Sarah Cannon Research Institute

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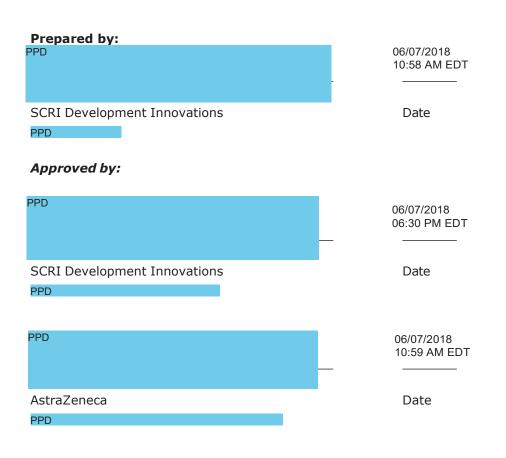
Statistical Analysis Plan

(v5.0)

Protocol Number: D6010C00004 (GYN49)

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Table of Contents

Glossary

AE	Adverse Event
ALT	Alanine Transferase
AST	Aspartate Transaminase
AUC	Area Under The Curve from time zero extrapolated to infinity
$AUC_{(0-t)}$	Area under the concentration-time curve from zero up to a definite time
BLQ	Below the Limit of Quantification
BSA	Body Surface Area
$C_{(8hr)}$	Observed plasma concentration at 8 hours after administration
$C_{(max)}$	Observed maximum plasma concentration after Administration
C_{trough}	Observed trough plasma concentration
CLss/F	Apparent total body clearance after multiple doses following extravascular administration
CA-125	Cancer Antigen-125
CL	Total body clearance after intravascular adminstration
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCIG	Gynaecologic Cancer Intergroup
ICH	International Committee for Harmonisation
ITT	Intent-To-Treat
λz	Terminal Elimination Rate Constant
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities

MR	Metabolite:Parent Ratio
NCI	National Cancer Institute
NE	Not Evaluable
NQ	Not Quantifiable
ORR	Overall Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PP	Per Protocol
PR	Partial Response
R_{ac}	Accumulation Ratio
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Stable Disease
SRT	Safety Review Team
TEAE	Treatment Emergent Adverse Event
t_{max}	Time to reach C_{max}
$t_{\frac{1}{2}\lambda z}$	Half Life associated with terminal slope of a semi-logarithmic concentration-time curve
UNK	Unknown
Vss/F	Apparent volume of distribution at equilibrium after oral administration
WHO	World Health Organisation

Modification History

Unique Identifier for SAP Version	Date of SAP Version	Author	Changes from the Previous Version
1.0	14 July 2015	PPD	
2.0	08 March 2016	PPD	Updates to align with Amendment 4 Updated Statistician Updated Director Biostatistics Updated PPD title to PPD Removed references to randomization Added coagulation CTCAE gradable measures Clarified concomitant medications section Added additional PK information
3.0	27SEP2016	PPD	Revised definitions of analysis sets Updated endpoint definitions and statistical methods Added AstraZeneca statistician approval
4.0	13July2017	PPD	Updated Signature Lines due to new project personnal Updated to align with wording in the

			amended clinical study protocol version 8.0, for example: objectives, study design, sample size justification, PK and timings of safety analysis. Provided further details on timings of the final analysis of the study. Updated definition of tumour response to align with the clinical study protocol and provided further detail on RECIST derivations ie added/expanded BOR, ORR, DCR and PFS sections. Updated the protocol deviations section to important protocol deviations of focus that will impact the interpretation of efficacy and safety Added further details on the analysis of genetic alterations
5.0	07JUN2018	<mark>PPD</mark>	Updated Signature Lines due to new project personnal Added DLT Analysis Set Definition Removed condition to exclude patients with non-

			measurable disease from ORR and DOR calculations
			Added list of TFLs in Appendix 8.1

1   Introduction

As per ICH E9 guidelines (ICH.org),) the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the D6010C00004 (GYN49) study protocol, "A Multicentre Phase II Study of AZD1775 plus Chemotherapy in Patients with Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer", and to include detailed procedures for executing the statistical analysis of the study endpoints and other collected data.

The Statistical Analysis Plan (SAP) is based on the working Clinical Study Protocol (CSP) dated 14 February 2018, Version 9 and electronic Case Report Form (eCRF) version 10.0 dated 16MAR2018. In particular, the SAP is based on the planned analysis specification as written in CSP Section 8. Any further amendments to the protocol or eCRF may necessitate an update to the SAP.

Results of the analyses described in this SAP will be included in the final Clinical Study Report (CSR). Any post-hoc or unplanned analyses performed to provide results for inclusion in publications or other reports but not identified in this prospective SAP will be clearly identified in the relevant documents.

1.1   Objectives

The overall objectives of this study are to assess the efficacy and safety of treatment with AZD1775 in combination with chemotherapy for patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Four separate chemotherapy agents will be considered: paclitaxel, gemcitabine, carboplatin and PLD (Pegylated liposomal doxorubicin). This is an open-label, four-arm lead-in safety and efficacy study.

1.1.1   Primary Objective

The primary objective is 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.

1.1.2   Secondary Objectives

The secondary objectives are to:

- evaluate the duration of response (DOR) of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

- 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

- evaluate the disease control rate (DCR) of AZD1775 in combination with

paclitaxel, gemcitabine, carboplatin, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

- evaluate the Cancer Antigen-125 (CA-125) response of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin, or PLD in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

- to characterize the PK of AZD1775 in combination with paclitaxel, gemcitabine, carboplatin, and PLD

- to assess the drug interaction between AZD1775 plus paclitaxel, AZD1775 plus gemcitabine, AZD1775 plus carboplatin, and AZD1775 plus PLD

1.1.3 Exploratory Objectives

The exploratory objectives of this study are to:

- identify genetic alterations in breast cancer gene 1 and 2 (BRCA1 or 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.

- 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].)

- obtain preliminary estimates of the overall survival (OS) and progression-free survival (PFS) of AZD1775 in combination with gemcitabine, paclitaxel, carboplatin or PLD.

- 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. (This exploratory analysis will be reported separately from the Clinical Study Report [CSR].)

1.2 Study Design

1.2.1 Lead-in safety and efficacy expansion

This is an open-label, four-arm lead-in safety and efficacy study in which AZD1775 will be combined with chemotherapy in four separate arms: AZD1775 plus gemcitabine (Arm A); AZD1775 plus weekly paclitaxel (Arm B); AZD1775 plus carboplatin (Arm C); and AZD1775 plus PLD (Arm D).
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, 2 and 3, or on Weeks 1 and 2 (2 weeks on followed by 1 week off).

1.2.2 Treatment Groups

The AZD1775 schedules and paired chemotherapeutic agents are presented below in Arms A, B, C and D:

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 (per CSP amendment 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). Carboplatin AUC 5 IV will be administered according to institutional standards on Day 1 of each 21 day cycle. AZD1775 should be taken approximately 2 hours before or 2 hours after food.

Arm C2 (AZD1775 plus carboplatin):

Five doses of AZD1775 (225 mg PO 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). Carboplatin AUC 5 IV will be administered according to institutional standards on Day 1 of each 21 day cycle. AZD1775 should be taken approximately 2 hours before or 2 hours after food.

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.

1.3 Statistical Considerations

1.3.1 Sample Size Justification

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.

1.4 Timing of Analysis

1.4.1 Safety Analysis

A review of safety data by the Safety Review Team (SRT) will take place on the the first six evaluable patients completing the Cycle 1 DLT evaluation. Refer to the protocol for further details, including the roles and responsibilities of the SRT.
Note, the SRT will include (but are not limited to):
- Innovations Medical Monitor
- Innovations Safety Lead
- Clinical Project Manager
- AstraZeneca representative

1.4.2 Final Analyses

An administrative interim analysis of ORR will take place after all patients in the paclitaxel arm (Arm B) have completed at least two RECIST follow-up assessments (i.e. 4months). At this time, DoR, PFS and safety/tolerability will also be summarised.

The CSR will report the analysis of all primary and secondary endpoints (including updated ORR and DoR, DCR, PFS, OS, and PK). This analysis will take place approximately 8 months after the last subject has started the first dose of AZD1775+paclitaxel, to allow responding patients to have a DoR greater than 6 months.

Note, updates as addenda to the CSR will be undertaken to summarise information collected in other treatment arms if they are not fully recruited and have had chance to complete 2 cycles of treatment (ie first tumour assessment) at the time the full CSR is reported.

1.5 Responsibilities

The safety and final statistical analyses of the D6010C00004 (GYN49) study will be performed by the SCRI Development Innovations assigned Statistical Programming team under the guidance of the Trial Statistician and according to this SAP.

After completion, final evaluation, and sign-off of the final clinical study report (CSR), all applicable data sets, outputs, programs, and specification documents will be transferred to the Sponsor for archival.

Pharmacokinetics analysis will be performed by Early Clinical Biometrics PK, Covance, Inc., Madison, WI on behalf of AstraZeneca.

1.6 Analysis Software

Statistical analyses will be performed using SAS® version 9.3 or higher. PK analyses will be performed using Phoenix WinNonlin Version 6.3 or higher.

2 Definition of Analysis Sets

The following analysis sets may be used in this study. There will be a review prior to database lock to determine the inclusion/exclusion of subjects in each analysis set. The use of the analysis sets in the statistical analyses is shown in Table 1.

2.1 All Patients Set

The All Patients Set will include all subjects who have signed the informed consent form (i.e. screening failures plus subject's enroled and treated). The All Patients Set will be used to list the patient accountability and patient deaths on study.

2.2 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.

2.3   DLT Analysis Set

The DLT Analysis set will include the first 6 patients in Arms A, B, C, and C2 and the first 12 patients in Arm D. Patients must receive at least 75% of the AZD1775 dose (at least 9 of 12 doses) and complete the minimum safety evaluation requirements during the first 21 days of treatment or who experienced a DLT during the first 21 days of treatment regardless of the amount of drug received.

2.4   CA-125 Analysis Set

The CA-125 Analysis Set will consist of all dosed subjects with a pre-treatment serum sample showing CA-125 $\geq$ 2 x Upper Limit of Normal (ULN) within 2 weeks before starting treatment. The CA-125 Analysis Set will be used to evaluate response according to Gynaecologic Cancer Intergroup (GCIG) CA-125 response criteria (Rustin et al 2011).

2.5   Biomarker Analysis Set

The Biomarker Analysis Set (BMS) for molecular markers analysis in tumor tissue will include all subjects who have consented to and provided a valid tumor tissue sample.

2.6   PK Analysis Set

The formal PK analysis will include all patients who receive at least one dose of the AZD1775/chemotherapy combination treatment and have at least one measurable plasma concentration, obtained without any protocol deviation, violation, or events thought to significantly affect the PK.

Table 1: Use of Analysis Sets in Statistical Analyses

Class of endpoint/variable	Population				
	ALL	**FAS**	**BMS**	**PK**	**DLT**
Accountability	X				
Primary endpoint		X			
Secondary efficacy endpoints*		X			
Disposition		X			
Safety variables		X			
Dose Limiting Toxicities					X
Demographic/baseline variables		X			
Biomarker variables			X		
Pharmacokinetic				X	

* CA-125 response will use the CA-125 analysis set

3   Efficacy Parameters / Endpoints

3.1   Tumor Response

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.

Progression of Target Lesions (TL) 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 non-evaluable (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 not evaluable 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 target lesion response will be NE. However, if the sum of non-missing target lesion 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.

Progression of non-target lesions is outlined below:

Visit Responses	Description
Complete Response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive Disease (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.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
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.
Not Applicable (NA)	Only relevant if there are no NTLs at baseline

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.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

Note, the overall visit response and RECIST outcomes (ie ORR, PFS, etc..) will be programmatically derived using TL, NTL and New lesion information from the site investigator data. See Appendix 2 for how overall visit responses will be assigned. The investigator reported overall visit response at each visit will be listed only.

3.1.1 Evaluation of Best Overall Response

The best overall response per subject will be derived as the best response recorded from the start of treatment until documented objective disease progression as defined by RECIST v1.1.

The following rules will be used to determine the best objective response in each patient, assuming Assessment 1 is Baseline/Pre-treatment tumor assessment, and assessments are performed every 8 weeks (± 1 week), with the exception of the carboplatin arm which are performed every 6 weeks (± 1 week). In the case of stable disease, measurements should have met the stable disease criteria for a minumum interval of 7 weeks (8 weeks minus the 7-day visit window) following the start of treatment for all arms, with the exception of the carboplatin arm with a minimum interval of 5 weeks (6 weeks minus the 7-day visit window).

Assessment 2	Assessment 3	Assessment 4	Best Overall Response
PD	-	-	PD
CR, PR, SD	PD	-	SD
UNK	PD	-	PD
CR, PR or SD	UNK	PD or UNK	SD
SD or UNK	CR, PR or SD	PD	SD
UNK	UNK	PD	PD
PR	SD[1]	PD	SD
PR	CR or PR[2]	PD or UNK	PR
PR	SD	PR[2]	PR
PR	UNK	PR[2]	PR
CR	CR[2]	PD	CR
CR	UNK	CR[2]	CR

(1) Only if the increase in diameter from Assessment 2 to Assessment 3 does not qualify for PD

(2) Assessment occurred at least 4 weeks after initial CR/PR

3.1.2 CA-125 Response

Serum samples will be collected for CA-125 tumour markers on all subjects at baseline (within 14 days prior to Cycle 1 Day 1), Day 1 of each cycle, and at the end-of-study treatment visit.

To be evaluated according to CA-125, subjects must have a baseline sample that is at least twice the ULN and within 2 weeks prior to starting treatment.

For subjects in the CA-125 analysis set, CA-125 response is defined as a 50% reduction in CA-125 levels from the baseline sample. The response must be confirmed and maintained for at least 28 days. For subjects 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.

3.2 Efficacy Endpoints

3.2.1 Primary Efficacy Parameter / Endpoint

Objective Response Rate (ORR) is the proportion of patients with a confirmed best overall response of complete response (CR) or partial response (PR).

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) and then respond will not be included as responders in the ORR (i.e. both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

3.2.2 Secondary Efficacy Parameters / Endpoints

3.2.2.1 Disease Control Rate

Disease Control Rate (DCR) = Proportion of patients with a best overall response of CR, PR, or SD.

The denominator is the number of subjects in the full analysis set (FAS) and includes subjects with best overall response of NE.

3.2.2.2 Duration of Response

Duration of response is defined as the time from the date of first documentation of response (CR or PR, which is subsequentyly confirmed) to the date of documentation of disease progression or death in the absence of disease progression (i.e date of PFS censoring – date of first response +1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed.

In the case where a patient does not progress following response, the duration of response censoring time will be the same as the PFS censoring time.

3.2.2.1 CA-125 Response Rate

The CA-125 Response Rate is defined as the proportion of subjects in the evaluable CA-125 population achieving a CA-125 response (see Section 3.1.2). The denominator is the number of subjects in the CA-125 Analysis Set.

3.2.3 Exploratory Efficacy Parameters/Endpoints

3.2.3.1 Progression Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from date of 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. For example, 18 weeks (i.e. 2 x 8 weeks + 1 week for an early assessment + 1 week for a late assessment = 18 weeks) for all arms with the exception of the carboplatin arm which will be 14 weeks (i.e. 2 x 6 weeks + 1 week for an early assessment + 1 week for a late assessment = 14 weeks).

If the patient has no evaluable visits or does not have baseline data they will be censored at day 1 unless they die within two visits of baseline (16 weeks plus 1 week allowing for a late assessment within the visit window for all arms except carboplatin which will use 12 weeks plus 1 week).

PFS (in days) is calculated as:
(Date of death or documented Progression or Censoring) – (Date of first dose) +1

Equivalently, PFS (in months) is calculated as:
12 X ((Date of death or documented Progression or Censoring) – (Date of first dose) +1)/365.25

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.

3.2.3.2 Overall survival (OS)

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

4   Safety Parameters / Endpoints

4.1   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.

AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.03, whenever possible. The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period.

All AEs (serious and non-serious) will be considered treatment emergent AEs (i.e. TEAEs) except AEs recorded with an onset date prior to the first day of dosing (unless a worsening of the event is recorded after first dosing date, in which case the event will be counted as TEAE). Patients will be followed for Adverse Events for 30 days after their last dose or until new cancer therapy is started.

A serious adverse event is an AE occurring during any study phase (i.e. run-in, treatment, washout, and 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 in the offspring of the treated patient

- Is an important medical event that may jeopardise the patient 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).

Adverse events will be graded using the NCI-CTCAE version 4.03 where applicable, or using the 5-point severity scale:

NCI-CTCAE Grade	Severity scale
1	Mild
2	Moderate
3	Severe
4	Life-Threatening
5	Fatal

In grading the adverse events the worst grade observed is to be reported. Adverse events will be coded using MedDRA, version 17.1 or higher.

4.2   Laboratory Parameters

Laboratory toxicity grading will be derived from the laboratory values using NCI-CTCAE version 4.03, where applicable. Laboratory results collected on the eCRF will be converted to standard units and compared to the JAMA reference ranges (reference) for the purpose of grading. Laboratory parameters that do not have corresponding toxicity grades will be identified as normal; abnormal, high; or abnormal, low, based on standard reference ranges.

5   Pharmacokinetic Parameters / Endpoints

Blood samples will be collected for assessment of AZD1775, gemcitabine, paclitaxel, carboplatin and PLD pharmacokinetics at the times outlined in the clinical study protocol. Note, sparse PK will be collected from all patients in the Arm B efficacy expansion and Arm C2 safety expansion.

The PK Analysis Set will be used in all PK analyses.

Actual blood sampling times post dosing will be used in calculation of PK parameters. If actual sampling time is missing, nominal time may be used with sponsor approval. Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with the amount or concentration in the unit, will be presented as they are received from the analytical laboratory.The PK parameters will be calculated using non-compartmental methods with plasma concentrations of AZD1775 and chemotherapy agents . As data permit, the following parameters will be determined:

AZD1775: C_{max}, dose-normalized C_{max}, C_{8hr}, t_{max}, t_{last}, $AUC_{(0-t)}$, dose-normalized $AUC_{(0-t)}$.

Gemcitabine and metabolite dFdU: C_{max}, t_{max}, $AUC_{(0-t)}$, t_{last}, metabolite:parent ratio [MR $AUC_{(0-t)}$]

Paclitaxel: C_{max}, t_{max}, $AUC_{(0-t)}$, t_{last}, AUC, $t_{\frac{1}{2}\lambda z}$, CL, V_z, and V_{ss}

Carboplatin: C_{max}, t_{max}, $AUC_{(0-t)}$, t_{last}, AUC, $t_{\frac{1}{2}\lambda z}$, CL, V_z, and V_{ss}

PLD: C_{max}, t_{max}, $AUC_{(0-t)}$, t_{last}, AUC, $t_{\frac{1}{2}\lambda z}$, CL, V_z, and V_{ss}

C_{max}, C_{8hr}, t_{max}, and t_{last} will be obtained directly from the plasma concentration-time profiles. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}. Where possible the terminal elimination rate constant (λ_z) will be calculated by log linear regression of the terminal portion of the concentration-time profiles when there are sufficient data, and $t_{\frac{1}{2}\lambda z}$ will be calculated as $\ln2/\lambda_z$. $AUC_{(0-t)}$ will be calculated using the linear up/ log down trapezoidal rule. CL will be determined from the ratio of dose/AUC. Vz will be determined from CL divided by λ_z, as appropriate. V_{ss} will be determined as CL multiplied by MRT

5.1   Treatment of Concentrations Below the Limit of Quantification in PK Analysis

Plasma concentrations that are below the limit of quantification (BLQ) prior to administration of the first dose and up to the first measurable concentration will be set to zero. Any other time points will be set to missing. Any deviation from this will be justified and documented in the PK Analyis Notes.

If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantifiable values will be excluded from the PK analysis unless there is a scientific rationale not to do so, which will be documented in the PK Analysis Notes.

5.2   Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the pharmacokinetic analysis. However, the exclusion of data must have strong justification and will be documented in the PK Analysis Notes and study report.

BLQ values occurring between two quantifiable concentrations may be considered anomalous depending on the route of administration and the characteristics of the drug.

6 Statistical Methods

All analyses will be performed on data entered into the study database to a data cut-off date agreed by the study team in advance of the interim and final analyses (see Section 1.4).

6.1 Definition of Dates / Days / Cycles

6.1.1 Deriving Study Day and Cycle Day

- Day 1 = Date of first Treatment in a patient
- Study Day
  = Study Date – Date of First Treatment + 1; if study date is on or after date of Date of First Treatment or
  = Study Date – Date of First Treatment; if study date is before date of Date of First Treatment
- Cycle Day = Cycle Date – Date of Treatment in current cycle + 1

6.1.2 Assigning Treatment Cycle Number

- Cycle n begins when the patient starts the n-th course of treatment.

- Adverse Events that occur on the same date as the n-th course of infusion will be assigned to cycle n. Laboratory values taken on the same date as the n-th course of infusion will be assigned to cycle n-1, as the samples are usually taken before the treatment.

6.1.3 Baseline

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of investigational product.

6.2 Descriptive Statistics

Binary and ordinal variables will be presented as frequencies and percentages. Continuous variables will be presented with the number of values, mean, standard deviation, median, minimum and maximum values, and number of missing values. Graphical data may also be presented where appropriate.

Unless specified otherwise, all summary tables will be presented by treatment arm and for all subjects.

6.3 Trial Subjects

The subsections in this section include specifications for reporting subject disposition and treatment/study discontinuations. Additionally procedures for reporting protocol deviations are provided.

6.3.1 **Patient Disposition and Accountability**

A primary table will provide the overall summary of the analyses sets using ALL subjects who signed the ICF:

- Subjects Consented
- Subjects Consented to Tumor Sample Biopsies
- Subjects Enroled
- Subjects Treated
- Subjects in the Full analysis set
- Subjects in the CA-125 analysis set
- Subjects in the Biomarker analysis set
- Subjects in the PK analysis set

Number of subjects in each category will be presented. This table will be presented for all subjects and by treatment arm, where appropriate.

A second summary table will provide the overall summary of subjects with treatment ongoing, treatment discontinued and reason off-treatment, together with the number of subjects still on study, discontinued study and reason off-study:

- Subjects with AZD1775 treatment ongoing
- Subjects with Chemotherapy treatment ongoing
- Subjects with AZD1775 treatment discontinuation and reason
- Subjects with Chemotherapy treatment discontinuation and reason
- Subjects still on study
- Subjects with study discontinuation and reason

Subjects in the FAS Population will be classed as 'on-treatment' if they have had one dose of study medication and either of the 'AZD1775 End of Treatment' or 'Chemotherapy End of Treatment' eCRF pages is not completed or date of last dose of AZD1775 or Chemotherapy is after the study cut-off date for the analysis. Any subject with completion of the AZD1775 End of Treatment eCRF page will be classed as off AZD1775 treatment, and the corresponding reason will be recorded on the eCRF. Any subject with completion of the Chemotherapy End of Treatment eCRF pages will be classed as off Chemotherapy treatment, and the corresponding reason will be recorded on the eCRF. The number and percentages of subjects in each category will be presented by treatment arm.

The listing of patient eligibility will include all subjects who signed ICF (i.e. including screening failures). The listing will include the following information: patient number, country/age/sex, date of informed consent, whether meets inclusion/exclusion criteria (yes/no), type of criteria failed, failed criteria number, protocol version enroled, whether the patient enrolled (yes/no), enrolment comment, assigned treatment arm, and planned doses of AZD1775 and chemotherapy.

A second listing giving the patient overview will include the following information: patient number, treatment arm, dosing cohort (if relevant), country/age/sex, date of informed consent, consented to tumor sample biopsies (yes/no), date consented to tumor sample biopsies, date of enrolment, date of first dose, date of last dose, number of cycles received, flag (yes/no) for the Full, CA-125, Biomarker and PK Analysis Set.

6.3.2 Important Protocol Deviations

A table summarizing the important protocol deviations, along with the number and percentage of subjects in each will be presented (based on FAS). Minor protocol deviations are not expected to affect the treatment response. A listing detailing the important protocol deviations for each enrolled subject will be also presented.

The following general categories will be considered important protocol deviations and will be programmatically derived from the eCRF data:

- Patients entered but who did not receive study treatment (Deviation 1).
- Patients who deviate from key entry criteria per the Clinical Study Protocol (CSP) (Deviation 2).
  - Histologic or cytologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer (Inclusion criteria 2).
  - 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 (Inclusion criteria 3).
  - No more than 2-4 prior treatment regimens for Stage III/IV disease defined as investigational, chemotherapy, hormonal, biologic, or targeted therapy (Inclusion criteria 4).
  - At least 1 measurable lesion according to RECIST v1.1 (Inclusion criteria 6).
  - Predicted life expectancy ≥12 weeks (Inclusion criteria 12).
- Baseline RECIST scan > 42 days before start date of treatment (Deviation 3).
- No baseline RECIST 1.1 assessment on or before date of first dose (Deviation 4).
- Received other systemic anti-cancer agents whilst on study treatment (Deviation 5).

Patients who receive the wrong treatment at any time will be included in the full analysis set as described in section 2. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

The important protocol deviations will be listed and summarised by treatment group. Deviation 1 will lead to exclusion from the full analysis set. None of the other deviations will lead to patients being excluded from the analysis sets described in section 2 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK).

In addition to the programmatic determination of the deviations above, other study deviations captured from the CRF module for inclusion/exclusion criteria will be tabulated

and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

6.4 Baseline Data

The following subsections describe the specifications for the baseline characteristics. All baseline data will be tabulated and listed using the full analysis set by treatment arm, unless otherwise stated. No formal statistical testing to compare the treatment groups will be performed on the baseline variables.

Data will be summarised by treatment arm and for all subjects. In all listings the treatment arm the subject was enroled in will be identified.

6.4.1 Demography

The demography table will summarize the following variables by treatment arm:

- Sex (Female, Male)
- Age (in years at enrolment), Age Categories: <65, ≥65
- Race (White/Caucasian, Black or African American, American Indian or Alaskan Native, Asian, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- ECOG Performance Status (0, 1, 2, 3 or 4)

The listing of demographic data will include the following information: patient number, treatment arm, date of enrolment, date of birth, age, gender, race, ethnicity.

6.4.2 Medical History

Data collected on Medical History will be listed, including the MedDRA v17.1 or higher Preferred Term and whether the condition is ongoing.

Note that Medical History will be coded using MedDRA v17.1 or later.

6.4.3 Disease History

The disease history table will summarize the following variables by treatment arm:

- Time from first positive biopsy for the disease to enrolment (weeks)
- Local or Regional recurrence (Yes, No)
- Time from Local/Regional recurrence to enrolment (weeks)
- Distant metastases (Yes, No)
- Time from distant metastases to enrolment (weeks)
- Tumor histology

- Histological Grade
- TNM stage T at initial diagnosis
- TNM stage N at initial diagnosis
- TNM stage M at initial diagnosis
- Stage at initial diagnosis

A second table will summarise the sites of metastatic disease at study entry by treatment arm:

- Presence of metastatic sites (Yes, No)
- Number of sites (0, 1, 2, >2)
- Sites of disease

A detailed listing of the specified disease characteristics will also be provided, including all relevant data (as collected on the eCRF).

6.4.4 Prior anti-cancer therapy

Prior anti-cancer therapy including prior systemic therapy, prior radiotherapy and prior surgery will be summarised for all subjects. The prior systemic therapy table will summarize the following variables:

- Prior systemic therapy for disease (Yes, No)
- Time from end of most recent prior regimen to enrolment (weeks)
- Number of prior regimens (0, 1, ≥2)
- Best overall response to most recent prior regimen (CR, PR, Non CR/Non PD, SD, PD, NE, NA)
- Reason most recent prior regimen ended (completed planned treatment course, progressive disease, toxicity, other)

A listing detailing all prior regimens will also be presented and will include medication, start and end dates, disease setting, best overall response and reason therapy ended. Prior systemic therapy will be coded using WHO Drug.

The prior radiotherapy table will summarize the following variables:

- Prior radiotherapy (Yes, No)
- Number of sites irradiated (0, 1, 2, >2)
- Time from end of most recent prior radiotherapy to enrolment (weeks)

A listing detailing all prior radiotherapy will also be presented and will include site(s) irradiated, total dose (Gy), start and end dates.

The prior surgery table will summarize the following variables:

- Prior surgery (Yes, No)
- Number of prior surgeries (0, 1, 2, >2)
- Time from most recent prior surgery to enrolment (weeks)

A listing detailing all prior surgeries will also be presented and will include type and date of surgery

Prior radiotherapy and surgery will be coded using MedDRA v17.1 or later.

6.4.5 Height, Weight and Vital Signs at baseline

The vital signs table at baseline will summarise the following variables by treatment arm:

- Height (cm)
- Weight (kg)
- Pulse rate (beats/min)
- Systolic BP (mmHg)
- Diastolic BP (mmHg)
- Temperature (degrees Celsius)
- Body surface area (m^2)

6.4.6 EJECTION FRACTION ASSESSMENTS

LVEF will be collected at screening, every 6 cycles and as clinically indicated for patients consenting to the PLD arm only. MUGA and ECHO results will be listed.

6.4.7 Laboratory Parameters at baseline

The laboratory parameters at baseline table will be summarised in the haematology and chemistry shift from baseline tables by treatment arm and include the following variables:
- Baseline CTCAE grade for each relevant parameter (missing, Grade 0, Grade 1, Grade 2, Grade 3, Grade 4)

- Hematology parameters will include: red blood cells, hemoglobin, haematocrit, platelets, white blood cells, granulocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, ANC.

- Chemistry parameters will include: Albumin, SGPT/ALT, SGOT/AST, Alkaline Phosphatase, Calcium, Carbon Dioxide, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Protein, Total Bilirubin, Blood Urea Nitrogen.

- Coagulation parameters will include: Prothrombin Time, Activated Partial Thromboplastin Time, Prothrombin Intl. Normalized Ratio.

- Urinalysis parameters will include: Blood, Protein, Glucose, Ketones, Leukocytes, Specific Gravity, pH.

6.5 Efficacy Analysis

6.5.1 Primary Endpoint

The ORR (according to RECIST v1.1) will be computed in each treatment arm. An exact two-sided 80%/95% CI for the ORR will be computed using the method of Clopper and Pearson. Best overall response will also be summarised.

The Investigator reported tumor response per time point will be listed, including the % change from baseline and % change from nadir in sum of longest diameters of target lesions. Listings of target lesions and non-target/new lesions will also be presented.

A Waterfall-Plot of Best Percent Change in Sum of Longest Diameters from baseline will be generated with each patient's best percentage change in TL tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease and each treatment arm highlighted in a different colour. A reference line at the −30% and +20% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial' response and 'progressive disease'. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked.

Additionally, 'spider' plots will be produced for each treatment group. The line plots will depict each patient's percentage change in TL tumour size as a line over time and the patients best overall response status will be indicated, as well as whether they had a genetic alterations of interest including (but not restricted to) BRCA1, BRCA2 and CCNE1. A reference line at the −30% and +20% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial' response and 'progressive disease'.

6.5.2 Secondary Endpoints

The variables for the secondary endpoints follow: DCR, DoR, CA-125 Reponse and CA-125 Complete Response

6.5.2.1 Disease Control Rate

DCR will be computed in each treatment arm. An exact two-sided 80%/95% confidence interval for the DCR will be computed using the method of Clopper and Pearson.

6.5.2.2 Duration of Response

Duration of Response will be analysed the same as Progression-free Survival, see Section 6.5.3.1 below.

6.5.2.3 CA-125 Response Rate

The number and percentage of subjects who do and do not achieve a CA-125 response and a CA-125 complete response will be presented based upon the CA-125 analysis set.

In each treatment arm deemed tolerated after the initial lead-in safety the CA-125 RR and CA-125 Complete RR will be computed and presented together with the exact 80%/90% CI, using the method of Clopper and Pearson.

The CA-125 response per time point will be listed, including the % change from baseline. A Waterfall-Plot of Best Percent Change in CA-125 level from baseline will be generated with each patient's best percentage change in CA-125 level presented as a separate bar, with the bars ordered from the largest increase to the largest decrease and each treatment arm highlighted in a different colour.

Additionally, 'spider' plots will be produced overall and for each treatment group. This depicts each patient's percentage change in CA-125 as a line over time and the patients CA-125 response status will be indicated. A reference line at the −50% CA-125 level will be added to the plots, which corresponds with the definition of CA-125 response.

6.5.3 Exploratory Endpoints

6.5.3.1 Progression Free Survival

Kaplan-Meier curves will be produced to provide a visual description of the time-to-event variables in each treatment arm.

Medians of PFS (in months) as well as 25th and 75th percentiles with the 80%/95% confidence intervals will be calculated from the Kaplan-Meier analyses. The confidence intervals will be calculated using the Brookmeyer and Crowley method.

In addition, the proportion of patients event-free at 3, 4, 5, 6, 9 and 12 months will also be presented by treatment.
Progression free survival times will be listed for each subject.

6.5.3.2 Overall Survival

Overall Survival will be analysed the same as Progression-free Survival. The proportion of patients surviving at 6, 12, and 18 months will also be presented by treatment.

6.6 Safety Analysis

The current section describes the specifications for the safety parameters analyses.

All safety analyses will be performed using the FAS population, unless otherwise specified. Analyses will be presented by treatment arm, as treated.

6.6.1 **Exposure**

Exposure to AZD1775 and Chemotherapy will be summarised by treatment arm in the following ways:
- Time on study (months)
- Time on AZD1775 treatment (months)
- Time on Chemotherapy (months)
- Total number of initiated cycles
- Cumulative actual dose of AZD1775 (mg)
- Cumulative actual dose of Chemotherapy (mg)
- Relative dose intensity of AZD1775 (%)
- Relative dose intensiy of Chemotherapy (%)

In a second table the number of patients and cycles with dose reduction and dose interruptions with the reasons for such dose modifications, will be summarised by treatment arm. An additional table will be generated to summarise the duration of Chemotherapy treatment infusion per cycle.

Listings of treatment administration, treatment modifications and infusion duration will be provided.

6.6.1.1 Definition of terms related to Treatment Administration

6.6.1.1.1 Infusion Duration

Infusion Duration (Minutes) = End Time of Infusion – Start Time of Infusion

6.6.1.1.2 Dose Calculations

The Carboplatin dose will be calculated by the site using the Calvert Formula based on the patient's glomerular filtration rate (GFR) which is estimated by using the CrCl.

6.6.1.1.2.1 Total exposure

Total (or intended) exposure of study treatment
- Total (or intended) exposure = min(last dose date where dose > 0mg, date of death, date of data cut off) – first dose date + 1

The total exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles started. A cycle corresponds to a period of 28 days (21 days for carboplatin). If a cycle is prolonged due to toxicity, this

should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

6.6.1.1.2.2 Relative Dose Intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation.

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or a censoring event) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or a censoring event) or the actual last day of dosing.

- If a patient received the planned dose at the scheduled time at every cycle, then RDI = 100%.

6.6.2 Adverse Events

AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.03, whenever possible. The AE reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post treatment follow-up period, defined as 30 days after last trial drug administration. AEs leading to permanent discontinuation are those events with action taken regarding study drug is "Drug withdrawn" (as recorded on the AEs CRF page).

All AEs (serious and non-serious) will be considered treatment emergent AEs (i.e. TEAEs) except AEs recorded with an onset date prior to the first day of dosing (unless a worsening of the event is recorded after first dosing date, in which case the event will be counted as TEAE) or with an onset date >30 days after last dose of treatment. Tables will summarise only TEAEs and TESAEs as applicable, but all AEs and SAEs will be listed in the listing documents.

The AE tables will include the number and percentage of subjects with at least one TEAE, by MedDRA primary System Organ Class (SOC) (sorted by decreasing SOC frequencies within the Overall Total (treatment group) column) and by preferred term (PT) (sorted by decreasing PT frequencies within SOC), and by treatment arm, unless otherwise stated. For counts by subject, subjects experiencing the same preferred term more than once will be counted once within each system organ class and once within each preferred term for each treatment group, or overall. Percentages will be calculated as a proportion of the number of subjects in the full analysis set reporting events, and not the number of events.

In the event of a missing TEAE start date, the following conventions will be implemented:

- If the day of the month is missing, the day will be set to the first day of the month. If the day and the month are both missing, then the date will be set to January 1st. If this imputed date is prior to the first administration of the IMP, or if the entire onset date is missing, the date of first administration of treatment will be used to replace the onset date. However, if it is clear from the recorded month or year that

the TEAE started prior to the first study treatment administration, then the day and / or month will be imputed as described above.

- In the event of missing relationship, the TEAE will be considered to be "related".

All Adverse Events

The overall summary of AE table will include the following summaries, displayed by treatment arm and for all subjects:

- TEAEs, Classified as NCI CTCAE Grade
- AZD1775-Related TEAEs, Classified as NCI CTCAE Grade
- Chemotherapy-Related TEAEs, Classified as NCI CTCAE Grade
- Serious TEAEs
- AZD1775-Related Serious TEAEs
- Chemotherapy-Related Serious TEAEs
- Serious TEAEs leading to death
- AZD1775-Related Serious TEAEs leading to death
- Chemotherapy-Related Serious TEAEs leading to death
- TEAEs leading to AZD1775 treatment discontinuation
- TEAEs leading to AZD1775 dose reduction
- TEAEs leading to AZD1775 treatment interruption
- TEAEs leading to Chemotherapy treatment discontinuation
- TEAEs leading to Chemotherapy dose reduction
- TEAEs leading to Chemotherapy treatment interruption

For the Lead-in safety phase, a DLT table will be generated showing the number of subjects experiencing a DLT together with the total number of DLTs by DLT category as specified in the CSP (Section 7.2.4). A listing will also be provided. These outputs will utilize the DLT analysis set.

The following AE tables will also be generated:

- TEAEs, by SOC, PT and Worst NCI CTCAE Grade
- TEAEs by Preferred Term
- AZD1775-Related TEAEs, by SOC, PT and Worst Grade
- AZD1775-Related TEAEs by Preferred Term
- Chemotherapy-Related TEAEs, by SOC, PT and Worst Grade

AZD1775-Related and Chemotherapy-Related adverse events are those events with relationship to study therapy reported by the investigator as 'yes'.

The listings of AEs will also be provided with the relevant information.

Serious Adverse Events

The following summary tables will be produced:

- Serious TEAEs, by SOC and PT
- Serious TEAEs by Preferred Term
- AZD1775-Related Serious TEAEs by Preferred Term

- AZD1775-Related Serious TEAEs by SOC and PT
- Chemotherapy-Related Serious TEAEs by SOC and PT

The listings of SAEs will also be provided with the relevant information.

Deaths

The following summary table will be produced by treatment arm:

- Summary of Deaths

The death data will be ascertained from the dedicated Death CRF form.

6.6.3 Laboratory Data

For hematology and biochemical toxicity, patients with at least one laboratory assessment during the study treatment will be included in the analyses.

Assuming laboratory data on C1D1 were performed before first day administration of study therapy, the evaluations collected prior to (and including) C1D1 will be reported as baseline data. The evaluations collected after (and including) C1D8 will be reported as on-treatment. All laboratory tables will be restricted to the on-study measurements at protocol specified time points (no unscheduled visits). The laboratory listings will however include all measurements (whether on-treatment or not).

The analysis population for each laboratory parameter will be restricted to the treated subjects who had the laboratory test performed.

The worst grade per subject is defined as the highest CTC grade among the on-study evaluations. This applies to hematology and chemistry evaluations which can be graded per NCI-CTCAE.

The following laboratory assessments will be performed according to the schedule of assessments:

- Hematology profile, including red blood cells, hemaglobin, haematocrit, platelets, white blood cells, granulocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, ANC
- Serum chemistry profile, including BUN, creatinine, AST, ALT, total bilirubin, total protein, albumin, alkaline phosphatase, sodium, chloride, potassium, calcium, glucose, LDH, phosphorus, carbon dioxide and magnesium (for carboplatin only).
- Coagulation, including prothrombin time, Activated Partial Thromboplastin Time and Prothrombin Intl. Normalized Ratio
- Urinalysis, including blood, protein, glucose, ketones, leukocytes, specific gravity and pH.

The required laboratory parameters will be summarized by treatment arm. For laboratory assessments that are repeated then the first value will be used in the summary statistics.

Local Laboratory Conversion Factors

Local laboratories will provide data for this study – conversions will be done to convert to SI units and will be compared to the JAMA reference ranges.

Shifts in Laboratory Results from Baseline

The CTC gradable laboratory parameters will be tabulated using the shift from baseline in the worst CTC grade, by treatment arm. Parameters with both hyper and hypo grades, will be separated accordingly.

CTC gradable parameters
- Hematology: shift from baseline in the CTC grade.   The CTC gradable hematology parameters are: White Blood Cells; Haemoglobin; Platelets; Lymphocytes; Neutrophils.
- Serum chemistry: shift from baseline in the CTC grade.   The CTC gradable chemistry parameters are: Total Bilirubin; AST; ALT; Albumin; Alkaline Phosphatase; Calcium; Creatinine; Glucose; Potassium; Sodium; Magnesium (for carboplatin only).
- Coagulation: shift from baseline in the CTC grade. The CTC gradable coagulation parameters are: prothrombin time and Activated Partial Thromboplastin Time.

Non-CTC gradable parameters
- Hematology: Red Blood Cells; Haematocrit; Granulocytes; Basophils; Eosinophils; Monocytes.
- Serum chemistry: Total Protein; Blood Urea Nitrogen; Chloride; Carbon Dioxcide; LDH; Phosphorus.
- Coagulation: Prothrombin Intl. Normalized Ratio.

The listings (hematology and chemistry separately), will include all the laboratory parameters as available in the data base (including laboratory tests codes as "Other") with the corresponding relevant information. All laboratory data will be listed and values outside the normal ranges will be flagged.

Liver Related abnormalities

Liver related abnormalities occurring while on study treatment will be tabulated using the following criteria:
- 3x-, 5x-, 10x-, and 20xULN elevations of AST, ALT, and either ALT or AST
- Any elevations of total bilirubin to >2xULN
- Any elevations of ALP >1.5xULN
- Elevation of AST or ALT (>3xULN) and bilirubin (>1.5xULN, >2xULN), at any time point

6.6.4 **Electrocardiographic Assessments**

Triplicate ECGs are performed at baseline and at the beginning of each treatment cycle. The baseline ECG value per subject will be the last one recorded prior to, or pre-dose on the first dosing date.

In Arm D the ECG will performed at baseline and thereafter, patients will have triplicate ECG on C1D1 (pre-dose, 2 and 4 hr post-dose) and C1D3 (predose, and 2 hours and 4 hours post-dose) and on C3D3.

A table summarizing clinically significant ECG findings will be presented by treatment arm and for all subjects in the FAS. The listings with ECG overall qualitative conclusion per time point and the abnormal ECG findings will be provided.

6.6.5 Vital Signs

Systolic and diastolic blood pressure, pulse rate, temperature, weight and body surface area will be collected at Screening, and then on Day 1 of each treatment cycle prior to chemotherapy administration. The time window for the assessment of vital signs is ±2 days. Measurements will also be taken at the end of treatment visit. Height will only be collected at the screening visit.

Summaries of absolute and change from baseline cacluations will be presented at each protocol timepoint by treatment arm based upon the FAS.

All data collected for vital signs will be listed.

6.6.6 ECOG Performance Status

ECOG PS is collected for all patients at screening, prior to the first dose of study treatment on day 1 of each cycle and at the end of study treatment visit.

ECOG PS will be summarised by treatment arm and for all subjects at each timepoint. Values will be included in the vital signs listing.

6.6.7 Physical Examinations

Physical Examination will take place a screening, day 1 of each cycle, at the end of study treatment and during follow-up visits. Only the date of the exam will be recorded and reported with vital signs.   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.

6.7 Concomitant Medications

World Health Organization (WHO) Drug Dictionary March 2014 will be used for coding medication terms. Medications taken 28 day prior to the first dose of study medication through 30 days following the last dose of study medication will be summarized (frequency and percentage of patients) by ATC level 4 and preferred name. Multiple unique drugs will be counted once per patient. The summary will be ordered by decreasing total frequency of use. Medication start and stop dates will be compared to the date of first dose of study medication to allow medications to be classified as either prior or concomitant.

Medications that start and stop within 28 days prior to the date of first dose of study drug will be classified as "prior". If a medication starts within 28 days before the date of first dose of study drug and stops on or after the date of first dose of study medication, then the medication will be classified as "concomitant". Additionally, medications will be classified as "concomitant" if they have a start date on or after the date of first dose of study drug and overlap with administration of the study drug. If a medication starts

within 30 days after the last dose of study drug, then the medication will be classified as "post-treatment". Partial dates will be handled as follows in the summary tables: Missing day only (assume Day 1 of each respective month), missing month and/or year will be considered missing in the summarization. If partial dates do not allow for accurate categorization of a medication, it will be assumed to be 'concomitant'. A summary table for concomitant medications only will be provided (no prior or post-treatment).

Any concomitant medications taken by a patient that are explicitly disallowed by the protocol will be flagged in the listings.

Individual subject details will be fully listed, and will include the name of the concomitant medication, the start and end date, indication, prophylaxis, prior/concomitant/post-treatment status, and whether the medication is ongoing at the time of analysis.

6.8 Biomarker Analysis

Biomarker data will be provided by an external vendor (Foundation Medicine). This data will be converted into a SAS dataset for generation of outputs for inclusion in the CSR.

The presence or absence of genetic alterations will be summarised by gene. This data will be summarised using counts and percentages and will make use of the Biomarker Analysis Set.

A listing of relevant genetic data as provided by Foundation Medicine will be provided.

6.9 Pharmacokinetic Analysis

PK Plasma concentrations of AZD1775 and Chemotherapy agents will be summarised and listed, as appropriate.

6.9.1 Descriptive Statistics for PK Data Summaries

The following summary statistics will be presented for plasma concentrations at each time point and derived PK parameters: $AUC_{(0-t)}$, AUC, C_{max}, C_{8hr}, and dose normalized C_{max}, and dose normalized $AUC_{(0-t)}$:

- Number of observations
- The geometric mean (gmean) calculated as $\exp[\mu]$, where μ is the sample mean of the data on a logarithmic scale
- Coefficient of variation (CV), calculated as $100*\sqrt{[\exp(s2) - 1]}$, where s is the standard deviation of the data on a log-scale
- Gmean ± standard deviation (SD) (calculated as $\exp[\mu \pm s]$)
- Arithmetic mean calculated using untransformed data
- SD calculated using untransformed data
- Median
- Minimum
- Maximum

The following summary statistics will be presented for MR, CL, V_z, V_{ss}, and $t_{1/2\lambda z}$:

- Number of observations
- Arithmetic mean
- SD
- Median
- Minimum
- Maximum

For t_{max} and t_{last} only: Number of observations, Median, Minimum, and Maximum will be presented in summary tables.

6.9.2 Presentation of Pharmacokinetic Concentration and Parameter Data

All plasma concentration data and PK parameters for AZD1775 and chemotherapy agents will be listed.

Plasma concentrations below the lower limit of quantification (LLOQ) will be reported as not quantifiable (NQ) with the LLOQ defined in the TFLs.

For calculation of descriptive statistics for plasma concentrations:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the gmean, CV, geometric SD, arithmetic mean and SD will be calculated by substituting the limit of quantification (LOQ) for values which are NQ.

- If more than 50%, but not all, of the concentrations are NQ, the gmean, CV, geometric SD, arithmetic mean and SD will be reported as not calculable (NC). The maximum value will be reported from the individual data, and the minimum and median will be set as NQ.

- If all the concentrations are NQ, the gmean and arithmetic mean will be reported as NQ and the CV, geometric SD and SD as NC.

The number of values above LLOQ will be reported for each time point along with the total number of collected values.

Three observations >LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values will be presented as a minimum and maximum with the other summary statistics as NC.

Plasma concentrations of AZD1775 and chemotherapy agents will be summarized by nominal time point and visit for each treatment group. PK parameters will be presented according to the conventions listed in the table below.

Table 1: Conventions for Reporting PK Parameters

Parameter	Reporting in Summary Tables[a]	Listings
$AUC_{(0-t)}$	gmean/CV/gmeanSD/mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
AUC	gmean/CV/gmeanSD/mean/SD/med = 4 s.f.	3 s.f.

	min/max = 3 s.f.	
CL	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
C_{8hr}	gmean/CV/gmeanStD/mean/SD/med = 4 s.f. min/max = 3 s.f.	same s.f. as supplied from bioanalysis
C_{max}	gmean/CV/gmeanStD/mean/SD/med = 4 s.f. min/max = 3 s.f.	same s.f. as supplied from bioanalysis
Dose normalized $AUC_{(0-t)}$	gmean/CV/gmeanSD/mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
Dose normalized C_{max}	gmean/CV/gmeanSD/mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
MR $AUC_{(0-t)}$	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
$t_{1/2\lambda z}$	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
t_{max}	med = 2 d.p. min/max = 2 d.p.	2 d.p.
t_{last}	med = 2 d.p. min/max = 2 d.p.	2 d.p.
V_z	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.
V_{ss}	mean/SD/med = 4 s.f. min/max = 3 s.f.	3 s.f.

[a] N number included in summary table for all parameters as whole numbers.

d.p. decimal places

s.f. significant figures

The concentration data for AZD1775 and chemotherapy agents will also be displayed graphically. Displays will include individual subject plasma concentration versus time profiles, on both the linear and log-scales, and the gmean concentration (±SD) versus time profiles, stratified by treatment group. For consistency, the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

A preliminary assessment of the effect of chemotherapy agents on AZD1775 PK will be conducted. The geometric mean $AUC_{(0-t)}$ values for AZD1775 following coadministration of AZD1775+chemotherapy agent will be compared to the geometric mean $AUC_{(0-t)}$ values for AZD1775 following monotherapy of AZD1775. Since AZD1775 was not administered as monotherapy in study D6010C00004, the preliminary data from studies D6015C00001, D6015C00003, and/or PN001 will be used for this preliminary assessment of drug interaction.

6.10 Further Anti-Tumor Therapy

A table of the number and percentage of subjects who have received systemic anti-cancer therapy for the disease after discontinuing protocol treatment will be presented by treatment arm using the FAS. The time from treatment discontinuation to first subsequent systemic therapy will also be summarised.

A listing of further systemic therapy, radiotherapy and surgical intervention will also be provided.

7   References

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8 Appendices

8.1 Appendix 1: List of Tables, Figures and Listings

8.1.1 Tables and Figures

Table 11.1.1 Patient Disposition

Table 11.1.2 Important Protocol Violations

Table 11.1.3 Patient Accountability

Table 11.1.4 Patient Demographics

Table 11.1.5 Vital Signs at Baseline

Table 11.1.6 Summary of Genetic Alterations

Table 11.1.7 Prior Systemic Therapy for Disease

Table 11.1.8 Prior Radiotherapy for Disease

Table 11.1.9 Prior Surgery for Disease

Table 11.1.10 Disease History

Table 11.1.11 Sites of Disease at Study Entry

Table 11.1.12 Concomitant Medications

Table 11.1.13 Further Anti-Tumour Therapy

Table 11.2.1.1 Progression Free Survival via RECIST v1.1

Table 11.2.1.2 Progression Free Survival via RECIST v1.1 (investigator assessment) according to genetic alteration status

Figure 11.2.1.3 Progression-free survival, Kaplan-Meier plot

Table 11.2.1.4 Overall Response Rate and Disease Control Rate via RECIST v1.1

Table 11.2.1.5 Overall Response Rate & Disease Control Rate via RECIST v1.1 (investigator assessment) according to genetic alteration status

Table 11.2.1.6 Duration of Response

Figure 11.2.1.7 Duration of Response, Kaplan-Meier plot

Figure 11.2.1.8.1 Best Percent Change in Sum of Longest Diameters of Target Lesions - Waterfall Plot

Figure 11.2.1.8.2 Best Percent Change in Sum of Longest Diameters of Target Lesions - Waterfall Plot by Cohort

Figure 11.2.1.9.x Spider Plot of % Change in Tumour Size

Figure 11.2.1.9.x Spider Plot of % Change in Tumour Size

Table 11.2.1.10 Overall Survival

Figure 11.2.1.11 Overall Survival, Kaplan-Meier plot

Table 11.2.1.12 CA-125 Response Rate via Gynecological Cancer Intergroup Guidelines

Figure 11.2.1.13.1 Waterfall Plot of Best Percent Change in CA-125

Figure 11.2.1.13.1 Waterfall Plot of Best Percent Change in CA-125 by Cohort

Figure 11.2.1.14.x Spider Plot of Change in CA-125

Table 11.2.1.15.1 Summary of Plasma AZD1775 Concentration

Table 11.2.1.15.2 Summary of Plasma Concentrations of Chemotherapy Agents

Table 11.2.1.15.3 Summary of PLD Concentration - Additional Cycle 1 Time Points

Figure 11.2.1.16.x Individual AZD1775 plasma concentrations (<<unit>>) of AZD1775[a] versus time for AZD1775<dose>+Chemotherapy<dose> on Cycle 1 Day 1[b]*

Figure 11.2.1.17.x Geometric mean (+/- GSD) plasma concentrations (unit) of AZD1775[a] versus time on Cycle 1 Day 1

Table 11.2.1.18.1 Summary of Plasma AZD1775 PK Parameters

Table 11.2.1.18.2 Summary of Plasma Chemotherapy Agents PK Parameters

Table 11.3.1.1 Time on Treatment and Exposure

Table 11.3.1.2 Duration of Chemotherapy Infusion By Cycle

Table 11.3.1.3 Treatment Modifications

Table 11.3.2.1 Adverse Events Overview

Table 11.3.2.2 All Treatment Emergent Adverse Events by SOC, PT and Worst Grade

Table 11.3.2.3 All Treatment Emergent Adverse Events by PT

Table 11.3.2.4 AZD1775 Related TEAE by SOC, PT and Worst Grade

Table 11.3.2.5 AZD1775 Related TEAE by PT

Table 11.3.2.6 Chemotherapy Related TEAE by SOC, PT and Worst Grade

Table 11.3.2.7 Chemotherapy Related Serious TEAEs by SOC and PT

Table 11.3.2.8 Dose Limiting Toxicity Overview

Table 11.3.2.9 Summary of Deaths

Table 11.3.4.1 Serious TEAEs by SOC and PT

Table 11.3.4.2 Serious TEAEs by PT

Table 11.3.4.3 AZD1775 Related Serious TEAEs by SOC and PT

Table 11.3.4.4 AZD1775 Related Serious TEAEs by PT

Table 11.3.7.1.1.x Laboratory tests - Summary over time

Table 11.3.7.1.2 Haematology and clinical chemistry, CTCAE grade change from baseline to maximum on treatment (Safety analysis set)

Table 11.3.7.1.3 Clinical chemistry, CTCAE grade change from baseline to maximum on treatment for electrolytes (Safety analysis set)

Table 11.3.7.1.4 Summary of Elevated AST, ALT, Total Bilirubin and Alkaline Phosphate

Table 11.3.8.1.1 Vital Signs Summary over time

Table 11.3.8.1.2 Vital Signs Change from Baseline Summary over time

Table 11.3.8.1.3 ECOG PS Summary over time

Table 11.3.8.1.4 Summary of Electrocardiogram Tests

8.1.2 **Listings**

Appendix 12.2.1.1 Date Informed Consent Form was Signed

Appendix 12.2.1.2 Eligibility

Appendix 12.2.2.1 Subjects with Important Protocol Deviations

Appendix 12.2.4.1 Demographic and Baseline Characteristics

Appendix 12.2.4.2.1 Medical History and Current Medical Conditions

Appendix 12.2.4.2.2 Disease History

Appendix 12.2.4.2.3Prior Systemic Therapy

Appendix 12.2.4.2.4 Prior Rradiotherapy

Appendix 12.2.4.2.5 Prior Surgery for the Disease

Appendix 12.2.4.3 Concomitant medication on entry and during the study

Appendix 12.2.4.4 Biomarker Results

Appendix 12.2.4.5.1 Anti-tumour therapies after study treatment

Appendix 12.2.4.5.2 Post Discontinuation Radiotherapy

Appendix 12.2.4.5.3 Post Discontinuation Surgery

Appendix 12.2.5.1 Administration of investigational product, AZD1775

Appendix 12.2.5.2 Administration of investigational product, Chemotherapy

Appendix 12.2.6.1 Overall Response via RECIST 1.1

Appendix 12.2.6.2.1 Target lesion data

Appendix 12.2.6.2.2 Non-target lesion data

Appendix 12.2.6.2.3 Progression-Free Survival

Appendix 12.2.6.2.4 CA-125 Response

Appendix 12.2.6.3.1 Pharmacokinetic parameters, AZD1775

Appendix 12.2.6.3.2 Pharmacokinetic parameters, Chemotherapy

Appendix 12.2.6.3.3.x Lambda_z Related PK Parameter Results for <analyte>

Appendix 12.2.6.4.1 Drug concentration data, AZD1775

Appendix 12.2.6.4.2 Drug concentration data, Chemotherapy

Appendix 12.2.7.1 Adverse Events

Appendix 12.2.7.2 Serious Adverse Events

Appendix 12.2.7.3 Dose Limiting Toxicities

Appendix 12.2.7.4 Deaths

Appendix 12.2.8.1.1 Individual laboratory measurement - haematology

Appendix 12.2.8.1.2 Individual laboratory measurement - chemistry

Appendix 12.2.8.1.3 Individual laboratory measurement - coagulation

Appendix 12.2.9.1 Individual vital signs data

Appendix 12.2.10.1 Electrocardiogram data

Appendix 12.2.10.2 Ejection Fraction Assesments

8.2   Appendix 2: Overall Visit Responses

Target Response	Non-target Response	New Lesions	Overall Response at this assessment
CR	CR	NO	**CR = Complete Response**
CR	NA	NO	
NA	CR	NO	
CR	NonCR/NonPD	NO	**PR = Partial Response**
CR	NE	NO	
PR	NA	NO	

PR	CR	NO	
PR	NonCR/NonPD	NO	
PR	NE	NO	
NA	NonCR/NonPD	NO	**NonCR/NonPD**
SD	NA	NO	**SD = Stable disease**
SD	CR	NO	
SD	NonCR/NonPD	NO	
SD	NE	NO	
PD	ANY	YES or NO	**PD = Progressive Disease**
ANY	PD	YES or NO	
ANY	ANY	YES	
NE	NA	NO	**NE = Not Evaluable**
NE	NonCR/NonPD	NO	
NE	CR	NO	
NE	NE	NO	
NA	NE	NO	
NA	NA	NO	**NA = Not Assessed**