied in high-density polyethylene (HDPE) bottles, which sufficiently protect the drug from light. The different capsule strengths (see table below) should not be combined in the same bottle at any time. Additional information about the IP may be found in the IB.

Investigational product	Dosage form and strength
AZD1775	25 mg, 50 mg, 75 mg, or 100 mg capsules

7.2 Dose and treatment regimens

7.2.1 AZD1775

AZD1775 will be taken with 8 ounces of water, approximately 2 hours before or 2 hours after food. The administration schedules for AZD1775 and chemotherapy will differ in the arms.

If a patient missed a dose according to schedule, the dose should be taken as soon as possible, but not more than 6 hours after the missed dose was scheduled. If greater than 6 hours, the missed dose should be skipped and the patient should take the next dose when scheduled. If the patient missed the 5th dose of the cycle (single dose taken on Day 3 of dosing), the dose should be taken as soon as possible.

If vomiting occurs after the patient takes the AZD1775, the patient should be instructed not to retake the dose, but to wait until the next scheduled dose of AZD1775. If vomiting persists, the patient should contact the Investigator.

AZD1775 dosing compliance should be reviewed with the patient at the beginning of each new treatment cycle when study drug is dispensed. All patients will be required to complete a Dosing Diary, which must be returned to the clinic for review at each visit. The patient should be instructed to record each date and time the dose(s) were taken on the dosing diary. If a dose is missed, the reason must be noted in the diary. A copy of the Dosing Diary is provided in the study reference materials. In addition, patients should be advised to return any unused AZD1775 in the original bottles, in addition to returning any empty bottles.

All study drugs must be kept in a secure place under appropriate storage conditions. The IP label on the bottle and the IB specifies the appropriate storage.

7.2.2 Chemotherapy

7.2.2.1 Gemcitabine

800 mg/m^2 IV Days 1, 8 and 15 every 28 days

Commercially available gemcitabine 800 mg/m^2 IV will be infused over approximately 30 minutes or according to institutional standards.

Refer to the gemcitabine package insert for additional information.

7.2.2.2 Paclitaxel

80 mg/m^2 IV Days 1, 8 and 15 every 28 days

Commercially available paclitaxel will be administered as a 1-hour IV infusion (± 10 minutes) at a dose of 80 mg/m^2 according to institutional standards.

Patients should be pre-medicated with corticosteroids, diphenhydramine and/or H_2 antagonists according to institutional standards (see Section 7.7).

Refer to the paclitaxel package insert for additional information.

7.2.2.3 Carboplatin

Area Under the Curve (AUC) 5 IV Day 1 every 21 days

Carboplatin, at a dose calculated to produce an AUC of 5 will be administered by intravenous infusion according to institutional standards.

The carboplatin dose will be calculated using the Calvert Formula based on the patient's GFR which is estimated by using the CrCl.

Calvert Formula: Carboplatin dose (mg) = target AUC x (GFR + 25)

The FDA has recommended that physicians consider capping the dose of carboplatin for the desired exposure (AUC) to avoid potential toxicity due to overdosing for all laboratories using the IDMS-derived serum creatinine measurements. Therefore the maximum dose of carboplatin should be based on a CrCl no greater than 125 mL/min for patients with normal renal function. In these, carboplatin can be safely dosed according to the instructions in the drug's labelling.

Refer to US FDA, Center for Drug Evaluation and Research website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm228974.htm for more specific guidelines.

Cockcroft-Gault Formula:

$$\text{CrCl (GFR)} = \frac{[(140 - \text{age}) \times (\text{wt in kg})] \times (0.85 \text{ for female})}{(72 \times \text{serum creatinine [mg/dL]})}$$

Patients may receive prophylactic anti-emetic therapy for moderately emetogenic chemotherapy according to institutional standards, excluding aprepitant (Emend), (see Section 7.7).

Refer to the carboplatin package insert for additional information.

7.2.2.4 Pegylated liposomal doxorubicin (PLD)

Commercially available PLD (40 mg/m^2) will be administered on Day 1 of each 28-day Cycle. PLD should be administered at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion related reactions occur, the rate of infusion can be increased to complete administration over 1 hour. A bolus injection or undiluted solution should not be administered. PLD should not be mixed with any other drug.

Refer to the package insert for additional information.

7.2.3 Lead-in safety and efficacy selection

A lead-in safety and efficacy phase will be implemented to establish safety and tolerability and to thereafter evaluate efficacy.

AZD1775 schedules and paired chemotherapeutic agents are presented below:

Arm A (AZD1775 plus gemcitabine):

AZD1775 (175 mg PO) will be taken once a day on Days 1-2, 8-9 and 15-16. Gemcitabine 800 mg/m^2 will be administered by intravenous infusion according to institutional standards on Days 1, 8, and 15 of each 28 day cycle. AZD1775 should be taken approximately 2 hours before or 2 hours after food.

Arm B (AZD1775 plus weekly paclitaxel):

Five doses of AZD1775 (225 mg PO BID) will be taken in approximate 12 hour intervals over 2.5 days weekly (Days 1-3, 8-10 and 15-17). Weekly paclitaxel 80 mg/m^2 IV will be administered according to institutional standards on Days 1, 8 and 15 of each 28 day cycle. AZD1775 should be taken approximately 2 hours before or 2 hours after food.

Arm C (AZD1775 plus carboplatin):

Five doses of AZD1775 (225 mg PO BID) will be taken in approximate 12 hour intervals over 2.5 days (Days 1-3). AZD1775 should be taken approximately 2 hours before or 2 hours after food. Carboplatin AUC 5 IV will be administered according to institutional standards on Day 1 of each 21 day cycle.

Arm C2 Safety Expansion

Patients will receive carboplatin AUC 5 IV on Day 1 of a 21 day cycle in combination with AZD1775 BID for 2.5 days per dosing week (QW), on Weeks 1 (D1-3), 2 (D8-10) and 3 (D15-17), or on Weeks 1 (D1-3) and 2 (D8-10) (2 weeks on followed by 1 week off).

Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of

12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing may be modified to 2 weeks on followed by 1 week off.

All decisions which include but are not limited to cohort dosing, dose escalation or de-escalation will be reviewed by the Safety Review Team (SRT).

Arm D (AZD1775 plus PLD):

Two dose levels of AZD1775 will be tested with 40 mg/m^2 PLD. The starting dose of AZD1775 of this combination arm will be 175 mg, which will be escalated to 225 mg, if the lower dose is tolerated.

Five doses of AZD1775 (175 mg or 225 mg) will be taken in approximate 12 hour intervals over 2.5 days on week 1 (Days 1, 2 and 3) of each 28-day cycle. PLD will be administered on Day 1 of each cycle.

Alternative dose levels/cohorts and dosing schedules which may be informed by emerging pre-clinical and clinical data, including the tolerability data, may be evaluated before the MTD/RP2 dose is defined. Modified PK assessments would be obtained to harmonize and accommodate the investigation of alternative dose levels and/or schedules.

7.2.3.1 Arms A, B, & C - First 6 patients and Arm D-First 12 patients

An SRT will assess the safety and tolerability of the first 6 patients in each arm by incidence and severity of AEs after a minimum of 1 treatment cycle as determined by NCI CTCAE v4.03 and the occurrence of pre-defined dose-limiting toxicities (DLTs). Patients must complete Cycle 1 safety evaluations, and return to the study centre for Cycle 2 Day 1 evaluations to be considered evaluable for the 6 patient lead-in safety cohort unless a DLT occurs prior to completion of Cycle 1. The responsibilities and general procedures of the SRC are described in Section 6.10.

Lead-in safety patients will be considered non-evaluable (NE) and will be replaced if:

- They are enrolled, but not treated with study drug(s)
- They discontinue from the study prior to completing all safety evaluations without experiencing a DLT during Cycle 1

Non-evaluable patients will not be counted toward the lead-in safety cohort for total DLT evaluation.

Patients may continue on study as long as they are benefiting, have no evidence of disease progression, and do not meet any criteria for discontinuation or withdrawal.

7.2.4 Definition of dose-limiting toxicity (DLT)

Toxicity will be assessed utilizing the NCI CTCAE v4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless otherwise specified.

Dose limiting toxicities thought to be related to the study drug during the lead-in safety phase will be defined as any of the following toxicities not attributable to the disease or disease-related processes under investigation, which occur from the first dose of study treatment up to the last day of Cycle 1 (first 28 days [Arm A, Arm B and Arm D] or first 21 days [Arm C]), and that meets at least 1 of the hematologic or non-hematologic criteria below:

- Grade 4 haematological toxicity present for more than 7 days including:
- Infection with febrile neutropenia
- Grade 3 thrombocytopenia associated with haemorrhage
- Non-haematological toxicity ≥ Grade 3
- Any other toxicity that is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 7 days, or is judged to be a DLT by the Investigator in collaboration with the MM.

A DLT excludes:

- Alopecia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance

If appropriate the DLT observation period can be expanded by up to 2 weeks in case of treatment delay due to study drug-related AEs. A treatment combination will be considered non-tolerated if 2 or more of up to 6 evaluable patients experience a DLT in the lead-in safety cohort. If the initial dose or schedule of the treatment combination is not tolerated, patient enrolment to the treatment combination will be stopped and either the combination will be taken no further or the dose level or schedule of AZD1775 may be adjusted to evaluate safety in a second 6 patient cohort at the next lower dose level or revised schedule. The DLT criterion applies to only the lead-in safety patients during Cycle 1. Lead-in safety patients continuing treatment beyond Cycle 1 will have dose modifications applied according to Section 6.8.

If fewer than 2 out of 6 patients experience a DLT in a treatment arm then enrolment may continue for evaluation of efficacy.

7.2.4.1 Reporting a DLT

Any DLT occurring in a patient in the lead-in safety cohort during Cycle 1 must be reported to the MM by the Investigator or designee within 24 hours of first knowledge, and to the Innovations Safety Department as an SAE when appropriate (see Section 6.5).

7.2.5 Evaluation of Efficacy

Once the AZD1775 plus carboplatin arm is evaluated as safe and tolerated by the SRT, this arm will continue enrolling until 23 patients have been evaluated for efficacy (i.e., tumour response). At least 5 of the 23 patients must achieve an objective tumour response according to RECIST v1.1 for the treatment arm to be considered as sufficiently efficacious.

The AZD1775 plus paclitaxel arm will enrol approximately 30 additional patients. For decision making, ORR will be considered in addition to the observed safety and tolerability data and the other efficacy endpoints.

If there are tolerability challenges with the delivery of the initial planned treatment in this particular arm, revised dose levels or schedules of AZD1775 and/or the chemotherapy agent may be considered. Such revisions will be documented and communicated in writing to the Investigator and the Institutional Review Board (IRB).

7.2.6 Restaging during treatment

Tumour assessments will be performed at Screening (within 28 days of first dose) as outlined in the Study Plan and then every 2 cycles (6 weeks [±7 days] or 8 weeks [±7 days]) depending upon the treatment arm, for the first 12 months and every 3 cycles (9 weeks or 12 weeks) thereafter until objective disease progression as defined by RECIST v1.1.

Patients will be eligible to continue treatment as long as they are benefiting, have no evidence of disease progression, and do not meet any criteria for discontinuation or withdrawal.

7.2.7 End of study treatment visit

Patients are allowed to continue treatment until disease progression, until the patient is discontinued due to unacceptable toxicity, or until a decision to discontinue treatment by the patient or Investigator. After withdrawal from or completion of protocol treatment, patients must be followed for any new AEs for 30 calendar days after the last dose of study drug or until new therapy.

The end of study treatment visit will be performed 30 days from last treatment dose or prior to new therapy. At the end of study treatment visit the patient will be assessed for toxicity, disease progression, and survival according to the Study Plans in Table 1 –Table 4

7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the bottle specifies the appropriate storage.

7.5 Compliance

The administration of all study drugs (including IPs) should be recorded in the appropriate sections of the eCRF.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the subject.

The study personnel at the investigational site will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

7.7 Concomitant and other treatments

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

7.7.1 Permitted concomitant medications

Supportive Medication/Class of drug:	**Usage:**
Anti-emetics (excluding aprepitant [Emend] and fosaprepitant)	Premedication with anti-emetics is mandatory (excluding aprepitant [Emend] and fosaprepitant)
Loperamide (Imodium)	Loperamide (Imodium) is required at the first onset of diarrhoea according to ASCO guidelines (see Section 6.9.3.1).

Medications including but not limited to the following: • Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. denosumab). • Patients requiring therapeutic warfarin or coumadin-derivative anticoagulants will be monitored with INR and Prothrombin Time (PT) as clinically indicated. • Low molecular weight heparin, rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated. • Patients may receive treatment with megestrol acetate when prescribed for appetite stimulation.	Medications may be administered for maintenance of existing conditions prior to study enrolment or for a new condition that develops while on study.
Prophylactic hematopoietic growth factors	Hematopoietic growth factors may be used to treat neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) or Institutional guidelines, but should not be used as a substitute for the appropriate dose reductions/delays as specified in Section 6.8.

7.7.2 Restricted concomitant medications

The following treatments and the medications listed below, as listed in Appendix G, should be used with caution while in this study. Any further questions regarding concomitant treatments should be referred to the MM.

Restricted Medication/Class of drug:	Usage:
In vitro data suggests that AZD1775 may also be a weak reversible inhibitor of CYP2C19.	Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range. Refer to Appendix G for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range
AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* with a maximum measured response between donors of 39.9% to 93.1% (at 10 µM) and 18.6% to 32.5% (at 5 µM) of the positive control omeprazole (50 µM), respectively. Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low.	Be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Restricted Medication/Class of drug:	Usage:
Inhibitors or substrates of P-gp.	*In vitro* studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein (P-gp). Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775 (see Appendix G).
Aminoglycosides	Caution must be exercised with the concomitant use of aminoglycosides in keeping with the treatment guidelines for carboplatin.
Gemfibrozil and Rifampin	Caution must be exercised with the concomitant use of Gemfibrozil (strong CYP2C8 inhibitor) and Rifampin (strong CYP2C8 inducer) for patients receiving paclitaxel in this study.
BCRP substrates with narrow therapeutic index	Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC50 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered, or substituted by an alternative drug.
Metformin	AZD1775 has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

7.7.3 Prohibited concomitant medications

Prohibited Medication/Class of drug:	Additional Information
Anticancer agents other than the study medications	If such agents are required for a patient, then the patient must first be withdrawn from the study treatment.
Monoclonal antibodies against PD-1, PD-L1, and PD-L2, CXCR2 inhibitors, and therapeutic anticancer vaccines	May not be administered through 90 days after the last dose of study drug.

Prohibited Medication/Class of drug:	Additional Information
Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation. Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction becomes available. See Appendix G for a list.	No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by ~60% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance.
Grapefruit, Seville oranges and their products (e.g., juice, marmalade, etc.)	As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking AZD1775.
Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.	Patients should stop using these herbal medications 7 days prior to first dose of AZD1775.
Administration of substances known to prolong ECG QTc	The potential risk of concomitant use of AZD1775 with ondansetron (known to prolong the QTc interval) should be taken into account.

7.7.4 Palliative radiotherapy

Patients may receive palliative radiotherapy during the trial only for local pain control, and only if in the opinion of the treating Investigator the patient does not have progressive disease (PD). The radiation field cannot encompass a TL. Radiation to a TL is considered PD and the patient should be removed from study treatment.

7.7.5 Other concomitant treatment

Medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

A comprehensive description of the statistical analyses and related activities for this study will be documented in a statistical analysis plan (SAP) which will be finalized prior to DBL. Note that data will be presented separately from the two parts of the study.

8.2 Sample size estimate

Sample size calculations for Arm C of the study are based upon testing a primary endpoint of ORR according to RECIST v1.1. In order to test the null hypothesis of an ORR of 10% versus an alternative hypothesis with an ORR of 30%, 23 patients are required in order to have 85% power to test the null hypothesis using a one-sided exact binomial test at the 0.10 significance level. The null hypothesis will be rejected if at least 5 responses are observed from 23 patients.

The Part C2 expansion will enrol approximately 12 patients to assess a weekly AZD1775 dosing regimen in combination with carboplatin in a 3 week cycle. Initially, 6 patients will be enrolled in a 3-weekly AZD1775 dosing cycle; if 1 patient or less experiences a DLT during Cycle 1, then an additional 6 patients will be enrolled for a total of 12 patients. However, if 2 or more of the first 6 patients experience a DLT then the AZD1775 dosing schedule will be shortened to 2 weeks on and 1 week off. .

The AZD1775 plus paclitaxel arm (Arm B) will enrol approximately 30 additional patients. Historical response rates using weekly paclitaxel in platinum-resistant and refractory ovarian cancer are in the region of 20% to 40% (Pignata et al 2015, Lortholary et al 2011, McNeish et al 2014). The following examples give an indication of the level of precision that will be achieved in the paclitaxel treated patients.

If the observed response rate is 30% (9/30), the 2-sided 80% confidence interval (CI) will be (19%, 43%). If the observed response rate is 50% (15/30), the 2-sided 80% CI will be (37%, 63%). For decision making, ORR will be considered in addition to the observed safety and tolerability data and the other efficacy endpoints.

8.3 Definitions of analysis sets

8.3.1 All patients set

The All Patients Set will include all patients who have signed the informed consent form (i.e. screening failures plus patients enrolled). The All Patients Set will be used to describe the patient disposition.

8.3.2 Full analysis set

The Full Analysis Set (FAS) will include all patients who received at least one (non-zero) dose of study treatment. Information using this population will be tabulated by treatment arm unless otherwise indicated. This population will be used for the primary analyses of the efficacy and safety endpoints.

8.3.3 PK analysis set

Pharmacokinetics will be summarised as per the PK analysis set.

The PK analysis set will include all dosed patients who had at least one measurable plasma concentration collected post-dose which was obtained without any protocol deviation, violation, or events thought to significantly affect the PK.

All plasma concentration data for AZD1775, paclitaxel, carboplatin, gemcitabine and PLD, and derived PK parameters will be summarised and presented according to AstraZeneca standards. This will be described in the SAP.

8.3.4 CA-125 analysis set

The CA-125 Analysis Set will consist of all dosed patients with a pre-treatment serum sample showing CA-125 ≥ 2 x ULN within 2 weeks before starting treatment. The CA-125 Analysis Set will be used to evaluate response according to GCIG CA-125 response criteria.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variable(s)

8.4.1.1 Tumour response rate

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST v1.1 (Eisenhauer et al 2009). At each restaging visit the RECIST data for a patient will be assigned a response of CR, PR, SD, or PD depending on the status of the disease compared with baseline and previous assessments (see Appendix D).

The objective response rate (ORR) is defined as the number of the patients with a confirmed best overall response of CR or PR divided by the number of patients in the FAS for whom measureable disease is present at baseline. Similarly, the disease control rate (DCR) is defined as the percentage of FAS patients with a best overall response of CR, PR or SD.

Progression of TLs will be calculated in comparison with what the tumour burden was at a minimum (i.e., smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR, or SD) will be calculated in comparison to the baseline tumour measurements obtained before starting treatment.

If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

For TL measurements, if ≤1/3 of the TL sizes are missing (either NE or not read, or the scan was not done) then a scaling up rule will be applied as follows:

- If ≤1/3 of lesions recorded at baseline are missing, then the results will be scaled up (based on the nadir sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)
- If >1/3 of lesions recorded at baseline are missing, then the TL response will be NE. However, if the sum of non-missing TL diameters would result in PD (i.e., if using a value of 0 for missing lesions the sum of diameters has still increased by >20% or more compared with the smallest sum of diameters on study and has an absolute increase ≥5 mm) PD takes precedence over NE.
- A visit response of CR will not be allowed if any of the TL data are missing.

8.4.1.2 Progression-free survival

Progression-free survival is defined as the time from first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment.

If the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data they will be censored at 0 days unless they die within two visits of baseline.

Progression-free survival will be derived based on scan/assessment dates not visit dates. If RECIST assessments/scans contributing towards a particular visit are performed on different dates then the date of progression will be determined based on the earliest of the dates of the component that triggered the progression. With regard to censoring, a patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

8.4.1.3 Overall survival

Overall survival is defined as the time from the date of first dose until death due to any cause. Any patient not known to have died at the time of the analysis will be censored based on the last recorded date on which the patient was known to be alive.

8.4.1.4 Changes in tumour size

Percent changes in tumour size from baseline will also be determined for patients with measurable disease at baseline and is derived at each visit as the % change in the sum of the diameters of TLs. % change = [(post baseline TL sum – baseline TL sum) / baseline TL sum] *100.

8.4.1.5 Duration of response

Duration of response is defined as the time from the date of first documented response until the date of documented progression or any cause death. In the case where a patient does not progress following response, the DoR censoring time will be the same as the PFS censoring time.

8.4.2 Calculation or derivation of safety variable(s)

8.4.2.1 Exposure to investigational product

The total time on study treatment, as well as total exposure to study treatment and the amount delivered relative to the intended amount will be summarised. The number of patients with pauses and reductions and the dose intensities of AZD1775, gemcitabine, paclitaxel, and carboplatin will also be summarised.

8.4.2.2 Adverse events, laboratory changes, vital signs

Safety profiles will be assessed in terms of AEs and laboratory data, vital signs, and ECG data that will be collected for all patients.

8.4.2.3 Other significant adverse events (OAE)

During the evaluation of the AE data, the MM will review the list of AEs that were not reported as SAEs and other adverse events (OAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Medical Science Director, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

8.4.3 Calculation or derivation of pharmacokinetic variables in plasma

Pharmacokinetic analysis of plasma for AZD1775, gemcitabine, paclitaxel, carboplatin and PLD concentration data will be performed by Covance on behalf of AstraZeneca. Real time PK analysis will be conducted prior to each cohort, as appropriate. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard non-compartmental methods.

Where possible the following PK parameters will be determined using non-compartmental analysis:

- Maximum plasma concentration (C_{max}) obtained directly from the observed concentration versus time data
- Time to maximum plasma concentration (t_{max}) obtained directly from the observed concentration versus time data
- Area under the plasma concentration-time curve from zero to the time of the last measurable concentration (AUC_{0-t}) calculated by linear up/log down trapezoidal summation
- Area under the plasma concentration time curve from zero to 8 or 10 hours ($AUC_{(0-8/10)}$) calculated by linear up/log down trapezoidal summation
- Terminal half-life ($t_{½}$). Visual assessment will be used to identify the terminal linear phase of the concentration-time profile
- $C_{(8/10\ hr)}$, concentration at 8/10 hr time point
- C_{trough}

Additional PK parameters may be determined if deemed appropriate.

8.5 Pharmacokinetics/Pharmacodynamic Analysis

The plasma concentration data for AZD1775 may be analysed using a population PK approach, which may include exploring the influence of covariates on PK, if the data allows. A population PDx approach will be used to investigate the relationship between PK and selected primary, secondary and/or exploratory endpoints, where deemed appropriate. Results may be reported separately from the CSR for the main study. The PK, PDx, demographic, safety and tumour response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-PDx methods. The results of any such analyses will be reported separately from the CSR.

8.6 Methods for statistical analyses

A comprehensive description of the statistical analyses and related activities for this study will be documented in a statistical analysis plan (SAP) which will be finalized prior to DBL.

The study will have a primary cut-off date for the CSR (see Section 9.3). Following the primary analysis data cut-off, no further statistical analysis of the data will be conducted. All safety data collected after the primary analysis and up to (and including) the last of the FPVs will be listed and/or summarised as appropriate.

8.6.1 Lead-in safety and efficacy selection

There will be no formal statistical comparisons made between the four treatment arms.

8.6.2 Lead-in safety dose-limiting toxicities

In the first six evaluable patients of each treatment arm the number of patients experiencing a DLT will be reported, based on DLT observations during the first cycle of treatment. If 2 or more patients experience a DLT within an individual treatment arm then the treatment arm will be considered as not tolerated. Consideration may be given to opening a second cohort of six patients at a reduced dose or different schedule of AZD1775 at the discretion of the Study Review Team (see Section 6.10).

8.6.3 Objective response rate

In each treatment arm deemed tolerated after the initial lead-in safety the ORR (according to RECIST v1.1) will be computed and presented together will the exact 90% CI, using the method of Clopper and Pearson (Clopper and Pearson 1934).

8.6.4 Disease control rate

In each treatment arm deemed tolerated after the initial lead-in safety the DCR will be computed and presented together will the exact 90% CI, using the method of Clopper and Pearson.

8.6.5 CA-125 response rate

In each treatment arm deemed tolerated after the initial lead-in safety the CA-125 RR will be computed according to GCIG criteria and presented together with the exact 90% CI, using the method of Clopper and Pearson.

8.6.6 Safety analysis

The following minimum data summaries will be presented by treatment arm using the Full Analysis Set:

- Treatment-emergent adverse events of any CTCAE grade – summarised by MedDRA preferred term and system organ class and CTCAE grade
- SAEs
- Deaths summarised by primary cause
- Laboratory parameters (haematology and chemistry), vital signs, ECG data and concomitant medications will be summarized appropriately

8.6.7 Changes in target lesion

The absolute and percentage changes in TL tumour size will be summarised using descriptive statistics and presented for each time point by treatment arm.

8.6.8 Demographic and baseline data

Baseline characteristics of the patients, including demography, medical history and disease characteristics will be listed for each patient and summarised by treatment arm.

8.6.9 Exposure

Exposure to all components of study treatment (AZD1775 and chemotherapy), i.e., total amount of study drug received, will be listed and summarised for all patients and by treatment arm. Total exposure, time on study drug, and dose intensity will be summarised, along with the number and percentage of patients with at least one dose interruption and at least one dose reduction. Reason for discontinuation of study treatment will be summarised.

8.6.10 Progression-free survival

Medians with the 90% CIs will be calculated from the Kaplan-Meier analyses. The CIs will be calculated using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Kaplan-Meier curves will be produced to provide a visual description of PFS.

8.6.11 Overall survival

Overall survival will be presented and analysed using equivalent methods to those described for PFS.

8.6.12 Duration of response

Informational summaries and Kaplan Meier plots, without formal statistical comparisons, will be produced.

8.6.13 Exploratory biomarker analysis

The number and proportion of patients having a genetic alteration in each of the following markers at baseline will be presented: *TP53*, *BRCA1* and *BRCA2*. Note that additional markers may be considered and will be summarised if deemed relevant.

The relationship between clinical outcomes and the presence of genetic alterations in each marker will be summarised where appropriate as specified in the SAP.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA REPRESENTATIVE

9.1 Training of study site personnel

Before the first subject is entered into the study, an AstraZeneca or Innovations representative will review and discuss the requirements of the CSP and related documents with the investigational staff and also train them in any study specific procedures and the EDC system(s) utilised.

The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca or Innovations representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (SDV, a comparison of the data in the CRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The PI at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the PI should be in place before any study-related procedures can take place, or subjects are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The study is expected to start in Q4 2014 and to end by Q4 2018.

There will be a data cut-off for preparation of a CSR. Any patients still receiving AZD1775 ± chemotherapy at the time of the primary data cut-off will complete an FPV, which should occur at the next scheduled visit following implementation of the CSP Version 10. Refer to Section 4.4 for further information regarding the FPV.

After this point, patients may continue to receive study drug as long as they are continuing to derive benefit from treatment as judged by the Investigator and do not have disease progression or unmanageable drug-related toxicity. Patients continuing on study drug beyond the FPV (see Section 4.4) will continue to be monitored for all SAEs, overdoses and pregnancies while receiving AZD1775 ± chemotherapy. SAEs and pregnancy test results will be collected for 30 days after the last dose of the investigational products and should be cared for according to local clinical practice. Investigators must report SAEs and pregnancies directly to the AstraZeneca representative in accordance with Section 6.5, and continue to maintain study drug accountability as long as patients are receiving treatment with the study drug.

The Part B efficacy expansion and Part C2 safety expansion will be conducted at selected investigator sites. The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with AZD1775.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by Innovations, according to the Data Management Plan. Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary. Classification coding will be performed by AstraZeneca or Innovations.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by AstraZeneca or delegate

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports from eCRF are produced and reconciled with the Patient Safety database and/or the investigational site.

Data Management of genotype data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research will be reported separately from the CSR for the main study. Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (e.g., IWRS, etc.) will be tested / validated as needed.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An Ethics Committee (EC) or IRB should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The EC/IRB should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any subject into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, ECs, IRBs, and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

10.4 Informed consent

The PI(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Medical Science Director and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised CSP).

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to ECs/IRBs see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's EC/IRB are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC/IRB.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the centre, including SDV. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, (GCP), guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

A'Hern and Gore 1995
A'Hern R, Gore ME. The impact of doxorubicin on survival in advanced ovarian cancer. J of Clin Oncol 1995;13:726–32.

AZD1775 (MK-1775) IB
MK-1775 Investigator's Brochure. Merck Sharp & Dohme Corp. Edition Number 13. Release Date: 05 April 2016.

Bloss et al 1993
Bloss JD, Liao SY, Buller RE, Manetta A, Berman ML, McMeekin S, et al. Extraovarian peritoneal serous papillary carcinonoma: a case-control retrospective comparison to papillary adenocarcinoma of the ovary. Gyn Oncol 1993;50:347-351.

Bozas et al. 2007
Bozas G, Bamias A, Koutsoukou V, Efstathiou E, Gika D, Papadimitriou CA, et al. Biweekly gemcitabine and cisplatin in platinum-resistant/refractory, paclitaxel-pretreated, ovarian and peritonealcarcinoma. Gynecol Oncol 2007;104:580–5.

Brookmeyer and Crowley 1982
Brookmeyer R and Crowley J. A confidence interval for the median survival time. Biometrics, 1982;38:29-41

Clopper and Pearson 1934
Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika 1934; 26: 404-413.

D'Agostino et al 2003
D'Agostino G, Amant F, Berteloot P, Scambia G, Vergote I. Phase II study of gemcitabine in recurrent platinum and paclitaxel-resistant ovarian cancer. Gyn Oncol 2003;86:266-269

Eisenhauer et al 2009
Eishenhauer 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;45:228-247.

Gabizon 2001
Gabizon AA. Stealth liposomes and tumour targeting: one step further in the quest for the magic bullet. Clinical Cancer Research 2001;7:223–5.

Hainaut and Hollstein 2000
Hainaut P, Hollstein M. TP53 and human cancer: the first ten thousand mutations. Adv Cancer Res 2000;77: 81–137.

Hirai et al 2010
Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther. 2010: 9(7):514-22.

Igarashi et al 1991
Igarashi M, Nagata A, Jinno S, Suto K, Okayama H. WEE1+-like gene in human. Nature 1991; 353:80–3.

Janssen-Cilag 2011
Janssen-Cilag P, Ltd. CAELYX product information. http://www.janssen.com.au/Products/Caelyx. Amended 4 January 2011. (Accessed 11 November 2015.)

Kavanagh et al 1995
Kavanagh J, Tresukosol D, Edwards C, Freedman R, Gonzalez de Leon C, Fishman A, et al. Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. J Clin Oncol 1995;13:1584–8.

Kurman and Shih 2010
Kurman RJ and Shih IE. The origin and pathogenesis of epithelial ovarian cancer – a proposed unifying theory. Am J Surg Pathol 2010;34(3):433-443.

Leijen et al 2015
Leijen S, van Geel R, Sonke GS, de Jong D, Rosenberg EH, Marchetti S, et al. Phase II study with Wee1 inhibitor AZD1775 plus carboplatin in patients with p53 mutated ovarian cancer refractory or resistant (<3 months) to standard first line therapy. 2015 ASCO Annual Meeting. Abstract 2507.

Lortholary et al 2011
Lortholary A, Largillier R, Weber B, Gladieff L, Alexandre J, Durando X, Slama B, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomised phase II trial from Groupe d'Investigateurs Nationaux pour I'Etude des Cancers Ovariens (GINECO). Annals of oncology. 2011 May: mdr149.

Markman et al 2002
Markman M, Webster K, Zanotti K, Kulp B, Peterson G, Belinson J. Phase 2 trial of single-agent gemcitabine in platinum-paclitaxel refractory ovarian cancer. Gyn Onc 2002;90:593-596.

Markman et al 2006
Markman M, Blessing, Rubin S, Connor J, Hanjani, Waggoner S. Phase II trial of weekly paclitaxel (80 mg/m2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: A Gynecologic Oncology Group study. Gyn Onc 2006;101:436-440.

McGowan and Russell 1993
McGowan CH, Russell P. Human WEE1 kinase inhibits cell division by phosphorylating p34cdc2 exclusively on Tyr15. EBMO J 1993;12:75–85.

McNeish et al 2014
McNeish IA, Ledermann JA, Webber L, James L, Kaye SB, Hall M, Hall G, Clamp A, et al. A randomised, placebo controlled trial of weekly paclitaxel and saracatinib (AZD0530) in platinum-resistant ovarian, fallopian tube or primary peritoneal cancer. Annals of Oncology. 2014 Oct 1;25(10):1988-95

Medema and Macurek 2012
Medema RH and Macurek L. Checkpoint control and cancer. Oncogene Nature Publishing Group 2012;31:2601-2613.

Naumann and Coleman 2011
Naumann RW and Coleman RL. Management strategies for recurrent platinum-resistant ovarian cancer. Drugs 2011;71(11): 1397-1412.

OCMP 1991
Ovarian Cancer Meta-Analysis Project. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin and cisplatin chemotherapy of ovarian carcinoma. J Clin Oncol 1991;9:1668–74.

Oza et al 2015
Oza AM, Weberpals JI, Provencher DM, Grischke E-M, Hall M, Uyar D, et al. An international, biomarker-directed, randomized, phase II trial of AZD1775 plus paclitaxel and carboplatin (P/C) for the treatment of women with platinum-sensitive, TP53-mutant ovarian cancer. 2015 ASCO Annual Meeting. Abstract 5506.

Ozols et al 1980
Ozols RF, Wilson JK, Weltz MD, Grotzinger KR, Myers CE, Young RC. Inhibition of human ovarian cancer colony formation by adriamycin and its major metabolites. Cancer Research 1980;40:4109–12.

Parker and Piwnica-Worms 1992
Parker LL and Piwnica-Worms H. Inactivation of the P34(Cdc2)-cyclin-B complex by the human WEE1 tyrosine kinase. Science 1992;257:1955–7.

Pignata et al 2015
Pignata S, Lorusso D, Scambia G, Sambatoraro D, Tamberi S, Cinieri S, et al. Pazopanib plus weekly paclitaxel versus weekly paclitaxel alone for platinum alone for platinum-resistant or platinum-refractory advanced ovarian cancer (MITO 11): a randomised, open-label, phase 2 trial. The Lancet Oncology. 2015 May 31; 15(5):561-8.

Pinato et al 2013
Pinato D, Graham J, Gabra H, Sharma R. Evolving concepts in the management of drug resistant ovarian cancer: dose dense chemotherapy and the reversal of clinical platinum resistance. Ca Treat Rev 2013;39:153-160.

Pisano et al 2013
Pisano C, Cecere SC, di Napoli M, Cavaliere C, Tambaro R, Facchini, et al. Clinical trials with pegylated liposomal doxoruvicin in the treatement of ovarian cancer. J Drug Delivery 2013. Article ID 898146. doi:10.1155/2013/898146.

Rustin et al 2011
Rustin GJS, Vergote I, Eisenhauer EA, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST v1.1 and CA-125 agreed by the Gynecological Cancer Intergroup (CGIG). Int J Gynecol Cancer 2011;21: 419-423.

Schneider et al 2000
Schneider C, Wright E, Perucchini D, Haller U, Fink D et al. Primary carcinoma of the fallopian tube: a report of 19 cases with literature review. Eur J Gynecol Oncol 2000;21:578-82.

SEER Research Data 2014
Surveillance, Epidemiology, and End Results (SEER) Program Total U.S., 1969-2002 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.

TCGARN 2011
The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-615.

Vang et al 2009
Vang R, Shih LM, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol. 2009;16(5): 267-282.

Vogelstein et al 2000
Vogelstein, B, Lane D, Levine AJ. Surfing the TP53 network Nature 2000; 408:307-310.

Watanabe et al 1995
Watanabe N, Broome M, Hunter T. Regulation of the human WEE1HuCdk tyrosine 15-kinase during the cell-cycle. EMBO J 1995;14:1878–91.

Waterhouse et al 2001
Waterhouse DN, Tardi PG, Mayer LD, Bally MB. A comparison of liposomal formulations of doxorubicin with drug administered in free form: changing toxicity profiles. Drug Safety 2001;24:903–20.

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see **Definitions** within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see **Definitions** within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met
If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

Potential Hy's Law Criteria met
If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team

The MM contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the MM. This includes deciding which the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the MM) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases
The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the MM contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the MM if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in **Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?**

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the MM if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D6010C00004 study with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

Definition of measurable, non-measurable, target and non-target lesions

Patients with measurable and non-measurable disease at baseline should be included in Part A of the study. Only patients with measurable disease at baseline should be included in Part B of the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Measurable:

A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions**
- Skin lesions assessed by clinical examination***
- Brain metastasis***

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as (TLs) at baseline.

Non-Target lesions:

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

METHODS OF ASSESSMENT

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST assessment is provided below, and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Summary of methods of assessments

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET Scan

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In the D6010C00004 study it is recommended that CT examinations of the chest, abdomen, and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (IV) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method.

Clinical Examination

In the D6010C00004 study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

Chest x-ray

In the D6010C00004 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain x-ray

In the D6010C00004 study plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound

In the D6010C00004 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In the D6010C00004 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

Tumour Markers

In the D6010C00004 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

Cytology and histology

In the D6010C00004 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or SD.

In such circumstances, the cytology is necessary to differentiate between response/SD (an effusion may be a side effect of the treatment) and PD (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D6010C00004 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET Scans

In the D6010C00004 study fluorodeoxyglucose positron-emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

TUMOUR RESPONSE EVALUATION

Schedule of evaluation

Baseline assessments should encompass chest, abdomen and pelvis and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments will be performed every 2 cycles +/- 1 week window interval after start of treatment until objective disease progression as defined by RECIST 1.1 or withdrawal from study. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target Lesions (TA)

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), 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.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, 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 5mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response

Non-Target Lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic Deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown below.

Overall visit response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no NTL*s* at baseline).

CONFIRMATION OF RESPONSE

In the D6010C00004 study, imaging for confirmation of response (CR or PR) should be performed at next scheduled visit (certainly no less than 4 weeks) following the date the criteria for response were first met.

SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT Scans

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for

metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered NE from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All

images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scans

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. 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. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix 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.

For these reasons, CT is the imaging modality of choice.

FDG-PET Scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

PET/CT Scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, 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.

However, this is not recommended because the PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45 (2009) 228-247

Appendix E Definition of Women of Childbearing Potential and Acceptable Contraceptive Methods

DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL

Women of Child Bearing Potential (WoCBP) - Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

Women NOT of Childbearing Potential - Women who are permanently or surgically sterilized or postmenopausal (definitions below):

Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).

- Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (e.g. undergo pregnancy testing etc. as required by the study protocol).
- Women will be considered postmenopausal if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
- Women under 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.
- Women over 50 years of age will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

ACCEPTABLE CONTRACEPTION METHODS

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Nonclinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (e.g. less than 1 percent per year) when used consistently and correctly.

The following methods of highly effective contraception are considered acceptable.

Note that women should have been stable on their chosen method of birth control for a minimum of 2 weeks before entering the trial. Generic names and examples of trade names are given. As trade names may vary, Investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence: abstinence is only acceptable as 'total/true abstinence' when the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of AZD1775 for patients who do not receive paclitaxel, and for at least 6 months after the last dose of paclitaxel treatment for patients on the paclitaxel arm.
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intrauterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intrauterine System (e.g., Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (e.g., Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (e.g. ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill

UNACCEPTABLE CONTRACEPTION METHODS

The following methods are considered not to be highly effective and are therefore not acceptable contraceptive methods in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intrauterine Devices (IUDs)
- Fertility awareness methods (e.g, calendar, ovulation, symptothermal, post-ovulation methods)
- Coitus interruptus

Appendix F Stages of Heart Failure – New York Heart Association Classification

The Stages of Heart Failure – New York Heart Association Classification

Class I (Mild)

No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

Appendix G Disallowed Medications and Medications to be Administered with Caution

Formal drug-drug interaction studies have not yet been performed with AZD1775, therefore, the potential for drug-drug interaction described in this protocol are based on findings from in vitro studies and clinical experience.

In vitro data has shown that AZD1775 is metabolised predominantly by CYP3A4, with an FMO3 and/or FMO5 component. As a result, there is potential for the exposure of AZD1775 to be affected by drugs which inhibit or induce the metabolism of CYP3A4. In the clinic, co-administration of AZD1775 with the moderate CYP3A4 inhibitor, aprepitant, resulted in a 40% increase in the plasma levels of AZD1775. Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 are therefore prohibited for use in the current study, including aprepitant.

In vitro data suggests that AZD1775 may be a weak reversible inhibitor of CYP2C19 (IC_{50} 12 μM). Caution should therefore be exercised when AZD1775 is co-administered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

Based on in vitro studies, AZD1775 has been shown to be a weak reversible inhibitor (IC_{50} 14 μM) and a time-dependent inhibitor of CYP3A4 (K_{inact} 0.061/min, K_i 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8-10 fold increase in the exposure of sensitive CYP3A4 substrates when administered with AZD1775 (250 mg BID for 5 doses). To date, no significant DDI effects have been reported in the clinic that may be related to the TDI finding. However, sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window are prohibited.

AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro (39% increase in activity of positive control). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Transporter studies (in vitro) have shown that AZD1775 is both a substrate and inhibitor (IC_{50} 20 μM) of P-gp. Maximum impact of these finding is likely to occur for drugs administered orally at the same time as AZD1775. Caution should therefore be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775.

Recent in-vitro transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC_{50} 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is

normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

Use of metformin should be used with caution in this study as recent in vitro transporter data have shown AZD1775 is an inhibitor of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K.

Caution should be used when administering drugs that are substrates of these transporters (e.g. cimetidine, acyclovir, fexofenadine) as the clinical relevance of AZD1775 inhibition of the MATE pathway is not known in these compounds.

Herbal preparations/medications can be substrates, inhibitors and inducers, similar to any registered medication. Herbal preparations are therefore not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

In addition, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with AZD1775 may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates, inhibitors (strong and moderate) and inducers, CYP2C19 substrates, P-gp substrates and inhibitors and BCRP substrates are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751.

CYP3A4 Inhibitors

Strong

Boceprevir
Clarithromycin
Cobicistat (GS-9350)
Conivaptan
Danoprevir
Elvitegravir
Fosamprenavir
Grapefruit juice
Idelalisib
Indinavir
Itraconazole
Ketoconazole
LCL161
Lopinavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir
Troleandomycin
Voriconazole

Moderate

ACT-178882
Amprenavir
Aprepitant
Atazanavir
Casopitant
Ciprofloxacin
Crizotinib
Darunavir
Dronedarone
Diltiazem
Erythromycin
FK1706
Fluconazole
Fosamprenavir
Imatinib
Ledipasvir
Lomitapide
Netupitant
Schisandra sphenanthera
Tofisopam
Verapamil
Grapefruit
Seville oranges

Weak

Almorexant
Alprazolam
AMD070
Amiodarone
Amlodipine
Atorvastatin
Azithromycin
Berberine
Bicalutamide
Blueberry juice
Chlorzoxazone
Cilostazol
Cimetidine
Clotrimazole
Cranberry juice
Cyclosporine
Daclatasvir
Delavirdine
Everolimus
Faldaprevir
Fluvoxamine
Fosaprepitant (IV)
Ginkgo
Goldenseal
GSK1292263
GSK2248761
Isoniazid
Ivacaftor
Lacidipine
I Linagliptin
Lomitapide
M100240
Nilotinib
Oral contraceptives
Pazopanib
Peppermint oil
Propiverine
Ranitidine
Ranolazine
Resveratrol
Roxithromycin
Seville orange juice
Simeprevir
Sitaxentan
Suvorexant
Tabimorelin
Tacrolimus
Teriflunomide
Ticagrelor
Tipranavir/ritonavir
Tolvaptan
Zileuton

CYP3A4 Inducers (Strong and Moderate)

Avasimibe
Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Etravirine
Genistein
Lersivirine
Lopinavir
Mitotane
Modafinil
Nafcillin
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Ritonavir
Semagacestat
St John's Wort
Thioridazine
Tipranavir

CYP3A4 Inducers (Weak)

Amprenavir
Aprepitant
Armodafinil
AZD 7325
Bexarotene
Boceprevir
Brivaracetam
Clobazam
Danshen
Dexamethasone
Echinacea
Eslicarbazepine
Garlic
Gingko
Ginseng
Glycyrrhizin
LCL161
Methylprednisolone
Nevirapine
Oritavancin
Oxcarbazepine
PA-824
Pleconaril
Prednisone
Quercetin
Raltegravir
Ritonavir
Rufinamide
Sorafenib
Stribild
Telaprevir
Terbinafine
Ticagrelor
Ticlopidine
Topiramate
Troglitazone
Vemurafenib
Vicriviroc and ritonavir
Vinblastine

CYP3A and CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

ABT-384
Alfentanil
Aprepitant
Alfuzosin
Almorexant
Alpha-Dihydroergocryptine
Amiodarone
Aplaviroc
Aprepitant
Astemizole
Atazanavir
Atorvastatin
Avanafil
Bexarotine
BIRL 355
Bortezomib
Bosutinib
Brecanavir
Brotizolam
Budesonide
Buspirone
Capravirine
Carbamazepine
Casopitant
Cisapride,
Conivaptan
Cyclophosphamide
Cyclosporine
Danoprevir
Darifenacin
Darunavir
Dasatinib
Dihydroergotamine
Disopyramide
Dronedarone
Docetaxol
Dofetilide
Doxorubicin
Ebastine
Eletriptan
Elvitegravir
Eplerenone
Ergotamine
Erlotinib
Etoposide
Everolimus
Felodipine
Fentanyl
Fluticasone
Gefitinib
Halofantrine
Ibrutinib
Ifosfamide
Imatinib
Indinavir
Ironotecan
Ivacaftor
Ixabepilone
L-771,688
Lapatinib
Levomethadyl (LAAm)
Lomitapide
Lopinavir
Lovastatin
Lurasidone
Maraviroc,
Midazolam
Midostaurin
Mosapride
Neratinib
Nilotinib
Nisoldipine
Paclitaxel
Pazopanib
Perospirone
Pimozide
Propafenone
Propofol
Quetiapine
Quinidine
Ranolazine
Ridaforolimus
Romidepsin
Saquinavir
Sildenafil
Simeprevir
Simvastatin
Sirolimus
Tacrolimus
Temsirolimus
Terfenadine
Ticagrelor
Theoophylline
Thioridazine
Thiotepa
Tilidine
Tipranavir
Tolvaptan
Triazolam
Tretinoin
Ulipristal
Vardenafil
Vicriviroc
Voclosporin

CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Diazepam
Gliclazide
Lansoprazole
(R)-Lansoprazole
(S)-Lansoprazole
(S)-Mephenytoin
(R)-Mephobarbital
Omeprazole
(R)-Omeprazole
Pantoprazole
(+)-Pantoprazole
Rabeprazole
Tilidine

CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

P-gp Substrates

Colchicine
Digoxin
Fexofenadine
Indinavir
Paclitaxel
Topotecan
Vincristine

If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

P-gp Inhibitors (Strong)

Cyclosporine
Elacridar
Erythromycin
Itraconazole

Ketoconazole
LY335979Quinidine
Ritonavir
Valspodar
Verapamil

BCRP Substrates

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

SIGNATURE PAGE

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