AstraZeneca

Revised Clinical Study Protocol

Drug Substance	(Olaparib) AZD2281
Study Code	D0810C00021
Edition Number	6
Date	[redacted]

A Phase I, Open Label, Multi-centre Study of AZD2281 Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours

[redacted]

The following Amendment(s) and Administrative Changes are included in this amended protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2	[redacted]		
3	[redacted]		
4	[redacted]		
5	[redacted]		
6	[redacted]		

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1	[redacted]		
2	[redacted]		

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of an emergency you may contact the Study Leader. If the Study Leader is not available, contact the Study Team Physician at the AstraZeneca Research and Development site shown below.

Role in the study	Name	Address and Telephone number
Study Leader responsible for the protocol at central R&D site	[redacted]	[redacted]
Medical Science Director for the protocol at central R&D site	[redacted]	[redacted]
Study Team Physician	[redacted]	[redacted]
Global Safety Physician	[redacted]	[redacted]
Chief and Coordinating Investigator	[redacted]	[redacted]
Co-Investigators	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

For further clarifications regarding:

- Procedures in case of medical emergency see Section 9.2
- Procedures in case of overdose see Section 9.3
- Procedures in case of pregnancy see Section 9.4.

PROTOCOL SYNOPSIS

A Phase I, Open Label, Multi-centre Study of AZD2281 Administered Orally in Combination with Cisplatin, to Assess the Safety and Tolerability in Patients with Advanced Solid Tumours

Investigator

[redacted]

Study centre(s), type and number of patients planned

This will be a multi-centre study run from approximately 4 investigational sites in the USA and Spain. The maximum tolerated dose of AZD2281 (or the highest well tolerated dose explored) that can be combined with cisplatin will be established in patients with advanced solid tumours. Depending on the doses of AZD2281 explored it is expected that 60 patients will be enrolled.

Study period		**Phase of development**
Estimated date of first patient enrolled	[redacted]	I
Estimated date of last patient completed	[redacted]	

Objectives

- The primary objective is to determine the safety and tolerability of twice daily doses of AZD2281 when administered in combination with cisplatin to patients with advanced solid tumours.

The secondary objectives of the study are:

1. To compare exposure to AZD2281 when given alone and in combination with cisplatin. (Only in patients receiving continuous dosing of AZD2281)

2. To make a preliminary assessment of the anti-tumour activity of AZD2281 when given in combination with cisplatin, by measuring overall objective response rate.

The exploratory objectives of the study are:

- To obtain an optional blood sample for DNA extraction for future pharmacogenetic analysis and other potential correlative markers of the activity of AZD2281 and drugs taken in combination with AZD2281 (ie, cisplatin).

The exploratory analyses will be reported separately

Study design

The study is a non-randomised, open label, Phase I dose finding study, to determine the maximum tolerated dose of AZD2281 that can be combined with cisplatin in patients with advanced solid tumours.

Each cohort will comprise a minimum of 3 evaluable patients. If 1 patient from the initial 3 experiences DLT the cohort will be expanded to at least 6 patients. It is expected that 60 patients will be enrolled.

Once the desired doses or MTD of the combination therapy has been determined (or the highest dose level has been explored) the cohort will be expanded to ensure that there are 6 evaluable patients who have completed four cycles of combination treatment.

The Maximum Tolerated Dose (MTD) is defined as the prior dose level below the drug-combination that causes DLT, in at least 2 patients in a cohort of up to 6 patients. If toxicity is equivocal and it is not possible to determine a MTD with certainty, further cohorts of at least three patients may be recruited to allow an informed decision to be taken about further dose escalations with AZD2281.

The dose escalation may continue until the MTD is established; however the highest dose to be explored will be 400 mg bd. Intra-patient dose escalation is not permitted.

If continuous dosing is not tolerated, intermittent dosing will be explored. An intermittent dosing cohort will be opened to enrol 12 patients at the following dose:

- AZD2281 at 100 mg bd for days 1-10 of a 21 day cycle with 75 mg/m^2 of cisplatin on day 1 of a 21 day cycle

- Day 1 of cisplatin and day 1 of AZD2281 are the same day

In the event that the initial intermittent dose cohort is not tolerated, further cohorts may be investigated with a starting dose of AZD2281 at 50 mg bd for days 1-5 of a 21-day cycle with 75 mg/m^2 of cisplatin on day 1 of a 21-day cycle.

Investigational product, dosage and mode of administration

The doses of AZD2281 used in this study will be made up from the available 50 mg capsule strengths.
In all cycles, AZD2281 will be administered orally twice-daily on either a continuous or intermittent basis. Cisplatin will be administered on Day 1 of a 21-day cycle. On Day 1 cisplatin will be administered 2 hours after the first AZD2281 administration.

For the continuous dosing regimens, a single dose of AZD2281 (dose dependent on the cohort) will be given on visit 2 (up to a week before the combination). A full 12-hour plasma PK profile will be taken, this will be repeated when AZD2281 is given together with cisplatin

to enable a comparison of the plasma exposure to AZD2281 alone and repeated in the presence of cisplatin.

For the intermittent dosing regimens, the first dose of AZD2281 will be given on the same day as cisplatin, unless a different dose schedule is advised by the safety monitoring committee. PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort.

Duration of treatment

Each cycle of cisplatin treatment will last 21 days. AZD2281 will be taken twice-daily either continuously (day 1 through day 21) or intermittently. Dosing with AZD2281 will commence in relation to the day that cisplatin is administered, regardless of whether or not there have been any dosing delays or interruptions in the previous cycle.

Combinational treatment with AZD2281 and cisplatin will continue for as long as the Investigator feels that the patient is receiving benefit and is free from significant toxicity. In the event that cisplatin is permanently discontinued on the basis of cisplatin related toxicity, treatment with AZD2281 alone may continue. If the patient does continue on AZD2281 alone, at the discretion of the PI and in consultation with AstraZeneca Study Team Physician, the patient may be dose escalated to receive the optimal monotherapy dose (ie 400 mg bd).

Variables

- **Safety**

  Adverse events

  Blood pressure (BP) and Pulse Rate (PR)

  Body Temperature

  ECG

  Haematology

  Clinical chemistry

  Urinalysis

  Physical examination

- **Pharmacokinetic (AZD2281 only)**

  C_{max}, t_{max} and AUC_{0-t}

- **Response**

  ORR

Data cut-off

There will be a data cut off defined as the time when all patients receiving AZD2281 have been followed for a minimum of 3 months of monotherapy AZD2281 following combination treatment, or there are no more patients remaining on treatment in the study; whichever is the earlier date. At this time point, the clinical study database will close to new data. Patients are however permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with AZD2281. Patients continuing on study treatment will be followed for core safety assessments only (haematology, clinical chemistry, AEs/SAEs and concomitant medications, IMP dosing details). These patients should be followed according to routine clinical practice but visits should take place at least every 8 weeks.

Pharmacogenetics

An optional blood sample for the retrospective analysis of genes that may be involved in the response to AZD2281 and combination of AZD2281 with cisplatin will be taken.

Statistical methods

The primary objective of the study is to determine the safety and tolerability of different doses of AZD2281 in combination with cisplatin. The total number of patients has therefore been based on a desire to obtain adequate safety and tolerability data whilst exposing as few patients as possible to the study treatment and procedures. Once the desired dose or MTD of the combination therapy has been determined (or the highest dose level has been explored) the cohort will be expanded to ensure that there are 6 evaluable patients who have completed four cycles of treatment.

No formal statistical analyses will be performed on safety data (primary objective), PK data and efficacy data. All data will be summarised descriptively and where appropriate, confidence intervals will be presented as measures of study precision.

The exploratory Pharmacogenetic outcome variables will be analysed and reported separately.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
AC	doxorubicin and cyclophosphamide combination treatment
ADP	Adenosine diphosphate
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event (see definition in Section 5.10)
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial Thromboplastin time
AST	Aspartate Transaminase (SGOT)
AUC_{0-t}	Area under the plasma concentration-time curve during any dosing interval at steady state
Bid	Twice-daily *(Bis in die)*
BER	Base excision repair
BP	Blood pressure
BRCA	Breast cancer gene (type)
BUN	Blood Urea Nitrogen
C_{max}	Maximum plasma (peak) concentration in plasma during dosing interval
cPR	Complete pathological response
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case Report Form
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CT	Computerised tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal Cacinoma In Situ
DLT	Dose Limiting Toxicity

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
DSB	Double strand break
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
FAS	Full Analysis Set
FNA	Fine Needle Aspirate
FPI	First Patient In
FSH	Follicle stimulating hormone
GCIG	Gynaecologic Cancer InterGroup
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GM-CSF	Granulocyte/macrophage colony-stimulating factor
HDPE	High-density polyethylene
HER2	Human Epidermal growth factor Receptor 2
HFS	Hand-Foot Syndrome
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRD	Homologous recombination repair deficiencies
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Independent Review Board
LDH	Lactic dehydrogenase
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit

Abbreviation or special term	Explanation
LVEF	Left Ventricular Ejection Fraction
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin volume
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
MEq/day	Milliequivalents per day
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA scan	Multi-gated acquisition scan
NAD	Nicotine adenine dinucleotide
NE	Not evaluable
NTL	Non-target lesions
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment)
ORR	Objective Response Rate
PAR	Poly-(ADP-ribose)
PARP	Poly (ADP-ribose) polymerase
pCR	Pathological complete response
PD	Progressive disease
PFS	Progression-free survival
PGx	Pharmacogenetic research
PI	Principal Investigator
PK	Pharmacokinetics
po	By mouth (*Per os)*
pPR	Pathological partial response
PR	Partial response
prn	As needed (*Pro re nata*)
qd	Every day (*Quaque die*)
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 5.10)
SAP	Statistical Analysis Plan

Abbreviation or special term	Explanation
SD	Stable disease
SLN	Sentinel Lymph Node
SmPC	EU Summary of Product Characteristics
SSAR	Suspected Serious Adverse Reaction
SSB	Single strand break
SUSAR	Suspected Unexpected Serious Adverse Reaction
Study medication	Refers to both drug under investigation and comparators administered as part of the schedule
TAC	docetaxel, doxorubicin and cyclophosphamide
TL	Target lesions
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
TNM	Tumour, Node, (Lymph) Metastasis (staging method)
$t_{1/2}$	Terminal half life
TTP	Time To Progression
ULN	Upper limit of normal
WBC	White Blood Cells

1. INTRODUCTION

Investigators should be familiar with the olaparib Investigator's Brochure (IB).

1.1 Background

1.1.1 PARP and PARP-1 inhibition

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] or PAR polymerisation is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non proliferating cells following deoxyribonucleic acid (DNA) damage. This event represents an immediate cellular response to DNA damage and involves the modification of glutamate, aspartate and lysine residues with the addition of long chains of Adenosine diphosphate (ADP)-ribose units, derived from Nicotine adenine dinucleotide (NAD)+, onto the DNA-binding proteins. The enzymes that catalyse this process, poly (ADP-ribose) polymerases (PARPs), are critical regulatory components in DNA damage repair and other cellular processes. They now comprise a large and expanding family of 18 proteins, encoded by different genes and displaying a conserved catalytic domain in which PARP-1 (113 kDa), the initial member, and PARP-2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Moreover, many of the identified family members interact with each other, share common partners and common sub-cellular localisations suggesting functional redundancy and possibly fine-tuning in the regulation of post-translational modification of proteins.

The range of biological roles involving PARP proteins is wide. This includes DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, involvement in cell elimination pathway by necrosis and serving as a signal for protein degradation in oxidatively injured cells (Virag and Szabo 2002).

Of the various members of the PARP enzyme family, only PARP-1 and PARP-2 work as DNA damage sensor and signalling molecules. PARP-1 is a nuclear enzyme consisting of 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. It binds to both single and double-stranded DNA breaks through the zinc-finger domain. PARP-1 catalyses the cleavage of NAD+ into nicotinamide and ADP-ribose, the latter is then synthesised to form branched nucleic acid-like polymers covalently attached to nuclear acceptor proteins. This branched ADP-ribose polymer is highly negatively charged, thereby affecting the function of the target proteins. Histones have been found to be acceptors of poly ADP-ribose, the negative charge leads to electrostatic repulsion between DNA and histones. This has been implicated in chromatin remodelling, DNA repair and transcriptional regulation. Other transcriptional factors and signalling molecules shown to be poly-ADP-ribosylated by PARP-1 are nuclear factor-κB, DNA-dependent protein kinase, p53, topoisomerase-I, lamin B and PARP-1 protein itself (Virag and Szabo 2002).

PARP-1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP-1 have been shown to have delayed DNA repair function. Like PARP-1, PARP-2 also responds to DNA damage and will similarly lead to single strand DNA repair. For both proteins inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP-1 activity in cells or in knockout mice leads to both radio- and chemo-sensitisation. Moreover, increased PARP-1 activity has been found in many tumour types. The use of PARP inhibitors, like the knockout studies, has confirmed that in combination an enhancement of the antitumour activity of radiation and DNA damaging cytotoxics occurs (Virag and Szabo 2002) and (Nguewa et al 2005).

1.1.2 Homologous recombination deficiency and PARP

Due to the molecular targeting of AZD2281 to specific subsets of tumours, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP-1 inhibitor compared with conventional treatments such as chemotherapy. The Investigational Medicinal Product (IMP) displays antitumour activity to a variety of tumour cell lines and this sensitivity of the cells is known in some instances and believed in others to depend upon components of a defective homologous recombination (HR) capability. As a major example of this selective activity the breast cancer (BRCA) $^{-/-}$ gene tumours (both BRCA1 and BRCA2) are seen to be highly sensitive to PARP inhibition. Recent studies indicate that PARP inhibition in BRCA1 and BRCA2 homozygous null cells, but not the isogenic BRCA heterozygous cells, leads to selective cell death. The BRCA1 and 2 genes encode proteins that are implicated in homologous DNA strand break repair, known as homologous recombination. BRCA1 or BRCA2 dysfunction profoundly sensitises cells to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis (Farmer et al 2005). This sensitivity compared to unaffected heterozygous tissue, provides a large therapeutic window for PARP inhibition.

1.1.3 Cisplatin and breast cancer

Platinum was studied in breast cancer in the 1970s and shown to be quite active when given early in the course of the disease, but not adopted, perhaps because of the superior therapeutic index of other drugs then under development (the taxanes). The activity of cisplatin in the treatment of breast cancer appeared to be dependent on whether or not patients have received previous chemotherapy. The drug was initially tested in the treatment of advanced breast cancer, both as a single agent and in combination with other drugs. Cisplatin was evaluated in the treatment of metastatic breast cancer in the 1970's when, as a single agent in small studies, it demonstrated impressive objective response rates of 54% and 47% (Bryant et al 2005), but only in women who had not received prior chemotherapy for metastatic disease (Bryant et al 2005, Farmer et al 2005, Stommel et al 2007). When given after other chemotherapy, responses disappeared (Bremer et al 2002, Haupt et al 2006, Herrera-Gayol et al 2002, Toy et al 2005, Yasmeen et al 2007). Several combination regimens were also explored, particularly with taxanes, but there seemed little reason to continue these combinations when the taxanes were so active and relatively nontoxic (Al-Hajj et al 2003). There was also interest in the evaluation of docetaxel/platinum combination. In several studies in unselected metastatic disease, the overall response rate with this combination regimen is around 50% in patients, even with prior adjuvant anthracyclines (Al-Hajj et al 2003).

There appears to be some more recent interest in cisplatin for treatment of breast cancer. Strategies for managing its side effects have improved, particularly targeting nausea, which may make consideration of its use more reasonable. A 2004 Phase II study of preoperative paclitaxel and cisplatin demonstrated that 28% achieved a complete response, while 63% demonstrated partial response to this combination therapy (Shipitsin et al 2007). These response rates are comparable to other active regimens (see below). In a single agent neoadjuvant trial with 75 mg/m^2 every 21 days in triple negative breast cancers, a 22% complete response rate was observed. (Silver et al 2010).

Available data on response with cisplatin as single agent in Metastatic Breast Cancer, is summarized in the following Table 1:

Table 1 Published experience with cisplatin in Metastatic Breast Cancer

Cisplatin Dose	Response Rate	References
Prior Chemotherapy		
20 mg/m^2/d x 5 d every 4 wk	0/14	Bremer et al 2002
100 mg/m^2 every 3-4 wk	0/12	
100 mg/m^2 every 3-4 wk	2/17	Haupt et al 2006
60 mg/m^2 every 3-4 wk	0/18	Herrera-Gayol et al 2002
120 mg/m^2 every 3-4 wk	4/19	
15 mg/m^2/d x5 d every 4 wk	0/15	Toy et al 2005
100-120 mg/m^2 every 4 wk	2/13	
35 mg/m^2/d x 5 d every 4 wk	2/5	Yasmeen et al 2007
Total	10/113 (9%)	
NO Prior Chemotherapy		
30 mg/m^2/d x4 d every 3 wk	19/35	Bryant et al 2005
30 mg/m^2/d x4 d every 3 wk	5/12	Stommel et al 2007
30 mg/m^2/d x4 d every 3 wk	9/19	Farmer et al 2005
Total	33/66 (50%)	

1.1.4 Cisplatin and BRCA1

Accumulating data suggest that specific alterations in genes in the BRCA1 double strand break repair pathway may result in tumours that are less capable of repairing specific types of DNA errors. Limited *in vitro* data exist for the effect of cisplatin on BRCA1 mutated cell lines. These demonstrate particular sensitivity to the DNA damage induced by cisplatin and mitomycin, DNA damaging agents. Researchers have shown that BRCA1 mutated breast cells are more sensitive to cisplatin (Ince et al 2007). Treatment with the DNA alkylating and crosslinking agent cisplatin produced a dose-dependent reduction in cell growth in breast cell lines after 48 hours of treatment (Flaherty and Brose 2006). The BRCA1 defective cell line

was 2- to 3-fold more sensitive to cisplatin compared with BRCA1 competent cell lines. Further studies have evaluated the effect of taxanes in the same mutated cells, and they have shown an opposite pattern of chemosensitivity (that is, relatively less sensitivity to taxanes in the BRCA1-defective cells) compared with cisplatin (Lafarge et al 2001). In this setting, it appears that cisplatin may represent a good agent for breast cancer, and, perhaps, in particular, for BRCA1 mutated breast cancer. It seems reasonable to ask whether a subset of tumours with a similar phenotype to BRCA1-associated tumours (ie, ER/PR/HER2 negative) may also have involvement of the same DNA-repair pathway, and may also demonstrate relative sensitivity to the DNA-cross linking agent cis-platin. Of note, similar in vitro data for carboplatin, a relative of cisplatin currently being explored in HER2-positive breast cancer and often considered less toxic, are lacking.

This is potentially important in light of data that women with germline BRCA1 mutations have better survival with ovarian cancer, for which standard first-line therapeutic regimens include cis- or carboplatinum (Fedier et al 2003, Quinn et al 2003, Tassone et al 2003, Chetrit et al 2008). In a recent study from Belfast, low (vs high) in vitro chemoresistance was associated with tumour response to platinum chemotherapy in BRCA heterozygotes with epithelial ovarian carcinoma (Quinn et al 2007).

1.2 Relevant preclinical results

1.2.1 AZD2281

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure.

Key findings are summarised below.

The AZD2281 molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of ~2nM in HeLa cells.

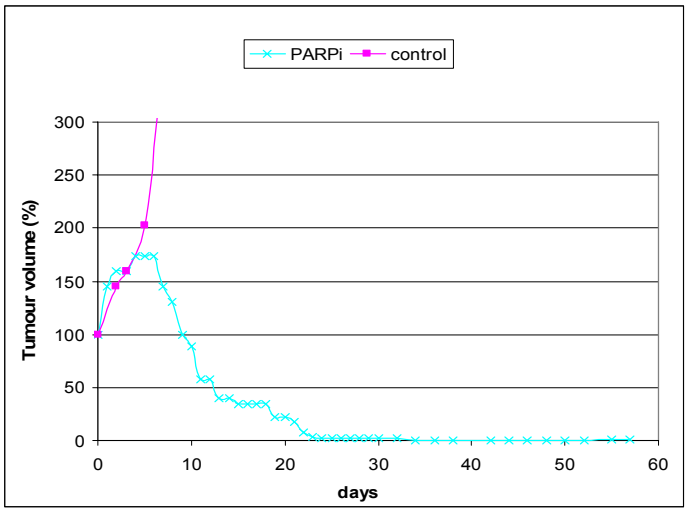
Pharmacokinetic data for the rat showed sex differences in absorption parameters for individual studies. However, these observations were variable and, as no gender difference in PK parameters was seen in the dog, it seems unlikely that these are of relevance to the proposed clinical study. Higher systemic exposure in female rats compared with males at the same dose level accounts for their apparently greater sensitivity to the drug, as seen by haematological and histological changes in the toxicology studies. In the dog, toxicokinetics were similar for males and females.

Distribution of AZD2281 is typical for an orally administered foreign compound, in the gastro-intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre-clinical studies, although their identification and activity have yet to be confirmed. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and, to a lesser extent, the urine. In a study of [C-14]-AZD2281 in the rat, excretion was 76±13% in faeces and 20±11% in urine.

1.2.2 Experimental animal models of BRCA deficiency

In transgenic mouse knockout models, where either the BRCA1 or BRCA2 protein has been lost, mice spontaneously develop mammary tumours that are characteristically similar to humans. These tumours take several months to develop but once established become very aggressive and are histopathologically similar to human breast tumours deficient in BRCA1 or BRCA2. The testing of the PARP inhibitor AZD2281 in animals which develop spontaneous tumours shows, as discussed above, significant antitumour effects. The sustained use of inhibitor over 4 weeks or more leads to stasis and loss of tumour mass with no toxic effects observed in the animals. This activity is highly selective to these BRCA1 and BRCA2 deficient tumour masses only. Dosing studies in these models have indicated that the antitumour effects are slow to appear ie, a noted lag-phase is observed, but will occur following tumour cell division leading to significant effects (see Figure 1 below).

Figure 1 Efficacy of PARP inhibitor versus Control in the Kcre;BRCA1/2$^{flox/flox}$; p53$^{flox/flox}$ Model



PARPi 50 mg/kg i.p. day 0-27
Untreated control

The AZD2281 molecule shows good cellular activity in the low nM range with a cellular dose for 50% inhibition (IC_{50}) of around 2 nM in HeLa cells.

In a study where BRCA2- deficient mouse mammary tumour cell lines were treated with 11 different anticancer drugs or with gamma-irradiation, AZD2281 was seen to have the strongest differential growth inhibition of BRCA2-deficient versus BRCA2-proficient tumour cells. AZD2281 given in combination with cisplatin showed synergistic cytotoxicity against BRCA2-deficient cells but not against BRCA2-proficient control cells, providing evidence for the use of selective PARP inhibitors in combination with platinum agents for the treatment of BRCA associated cancers and BRCA-like cancers with defects in homologous recombination repair (Evers et al 2008).

1.2.3 Summary of toxicological data

AZD2281 has been tested in a standard range of safety pharmacology studies ie, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific ex vivo work has been conducted exposing human bone marrow cells to AZD2281, which has confirmed that AZD2281 is also active against human marrow. However, the cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC50 of 2.7 μM for myelosuppression in n=4 human donors compared with 0.1μM for total PARP-1 activity inhibition). These data along with the 28-day dog and rat studies, show a myelotoxic effect that is mild-to-moderate and is reversible. Platelets appear first affected, followed by white blood cells. Twenty-six week repeat oral dose studies of AZD2281 in rat and dog have given similar results, with the drug being well tolerated and no drug-related mortality. Importantly, oncology clinics are well used to monitoring for the onset of such effects and are expert in their management.

AZD2281 showed no mutagenic potential in the Ames test, was clastogenic in the Chinese Hamster Ovary chromosome aberration test, and was genotoxic in the rat micronucleus test. These findings are not uncommon for many therapeutic agents used in oncology and so do not present an unacceptable risk when appropriately clinically managed.

In the male fertility study in the rat, administration of AZD2281 to male rats at doses of 5, 15 or 40 mg/kg/day prior to puberty and throughout spermatogenesis had no adverse effect on mating performance, fertility, embryonic survival, sperm parameters, male reproductive tract organ weights or histological appearance of testes or epididymides. Dosing males with 15 or 40 mg/kg/day resulted in dosage-related slight toxicity. Dosing with males 5 mg/kg/day caused no significant effects.

In the embryofoetal development study in the rat, administration of AZD2281 to female rats during the period of major embryonic organogenesis at a dose of 0.5 mg/kg resulted in slight maternal toxicity. There was no effect on pregnant animals after dosing with 0.05 mg/kg/day. After dosing with 0.5 mg/kg/day, early embryofoetal survival and foetal weights were reduced with the occurrence of major eye and vertebral/rib malformations and increased incidences of several visceral and skeletal minor abnormalities and variants. After dosing with 0.05 mg/kg/day, there was an associated increased incidence in a minor visceral abnormality and skeletal variant. There was also one foetus with a major eye malformation. A “no observed adverse effect” dose level for foetal abnormalities was not established.

Further information can be found in the current version of the olaparib Investigator’s Brochure.

2. SUMMARY OF CLINICAL EXPERIENCE

The clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

The first clinical study in man (D0810C00002) was a dose-escalation study in patients with advanced solid tumours. A total of 98 patients were recruited and doses started from 10 mg daily for 2 or 3 weeks, escalating to 600 mg bid continuously. After the maximum tolerated dose was identified (400 mg bid), an expansion phase at 200 mg bid was opened in ovarian, breast and prostate cancer patients who have genetic BRCA mutations.

Of the 98 patients treated across all tumour types, 49 had ovarian cancer and were BRCA mutation carriers as defined by a molecular test. One additional patient had not had a molecular test, but had a compelling family history and considered likely to be a BRCA mutation carrier. A further 4 patients with ovarian cancer were not BRCA mutation carriers.

All 49 ovarian cancer patients with genetic BRCA mutations had received prior platinum chemotherapy. In this study there were 12 (24.5%) confirmed responses per RECIST for this group. Five of the confirmed responders (4 at 200 mg bid and 1 at 400 mg bid dose level) were patients who were sensitive to platinum (38.5% ORR; 5/13 platinum sensitive patients), and 7 confirmed responders (5 at 200 mg bid and 2 at 400 mg bid dose level) were patients categorised as resistant to platinum (30.4% ORR; 7/23 platinum resistant patients).

Using the combined GCIG/RECIST criteria, 18 patients (36.7%) had a confirmed response. Responses were seen in 7 of 13 sensitive patients (53.8%), 9 of 23 resistant patients (39.1%) and 2 of 13 refractory patients (15.4%). The higher response rates observed in the platinum sensitive subgroup and lower response rate observed in the platinum refractory subgroup is consistent with the response rates seen using RECIST only, and time to disease progression.

Responses were seen at all dose levels of 100 mg bid and above.

Safety data from this study indicate that oral administration of olaparib was generally well tolerated by the majority of patients with various solid tumours at doses up to and including 400 mg twice daily, as monotherapy, although, as expected, all patients on olaparib experienced at least one adverse event. Most of the AEs were mild to moderate (CTCAE grade 1 or 2) in intensity at doses up to 400 mg bid. Dose Limiting Toxicity (DLT) was observed at 600 mg bid. The percentage of patients with CTCAE grade $\geq$3 events attributed to the study medication by the Investigator was 23.5% (23 patients), and increased with increasing dose. The percentage of patients with AEs leading to discontinuation of treatment was 21.4% (21 patients), with only 5.1% (5 patients) discontinuing treatment due to events that the Investigator attributed to study drug. There were only 4 dose reductions for adverse events in the entire population of 98 patients treated; all were at the 200 to 600 mg bid dose levels.

Study D0810C0009 is a Phase II open-label, non-comparative study to assess the efficacy and safety of olaparib given orally twice daily in ovarian cancer patients with genetic BRCA-1 or BRCA-2 mutations. A total of 57 patients were recruited into two separate sequential cohorts, the first treated at a dose of 400 mg bid and the second by a dose of 100 mg bid. Olaparib dosing was continuous and continued until there was no apparent clinical benefit or the patient was withdrawn from the study.

The objective response rate observed in both dose groups is indicative that olaparib is an active agent in this heavily treated population who had received a median of 3 previous lines of chemotherapy (35.5% at 400 mg bid and 13.6% at 100 mg bid). In this non-randomised study a higher level of activity was observed across all parameters in the 400 mg bid group compared to the 100 mg bid group (ORR, DoR (mean of 242.0 days at 100 mg bid and 301.0 days at 400 mg bid), CBR (45.5% at 100 mg bid and 71.0% at 400 mg bid), PFS (2.1 mths at 100mg bid and 7.4 mths at 400 mg bid) and best % change in tumour size [mean of -6.4% at 100 mg bid and –32.1% at 400 mg bid]). Confirmed objective responses were seen in patients with both BRCA1 and BRCA2 mutations.

As expected in patients with advanced cancer, most of the patients (98.2%) experienced at least one adverse event. In total, 49 patients (86.0%) experienced at least one adverse event that the Investigator attributed to study medication. AEs occurring in ≥25% of patients across the two dose cohorts were nausea (36 patients, 63.2%), fatigue (30 patients, 52.6%), diarrhoea (19 patients, 33.3%), abdominal pain (including “lower abdominal pain” and “upper abdominal pain”, 18 patients, 31.6%), and vomiting (17 patients, 29.8%). A total of 31 patients (54.4%) had at least 1 AE of CTC grade ≥3; 14 patients in the 100 mg bid group and 17 patients in the 400 mg bid group. The number of patients with CTC grade ≥3 events that the Investigator considered related to olaparib was 24.6% (14 patients overall, 7 in each treatment group). Most of the AEs were mild to moderate in intensity and manageable with continued dosing of olaparib. There were few dose interruptions and reductions required due to toxicity and only 5 patients had to discontinue olaparib due to AEs.

Overall results across the clinical trial program to date suggest that olaparib (in the capsule formulation) appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400 mg twice daily, as monotherapy.

Olaparib toxicity

Administration of olaparib has been associated with reports of laboratory findings and/or clinical diagnoses of:

- Haematological toxicity:
  - Anaemia, generally mild or moderate (CTCAE Grade 1 or 2)
  - Neutropenia, predominantly mild or moderate (CTCAE Grade 1 or 2)
  - Lymphopenia, generally mild or moderate (CTCAE Grade 1 or 2)

  - Thrombocytopenia, generally mild or moderate (CTCAE Grade 1 or 2) sometimes severe (CTCAE Grade 3 or 4)

  - Mean corpuscular volume elevation

- Nausea and vomiting, generally mild or moderate (CTCAE Grade 1 or 2), intermittent and manageable on continued treatment

- Dyspepsia, generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Dysgeusia, generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Fatigue (including asthenia) generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Headache, generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Dizziness, generally mild or moderate intensity (CTCAE Grade 1 or 2)

- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients

- Myelodysplastic syndrome/AML have been reported in a small number of patients with extensive previous exposure to chemotherapy

Cisplatin toxicity

Cisplatin has been used in combination regimens in the treatment of several malignancies including testes, head and neck (squamous carcinomas), and lung cancers. A summary of characteristic toxicities includes: (Go and Adjei 1999).

- **Nephrotoxicity**

The major dose-limiting toxicity of cisplatin is cumulative nephrotoxicity. Tubular necrosis of both proximal and distal renal tubules has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must return to normal before another dose of cisplatin can be given. Nephrotoxicity can be reduced by IV hydration and mannitol diuresis.

- **Nausea and Vomiting**

Cisplatin causes moderate to severe nausea and vomiting in almost all patients treated. Nausea and vomiting usually begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea, and/or anorexia may persist for up to 1 week after the treatment. Delayed nausea and vomiting (beginning 24 hours or more after chemotherapy) has occurred

with complete emetic control on the day of cisplatin therapy. The use of prophylactic and continuing antiemetic medication reduces these adverse effects.

- **Hypomagnesemia**

Hypomagnesaemia have been reported in patients treated with cisplatin and is probably related to renal tubular damage. It may become severe enough to cause tetany. Generally, serum electrolytes return to normal levels when cisplatin is discontinued and supplemental electrolytes are administered.

- **Ototoxicity**

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin (50 mg/m2) and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur occasionally. Ototoxicity can be more severe in children than in adults and more frequent and severe with repeated administration. Hearing loss can be unilateral or bilateral and is usually not reversible. During treatment with cisplatin, it is necessary to monitor hearing at each visit**.** An audiogram is recommended after a cumulative dose of 360 mg/m^2. Subsequent doses of cisplatin should not be given until an audiometric analysis indicates that auditory acuity is within normal limits.

- **Myelosuppression**

Myelosuppression occurs in 25% to 30% of patients treated with cisplatin. The nadirs in circulating platelets and leukocytes occur between days 18 and 23, with most patients recovering by day 39. Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m2). Anemia (a decrease in hemoglobin of 2 g/100 ml) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia.

- **Neurotoxicity**

Cisplatin neurotoxicity is characterized by peripheral neuropathies, which are sensory in nature but can also include motor difficulties such as reduced deep-tendon reflexes and leg weakness. The symptoms usually occur after prolonged therapy (4 to 7 months). Cisplatin therapy should be discontinued when serious neuropathy develops. The neuropathy, however, may progress further even after discontinuation of treatment.

In the DF/HCC neoadjuvant trial of 4 cycles of cisplatin 75mg/m^2 q21 days in 28 women with triple negative breast cancer, only one grade 4 toxicity was observed, an elevation in SGOT. There were 7 grade 3 symptomatic toxicities: one each, fatigue, abdominal pain, GI toxicity unspecified, myalgias, skin toxicity and tinnitus. Grade 3 toxicities in laboratory tests were seen in 2 women with low white blood cells and one each hyperkalemia and elevation in SGPT.

2.1 Rationale

2.1.1 Combination therapy of PARP-1 inhibitors with cisplatin in advanced solid tumours

Cisplatin interferes with the growth of cancer cells, slowing their advance in the body.

Cisplatin is currently approved by the Food and Drug Administration (FDA) to be used by itself to treat the following conditions:

- Bladder Cancer that cannot be treated with surgery or radiotherapy.
- Ovarian cancer that has metastasized (spread to other parts of the body) and has not gotten better with other drugs.

Cisplatin is approved to be used together with other drugs to treat the following conditions:

- Advanced ovarian cancer in patients who have already had surgery.
- Metastatic ovarian cancer in patients who have already had surgery or radiotherapy.
- Testicular cancer in patients who have already had surgery or radiotherapy.
- Locally advanced squamous cell carcinoma of the head and neck (SCCHN) that cannot be treated with surgery.
- Late-stage cervical cancer that cannot be treated with surgery or radiotherapy.
- Malignant mesothelioma that cannot be treated with surgery.
- Locally advanced, advanced, or metastatic non-small cell lung cancer (NSCLC) that cannot be treated with surgery.

In addition to the approved indications by the FDA, cisplatin is also used alone or with other drugs to treat other types of cancer. Cisplatin continues to be studied in the treatment of many types of cancer.

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer deaths after lung cancer in American women. In modern oncology, it is increasingly possible to recognize subsets of common cancers, and to target therapies based on particular features of specific subsets. In breast cancer, therapies targeting the oestrogen receptor (ER) are effective only in tumours expressing ER. The antibody therapy, trastuzumab, has shown remarkable efficacy against tumours shown to have amplified or overexpressed HER2 genes. The amplification of HER2 is an acquired event in tumour cells only.

Recent data from cell lines suggests that breast cancers arising in patients with BRCA1 mutations may be more sensitive to the cidal effects of cisplatin than other breast cancers (Bhattacharyya et al 2000, Moynahan et al 2001, Husain et al 1998,, Tassone et al 2003,

Quinn et al 2003). Accumulating data suggest that specific alterations in genes in the BRCA1 double strand break repair pathway may result in tumours that are less capable of repairing specific types of DNA errors. In addition, most BRCA1-associated cancers have been shown to be poorly differentiated, ER/PR negative, HER2 negative, and to belong to the basal-like subset of tumours as characterized in tissue microarrays (Sorlie et al 2003, Lakhani et al 2002). These basal-like tumours show high expression of proliferation-associated genes and over-expression of genes that are normally expressed in myoepithelial or basal cells of normal breast tissue such as the basal keratins and smooth muscle actin; hence the name, "basal-like" or "basaloid" (Sorlie et al 2003). Moreover, the "basaloid" tumours not associated with germline BRCA1 mutations are also typically lacking ER/PR receptors, are histologically high grade, and are reported to be positive for basal-like keratins. In fact, basaloid tumours appear to comprise 80% of ER/PR/HER2 negative breast cancers. Since the precise mechanism of the increased cisplatin sensitivity of the BRCA1-associated basaloid tumours is unknown, it is possible that it is maintained in the basaloid tumours not associated with germline BRCA1 mutations. In BRCA2 deficient mammary cell lines, tumor cells were demonstrated to be exquisitely sensitive to PARP inhibition with AZD2281 alone or, as a result of potent synergy, in combination with cisplatin (Evers et al 2008).

Agents that inhibit PARP have the potential to improve the therapeutic efficacy of several commonly used chemotherapeutics in oncology.

Previous ongoing studies to date with AZD2281 have demonstrated inhibition of PARP over a range of doses with evidence of clinical efficacy and an acceptable safety and tolerability profile.

The study is designed to provide a tolerated dose of AZD2281 combined with cisplatin which can be investigated in further studies.

3. STUDY OBJECTIVES

3.1 Primary objective

- The primary objective is to determine the safety and tolerability of twice daily oral doses of AZD2281 when administered in combination with cisplatin to patients with advanced solid tumours.

3.2 Secondary objectives

The secondary objectives of the study are:

- To compare exposure to AZD2281 when given alone and in combination with cisplatin. (Only in patients receiving continuous dosing of AZD2281)

- To make a preliminary assessment of the anti-tumour activity of AZD2281 when given in combination with cisplatin, by measuring overall response rate.

3.3 Exploratory objectives

- To obtain an optional blood sample for DNA extraction for future pharmacogenetic analysis and other potential correlative markers of the activity of AZD2281 and drugs taken in combination with AZD2281 (i.e. cisplatin).

The exploratory analyses will be reported separately.

4. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

4.1 Overall study design

The study is a Phase I non-randomised, open label, dose finding study, to determine the maximum tolerated dose of AZD2281 that can be combined with cisplatin in patients with advanced solid tumours.

Each cohort will comprise a minimum of 3 evaluable patients. If 1 patient from the initial 3 experiences DLT the cohort will be expanded to at least 6 patients. It is expected that 60 patients will be enrolled.

Once the desired dose or MTD of the combination therapy has been determined (or the highest dose level has been explored) the cohort will be expanded to ensure that there are 6 evaluable patients who have completed four cycles of treatment.

If continuous dosing is not tolerated, intermittent dosing will be explored. An intermittent dosing cohort will be opened to enrol 12 patients at the following dose:

- AZD2281 at 100 mg bid for days 1-10 of a 21 day cycle with 75 mg/m^2 of cisplatin on day 1 of a 21 day cycle

- Day 1 of cisplatin and day 1 of AZD2281 are the same day

In the event that the first intermittent dose cohort is not tolerated, further cohorts may be investigated with a starting dose of AZD2281 at 50 mg bid for days 1-5 of a 21 day cycle with 75 mg/m^2 of cisplatin.

Further cohorts may be considered following review by the safety monitoring committee. The cohort options to be considered are described in Table 3.

For the continuous dosing regimens, at visit 2, study day 1 (+3 days), only a morning dose of AZD2281 will be administered. On the morning of study day 1, patients will attend the clinic to begin cycle 0 where, in addition to receiving a cohort-specific oral dose of AZD2281, samples for a full 12-hour plasma PK profile will be taken. From Cycle 1 at visit 3 Study day

8 and on each day thereafter, AZD2281 will be taken orally twice-daily. Also on day 8, cisplatin will be administered 2 hours after AZD2281 administration. This will be day 1 of the 21-day cycle. A full 12-hour plasma PK profile will also be repeated at this visit to enable a comparison of AZD2281 PK when given alone and in combination with cisplatin. Pharmacokinetic (PK) blood samples will be collected for patients receiving continuous dosing of AZD2281 as described in Section 5.3.

For the intermittent dosing regimens, the first AZD2281 administration will be on the same day as cisplatin administration, unless a different dose schedule is advised by the safety monitoring committee. PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort.

The Maximum Tolerated Dose (MTD) is defined as the prior dose level below the drug-combination that causes DLT, in at least 2 patients in a cohort of up to 6 patients. If toxicity is equivocal and it is not possible to determine a DLT with certainty, further cohorts of three patients will be recruited to allow an informed decision to be taken about further dose escalations with AZD2281.

The dose escalation will continue until the MTD is established, however the highest dose to be explored will be 400 mg bid. Intra-patient dose escalation is not permitted.

4.1.1 Stopping criteria for dose escalation

AZD2281 will commence at 50 mg twice-daily in cohort 1, then increase to 100 mg twice-daily and 200 mg twice-daily. A further dose-escalation of AZD2281 to 400 mg twice-daily may be considered following review of the data. The dose of cisplatin will be 75 mg/m^2.

Dose-escalation of AZD2281 will stop if Dose Limiting Toxicity of the drug-combination occurs. At least three patients treated in a cohort must undergo repeated safety evaluations, up to and including Day 21, before enrolment of patients in the next dose cohort begins. Decisions to escalate to the next level, or, when appropriate, to an intermittent level, will be made jointly by the investigator and sponsor's Responsible Medical Officer based on review of all the available data.

If one patient in a cohort of 3 evaluable patients experiences a dose-limiting toxicity (DLT) during the first cycle that is considered related to combination-therapy, the cohort will be expanded to at least 6 patients.

In the continuous dosing schedule, Pharmacokinetic (PK) evaluations will be performed and may be utilised to guide appropriate changes to the regimen, if indicated. Cisplatin has the potential to cause nephrotoxicity which may affect clearance of other agents, including AZD2281.

Table 2 shows the continuous dosing escalation strategy to be adopted:

Table 2 Proposed dose escalation schedule for the continuous dosing regimens

Cohort	Number of patients recruited	Cisplatin dose Q21d	AZD2281 dose	Schedule
1	**3 – 6**	**75 mg/m^2**	**50 mg bid**	**Continuous**
2	**3 – 6**	**75 mg/m^2**	**100 mg bid**	**Continuous**
3	**3 – 6**	**75 mg/m^2**	**200 mg bid**	**Continuous**

In the event that the continuous dosing regimens are not tolerated, intermittent dosing regimens will be explored.

Table 3 shows the intermittent dosing strategy to be adopted:

Table 3 Proposed dose schedule for the intermittent dosing regimens

Cohort	Number of patients recruited	Cisplatin dose Q21d	AZD2281 dose	Schedule
4	12	75 mg/m^2	100 mg bid	Day 1-10 of the 21-day cycle
5	4-12	75 mg/m^2	50 mg bid	Day 1-5 of the 21-day cycle
Further cohorts may be considered following review by the safety monitoring committee. The cohort options below will be considered.				
	4-12	75 mg/m^2	50 mg bid	Day 1-3 of the 21-day cycle
	4-12	60 mg/m^2	50 mg bid	Day 1-5 of the 21-day cycle
	4-12	75 mg/m^2	50 mg bid	Day 2-6 of the 21-day cycle
	4-12	75 mg/m^2	100 mg bid	Day 1-5 of the 21-day cycle

The following additional points concerning the dose escalation strategy should be noted;

- Either agent may be dose-reduced, although only one agent should be modified at a time.
- No intra-patient dose-escalation will be permitted (whilst the patient is on combination therapy).
- A minimum of 3 patients per cohort must be treated, followed up and assessed for 21 days prior to recruiting patients into subsequent cohorts.
- Once the desired dose or MTD of the combination therapy has been determined (or the highest dose level has been explored) the cohort will be expanded to a to ensure that there are 6 evaluable patients who have completed four cycles of treatment.
- In the event that cisplatin is permanently discontinued on the basis of cisplatin related toxicity, treatment with AZD2281 alone may continue. If the patient does continue on AZD2281 alone, at the discretion of the PI and in consultation with AstraZeneca Study Team Physician, the patient may be dose escalated to receive the optimal monotherapy dose (ie: 400 mg bid).

A patient will be defined as evaluable for assessment of safety and tolerability for AZD2281 in combination with cisplatin if they:

- Complete at least 1 cycle of cisplatin (3 weeks) and also receives at least 75% of the planned continuous or intermittent dosing of AZD2281.

OR

- Experience DLT on combination treatment prior to fulfilling the above criteria.

Patients on the continuous dosing schedules are evaluable for PK evaluation if they are able to provide a full AZD2281 PK profile collected both with and without cisplatin.

4.1.2 Dose Limiting Toxicity

Toxicity will be graded using the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. Dose-limiting toxicity (DLT) is defined as the following study drug-related events experienced during Cycle 1:

- Grade 4 thrombocytopenia.
- Grade 4 neutropenia lasting >5 days.
- Febrile neutropenia (ANC <1.0 x109/L with fever ≥38.5°C).
- Treatment delay of >2 weeks.

- Other Grade 3 non-haematological toxicities; excluding non-optimally treated nausea, vomiting and diarrhea

Patients with dose-limiting toxicity after cycle 1 who have documented clinical benefit (stable disease or an objective response) may continue to be treated at a reduced dose level if considered clinically appropriate by the investigator.

Any patient in whom a DLT occurs during any cycle will have his or her treatment delayed until toxicity resolves to grade 1 or below.

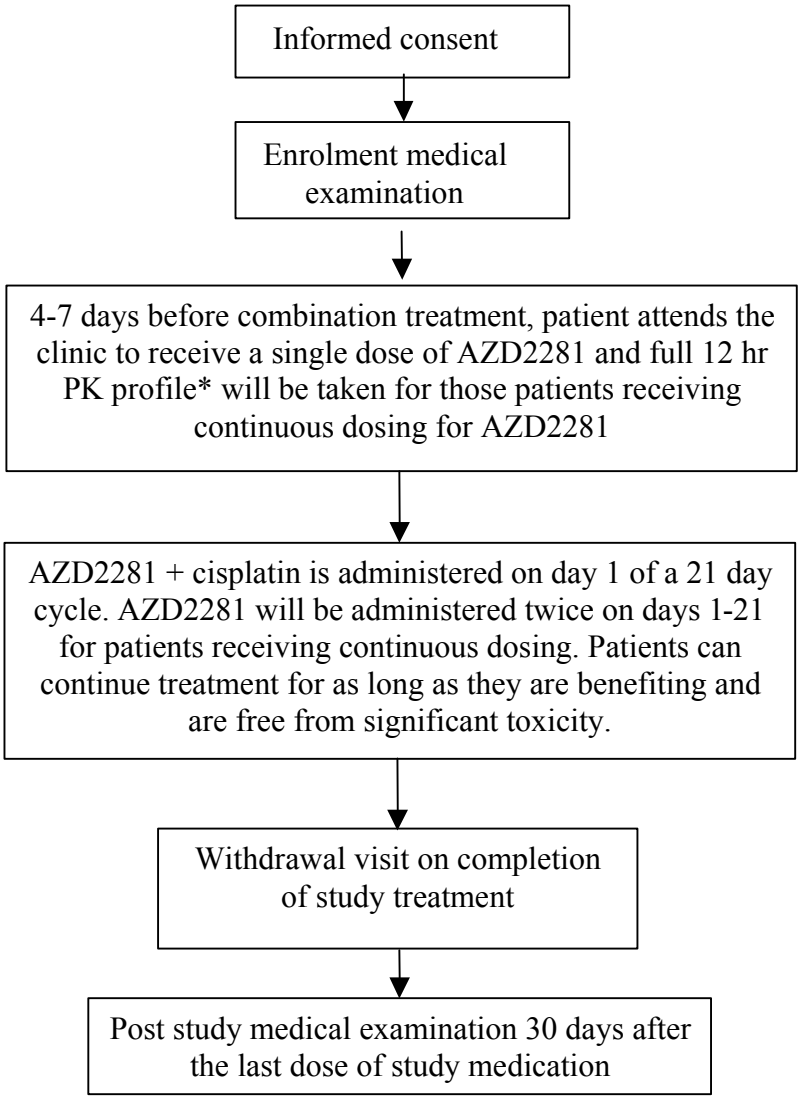
4.1.3 Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) is defined as the prior dose level below the drug-combination that causes DLT, in at least 2 patients in a cohort of at least 6 patients.

If, at any dose level, a patient fails to complete cycle 1 for reasons other than DLT, that patient is deemed unevaluable for determining the MTD and may be replaced. Such a patient will be included in the evaluation of toxicity and efficacy.

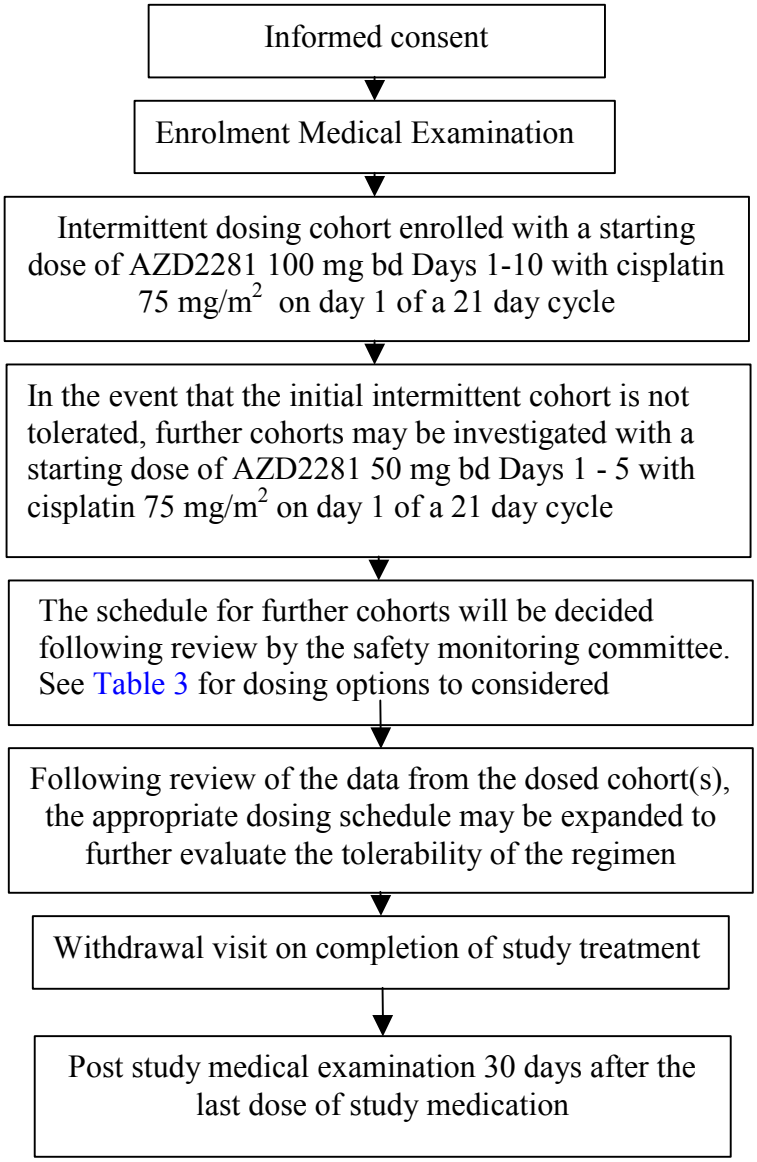
Exploration of different combination dosing regimens may be investigated to provide a tolerated dose of AZD2281 combined with cisplatin which can be investigated in further studies, however the highest dose to be explored will be 400 mg bid. (The MTD established in the monotherapy Phase I study).

Figure 2 Study flow chart - Continuous dosing schedule



* PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort

Figure 3 Study flow chart - Intermittent dosing schedule



Note: Patients can continue treatment for as long as they are benefiting and are free from significant toxicity. After patients complete 6 cycles of cisplatin based therapy, cisplatin may be discontinued and AZD2281 alone may be continued at the optimal monotherapy dose (i.e. 400 mg bid) at the investigators discretion. See Section 4.2.3 and Table 5 for full details.

4.2 Schedule of assessments, investigations and sampling

4.2.1 Baseline (Screening assessments)

The following assessments and procedures should be performed within 21 days prior to first dose of study treatment. A cycle of treatment is scheduled to last 3 weeks (21 days). For details of the schedule and nature of the assessments, see below

- Signed informed consent
- Date of birth and race
- BRCA1/2 mutation status, if known from previous testing (not required for enrolment)
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (preferably within 7 days prior to treatment start)
- Medical and surgical history
- Current and concomitant medications including previous cancer therapies (if applicable)
- Physical examination; ECOG performance status, vital signs (blood pressure and pulse rate, body temperature), 12-lead ECG, height and body weight
- Haematology, clinical chemistry and urinalysis
- Tumour assessment:
  - Chest/abdomen Pelvis CT or MRI & other regions as clinically indicated
- Adverse events must be captured from time of consent

4.2.2 On trial assessments

The first cycle of cisplatin treatment will be administered once the patient has been confirmed as being eligible for inclusion into the study. Treatment cycles of cisplatin will have duration of 21 days each. Patients will self administer AZD2281 at home except on the days when PK profiles will be taken. PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort.

Patients will attend the clinic on a periodic basis and the following assessments will be performed at timepoints specified in the study schedule (see Table 4)

- Physical examination including ECOG performance status (day 1 of each 21 day period) and vital signs every visit

- ECG
  - Baseline, at the end of each of the first two cycles of cisplatin, at the end of treatment and at the final follow-up and if clinically indicated at any other time
- Haematology, clinical chemistry
- Creatinine Clearance should be calculated every cycle based on serum creatinine
- Serum or urine pregnancy test for women of childbearing potential (prior to starting treatment). If the test is positive then a confirmatory test should be performed.
- PK samples for determination of plasma AZD2281 (visit 2 and 3)
  *Excluding patients on intermittent dosing
- AE & concomitant medications (every visit)
- Tumour assessment
  - Chest/Abdomen Pelvis CT or MRI & other regions as clinically indicated
- An optional pharmacogenetic sample will be obtained from consenting patients and stored for long-term experimental pharmacogenetic analysis
- Blood samples for pharmacokinetic analysis (Continuous dosing only**)**

4.2.3 AZD2281 Monotherapy

Upon completion of cycle 6 (ie, 21 days after last dose of chemotherapy), cisplatin may be discontinued and AZD2281 alone may be continued at the optimal monotherapy dose (i.e. 400 mg bid) at the investigators discretion.

The first dose of olaparib maintenance (Day 1 of olaparib maintenance phase) is the day after the chemotherapy discontinuation visit.

Following the patients' first dose of olaparib maintenance, they will return to the clinic for safety assessments at days 8, 15, 22 and 43, and then every 6 weeks thereafter relative to monotherapy day1 until objective disease progression as per RECIST criteria (assessed every 12 weeks), unless any other discontinuation criteria are met. See Table 5 for specific assessments and time points.

4.2.4 Treatment discontinuation visit

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 4.4.6.1). The assessments to be carried out at the visit are detailed in the study schedules (Table 4, and Table 5 for Monotherapy phase).

4.2.5 Withdrawal visit

Patients should be withdrawn from the study if discontinuation criteria are fulfilled (see Section 4.4.6.1). The assessments to be carried out at the visit are detailed in the study plans (Table 4 and Table 5 for Monotherapy phase).

4.2.6 Final follow up visit

A final follow-up visit should be conducted 30 days after the last dose of AZD2281. Any serious and/or non-serious AEs ongoing at the time of the Withdrawal Visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Section 5.10.3). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the Investigator, until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. The patient may have the 30-day follow-up blood samples taken at a local institution as an alternative to the investigator site, if the patient is too sick to travel. If the patient is lost to follow-up, then this should be noted in the CRF. The assessments to be carried out at the 30 day follow up visit are detailed in the study schedule (Table 4 and Table 5 for the monotherapy phase)

Table 4 Study plan (see Section 5 for further details)

Cycle	**0**	**0**	**1**			**2**			**3,4,5 [hq]**			**Withdrawal**	**30 Day follow up (+/-7days)**
Visit Number	**1**	**2***	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**		
Week	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Study Day	**Scr**	**1-4**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**		
Informed Consent	X[a]												
Demography	X[a]												
Confirm eligibility	X[c]												
Medical / Surgical History	X[a,]												
Physical Examination [b]	X[c]		X			X			X[j]			X	X
Audiometric testing	X[j]								X[j]			X[j]	
Vital signs [d]	X[c]		X	X	X	X	X	X	X	X	X	X	
Performance Status	X[c]		X			X			X[d]			X	
ECG [e]	X[c]				X			X				X	X
Pregnancy test [f]	X		X										
Tumour assessment [p]	X								X			X	
Haematology[g]	X[c]		X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry [g]	X[c]		X	X	X	X	X	X	X	X	X	X	X
Urinalysis [g]	X[c]		X	X	X	X	X	X	X	X	X	X	X
PGx blood sample		X[l]											
PK blood sampling AZD2281		X[i]	X[i]										
Cisplatin infusion			X			X			X[h]				

Table 4 Study plan (see Section 5 for further details)

AZD2281 dosing		X^{k}	X^{mn}	← dependent on cohort → continuous or intermittent bid dosing								
Adverse Events and con meds [o]	X	X	X	X	X	X	X	X	X	X	X	X

[*] Visit 2 is not applicable for patients enrolled in the intermittent dosing cohort, (PK is not required and therefore the single dose of AZD2281 is not applicable) – assessments that are scheduled for this visit can be done at visit 3 (Day 1 dosing with cisplatin)

[a] To be performed within 21 days of planned day –1

[b] Physical examination including weight and height for determination of cisplatin dose (height screening only)

[c] To be performed within 7 days before study day -1. Eligibility to be confirmed before commencing treatment on study day 1

[d] Vital signs to include blood pressure (BP), pulse rate (PR) and body temperature. BP and PR should be taken after the patient has been sitting at rest for 5 minutes and before blood sampling. At the PIs discretion and if the patient has completed 4 cycles of combination therapy, vital signs, performance status, haematology, and clinical chemistry assessments may be performed at the beginning of each cycle and not at each weekly visit, unless clinically indicated.

[e] ECG to be performed at baseline, at the end of each of the first 2 cycles of cisplatin, at the end of treatment and at final follow up and if clinically indicated at any other time

[f] Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to starting treatment and the other on Day 1 of the study prior to commencing treatment. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

[g] Haematology, clinical chemistry and urinalysis to be performed weekly +/- 1 day. Samples only need to be collected predose on day 1 if the screening assessments were performed more than 3 days before to day 1. At the PIs discretion and if the patient has completed 4 cycles of combination therapy, vital signs, haematology, and clinical chemistry assessments may be performed at the beginning of each cycle and not at each weekly visit, unless clinically indicated.

[h] Patients receiving benefit from treatment with AZD2281 and cisplatin can continue provided they are receiving benefit and are free from intolerated toxicity. Routine safety visits will be performed until discontinuation. Tumour assessments will be performed at the end of every 2 cycles of cisplatin (6 weekly intervals). In the event that cisplatin is permanently discontinued, treatment with AZD2281alone may continue. If cisplatin is permanently discontinued, patients should have weekly visits for the first two months (8 weeks) of AZD2281 monotherapy, and then every month (4 weeks) after 2 months of AZD2281 monotherapy. After the patients completes 4 cycles of cisplatin at the full dose of 75 mg/m2, subsequent cycles of cisplatin may be administered at a reduced dose as low as and including 50 mg/m2 at the investigator's discretion. After patients complete 6 cycles of cisplatin based therapy, cisplatin may be discontinued and AZD2281 alone may be continued at the optimal monotherapy dose (i.e. 400 mg bid) at the investigators discretion. See Section 4.5.2.2 for full details. Note: After protocol amendment 6 is approved, patients on AZD2281 monotherapy can have their visit schedule modified as per Table 5and Section 4.2.3.

[i] Blood samples for AZD2281 PK will be taken relative to the morning dose of AZD2281: predose, 1,2,3,4,6, 8, 12 hrs post dose. A 10 minute time window (+/- 10 minutes) will be allowed but the samples should be taken as close to the nominal time point as possible. If it is not possible to take the 12 hour sample at the correct time, take the sample as close to 12 hours as possible ensuring this sample is taken at the same time at Visit 2 and Visit 3. PK blood draws will not be performed for patients enrolled into an intermittent dosing cohorts.

[redacted]

j Audiometric testing should be performed at baseline, at the end of the 2nd, 4th and 6th cycles of cisplatin and as clinically indicated thereafter. A final audiogram should be done at study completion. In the event that cisplatin is permanently discontinued, only the final audiometric test done at study completion is required, unless otherwise clinically indicated.

k At visit 2, a single dose of AZD2281 (dose dependent on the cohort) will be given in conjunction with collection of PK samples (see footnote 'i' above). The medication bottle will have been labelled with the patient's E Code and be retained by the study site until the patient returns for Visit 3, when the same bottle will be dispensed to the patient. Note: the single dose is only applicable for patients enrolled in a continuous dosing cohort.

l Blood sample for PGx (optional), patients enrolled on an intermittent dosing cohort can have this blood sample taken at visit 3

m AZD2281 will be dispensed for twice daily dosing either on a continuous or intermittent basis. Instruct patients to return both used and unused study drug bottles and study drug at their next scheduled study visit.

n Throughout the duration of the study, dispense sufficient number of bottles for an appropriate number of days/cycles of treatment depending on the dose level. Used and unused study AZD2281 should be accounted for and compliance checked (including a review of the patient diary card)

o Adverse events must be collected from the time of informed consent, throughout the treatment period and up to and including the 30-day post-study follow-up period. All ongoing, AEs at discontinuation must be monitored until resolution unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution unless, in the opinion of the Investigator, the condition is unlikely to resolve due to the patient's underlying disease. All relevant concomitant medications including those stopped within 6 weeks of first dose AZD2281, should be recorded on the CRF. Con-meds should be recorded up until the 30 day follow up visit ensuring all medication stop dates have been entered where applicable.

p RECIST assessment by CT or MRI scans of chest abdomen, pelvis and other regions including chest as clinically indicated for the assessment of disease. Baseline assessment may be performed up to 28 days prior to study day 1 (see Appendix D). Follow up assessments performed at the end of every 2 cycles of treatment +/- 1 week (see Appendix D). Confirmation of response will be at the next scheduled assessment. Once a patient has completed 3 months (12 weeks) of monotherapy, tumour assessments are only required at the end of every 3 months (every 12 weeks (+/- 1 week). At withdrawal, RECIST assessment is required, however if the previous RECIST assessment was performed within 6 weeks of withdrawal, the withdrawal RECIST assessment should be performed but can be missed at the discretion of the investigator.

q Until a patient is withdrawn from the treatment or the study the assessments should be carried out as in visits 9/10/11

Table 5 Olaparib Monotherapy Phase – see Section 4.2.3

Visit Type	**Olaparib Monotherapy Phase[a]**						**Olaparib Monotherapy Treatment Discontinuation**	**Post Discontinuation Follow-up**
Timing of Visit	**Monotherapy Day 1[b]**	**Monotherapy Day 8[b]**	**Monotherapy Day 15[b]**	**Monotherapy Day 22[b]**	**Monotherapy Day 43[b]**	**Every 6 weeks**	**N/A**	**30 days post discontinuation**
Visit Window		± 2 days	± 2 days	± 2 days	± 4 days	± 4d	± 3 days	± 3 days
Physical Exam	X				X	X	X	
Vital signs (Includes BP [supine position], pulse rate (PR), body temperature	X				X	X	X	X
Performance Status	X				X	X	X	X
ECG[c]							X	
Haematology / Clinical Chemistry	X	X	X	X	X	X	X	X
Tumour Assessment (CT or MRI according to RECIST)[d]	Tumour assessments at weeks 9 and 18 (± 1 week) and every 12 weeks (± 1 week) thereafter relative to date of cycle 1 day 1 of the combination therapy until disease progression							
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Olaparib dispensed / returned[ef]	X				X	X	X	

[a] All patients should attend study visits until objective disease progression according to RECIST or the patient must discontinue due to unacceptable toxicity as outlined in the protocol

[b] Day is relative to the start of olaparib (AZD2281) monotherapy

[c] ECGs performed at baseline, completion of chemotherapy, and discontinuation of olaparib maintenance and if clinically indicated at any other time. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case.

[d] RECIST assessment by CT or MRI scans of chest abdomen, pelvis and other regions including chest as clinically indicated for the assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged 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. Mandatory tumour assessments will be performed at baseline, 9 weeks and 18 weeks and every 12 weeks thereafter relative to date of cycle 1 day 1 of combination therapy until disease progression **(**At withdrawal, RECIST assessment is required, however if the previous RECIST assessment was performed within 6 weeks of withdrawal, the withdrawal RECIST assessment should be performed but can be missed at the discretion of the investigator.

[e] When all other procedures have been performed, olaparib will be dispensed (sufficient for an appropriate number of days/cycles of treatment). Used and unused olaparib should be accounted for and compliance checked. At the discontinuation visit, no olaparib will be dispensed

[f] AZD2281 dose administration is not required in clinic

4.3 Rationale and risk/benefit assessment

4.3.1 Rationale for study design, doses and control groups

This is a Phase I non-randomised, open label, dose finding study, to determine the maximum tolerated dose of AZD2281 that can be combined with cisplatin in patients with advanced solid tumours.

This study is designed to provide safety and tolerability data for AZD2281 in combination with cisplatin and PK data for AZD2281 alone and in combination with cisplatin.

For the continuous dosing combination treatment regimen, patients will attend the clinic 1 week (4-7 days) before the combination treatment is due and a single dose of AZD2281 will be given (dose depending on cohort recruited into). Plasma PK samples will be obtained over 12 hours. A PK profile will be again taken on day 1 of cycle 1 of cisplatin (day 8) when AZD2281 will be given in the presence of cisplatin. This will permit a comparison of the exposure to AZD2281 when given with cisplatin and without. Patients will be closely monitored for safety and dose levels will be assessed once at least 3 evaluable patients have completed 21 days of combination treatment or have experienced a DLT.

For intermittent dosing cohorts, no PK is required; therefore patients are only required to start their AZD2281 dosing on the same day as cisplatin is administered, unless a different dose schedule is advised by the safety monitoring committee.

The dose levels of 50, 100, 200 and 400 mg (twice-daily) either continuous or intermittent have been chosen, as previous Phase I studies have demonstrated that they are all generally well tolerated, yield systemic concentrations of AZD2281 and are likely to be biologically active.

The Phase I study design takes into account patient population, the emerging toxicity profile of AZD2281, pharmacology of cisplatin and potential for interactions that might impart treatment related toxicities. There is little evidence to suggest that there will be an ADME based interaction when the two drugs are administered in combination.

The number of patients is based on the desire to gain adequate information whilst exposing as few patients as possible to the study medication and procedures.

4.4 Selection of study population

4.4.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrolment but never enrolled eg, subject screening log, according to local procedures. This information is necessary to establish that the subject population was selected without bias

Each patient 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.

4.4.2 Inclusion criteria

For inclusion in the study patients must fulfil all of the following criteria:

1. Fully-informed written consent.

2. Adequate bone marrow, hepatic and renal function including the following:

   - Haemoglobin ≥9.0 g/dL
   - White blood cell count (WBC) >3 x 10^9/L
   - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   - Platelet count ≥100 x 10^9/L;
   - Total bilirubin ≤1.5 x institutional upper limit of normal (ULN);
   - AST (SGOT), ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤5x ULN
   - Serum creatinine ≤1.5 mg/dL x institutional upper limit of normal (ULN)
   - Creatinine Clearance >50mL/min (calculated or 24 hour urine sample)

3. Male or female patients, age ≥18 years

4. Performance status (PS) ≤2 (ECOG scale) (see Appendix F)

5. The patient is willing and able to comply with the protocol for the duration of the study, including hospital visits for treatment and scheduled follow-up visits and examinations.

6. Negative pregnancy test for women of childbearing potential only.

7. Histologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent for whom no standard (or approved) therapy is available.

8. Life expectancy of at least 12 weeks.

9. Patients with measurable or non measurable disease according to RECIST (see Appendix D)

For inclusion in the genetic component of the study, patients must fulfil the following criterion:

- Provision of informed consent for genetic research

If a patient declines to participate in the pharmacogenetic component of the study, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this Clinical Study Protocol, so long as they consent.

4.4.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Major surgery within 4 weeks of starting the study

2. Co-existing active infection

3. Gastrointestinal disorders likely to interfere with absorption of the study drug (eg, partial bowel obstruction, malabsorption) or with the patient's ability to take regular oral medication

4. Patients requiring treatment with inhibitors or inducers of CYP3A4 (see 4.5.10 for guidelines and wash out periods)

5. Patients currently experiencing seizures or who were currently being treated with any anti-epileptic for seizures (use of anti-epileptic drugs to control pain is allowed in patients not suffering from seizures unless drug is excluded due to CYP3A4 induction – phenytoin, carbamazapine, phenobarbitone (see Section 4.5.10).

6. Patients who are unable to swallow oral medication

7. A positive pregnancy test. Pregnant or breast-feeding women or women of childbearing potential unless effective methods of contraception are used (lack of childbearing potential is met by being post-menopausal, being surgical sterile, practicing contraception with an oral contraceptive or other hormonal therapy [eg, hormone implants], intra-uterine device, diaphragm with spermicide or condom with spermicide, or being sexually inactive. Patients and their partners must agree to use two of the above forms of contraception throughout the treatment period and for 3 months after discontinuation of treatment. Male patients must refrain from fathering a child or donating sperm during the study and for 3 months following the last dose of AZD2281.

8. Renal dysfunction for which exposure to cisplatin would require dose modification or be completely unsafe (serum creatinine >1.5 mg/dL)

9. Immunocompromised patients eg, Patients who are known to be serologically positive for human immunodeficiency virus (HIV).

10. Patients with active or severe cardiovascular or pulmonary disease, including recent (<6 months) myocardial infarction or deep-venous thrombosis/pulmonary embolism, congestive heart failure, uncontrolled hypertension (systolic blood

pressure >180 mm Hg, diastolic blood pressure >105 mm Hg), or steroid-dependent asthma, are ineligible.

11. Patients with peripheral neuropathy of any etiology that exceeds grade 1 (see Appendix B) are ineligible

12. Patients with uncontrolled diabetes (fasting blood sugar >200 mg/dL) are ineligible

13. Any co-existing medical condition that in the investigator's judgement will substantially increase the risk associated with the patient's participation in the study e.g. patients with a clinically significant hearing impairment

14. Simultaneous participation in any other study involving an investigational medicinal product, or having participated in a study less than 28 days prior to the start of study treatment.

15. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

16. Prior use of any PARP inhibitor, including AZD2281, and any known hypersensitivity to AZD2281 or any of its excipients, cisplatin or other platinum containing compounds

17. Use of live virus vaccinations within 3 months before or after treatment

18. Less than 28 days from active therapy (i.e. any treatment used to treat the disease) or high dose radiotherapy (patients may continue concomitant use of a stable dose of bisphosphonates if used for at least 28 days prior to commencing study treatment and patients may receive palliative radiotherapy for bone disease during the study)

19. Brain metastases or spinal cord compression, unless irradiated at least 4 weeks before entry and stable without steroid treatment for ≥ 1 week.

20. Persistent CTCAE grade 2 or greater toxicities (excluding alopecia) caused by prior therapy

Procedures for withdrawal of incorrectly enrolled patients see Section 4.4.4.

4.4.4 Procedures for handling patients incorrectly enrolled or randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or randomised. There can be no exceptions to this rule.

Where patients that do not meet the selection criteria are randomised in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post initiation, a discussion should occur between the AstraZeneca Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. Once a decision is made, Investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review.

The AstraZeneca Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

4.4.5 Restrictions during the study

Patients will be required to:

1. Not donate blood during the study and for 3 months following their last dose of trial treatment

2. Refrain from concomitant use of known inhibitors or inducers of CYP3A4 (see Section 4.5.10)

3. Refrain from taking any additional medication without the prior consent of the investigator

4. Refrain from drinking grape fruit juice while taking the study medication and for 3 months after the last dose of study medication

4.4.5.1 Contraception

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception throughout their participation in the study and for 3 months after last dose of study drug(s).

- Condom with spermicide

and one of the following

- Oral contraceptive or hormonal therapy (e.g. hormone implants)

- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study and the drug washout period.

- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia

- Tubal occlusion plus male condom with spermicide

- Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded

Acceptable hormonal methods:

- Etonogestrel implants (eg, Implanon, Norplan)+male condom with spermicide

- Normal and low dose combined oral pills+male condom with spermicide

- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (eg, EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

4.4.5.2 Food intake restrictions

Patients should take AZD2281 no sooner than 1 hour after food. They should then refrain from eating for a further 2 hours due to potential effect of food on absorption. The olaparib capsules should be swallowed whole and not chewed, crushed, dissolved or divided.

See section 4.5.2 for further information.

4.4.5.3 Other Concomitant treatment

1. No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the course of the study for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above). Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present (see Section 4.5.8).

2. Live virus and bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

3. Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 4.5.6 from the time they enter the screening period until 30 days after the last dose of study medication. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, this restriction is required to ensure patient safety.

4.4.6 Discontinuation of Study Treatment

4.4.6.1 Criteria for Discontinuation from Study Treatment

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

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment

- Adverse event
- Severe non-compliance to study protocol
- Any CTCAE grade 3 or 4 events that have not reverted to CTCAE grade 1 or less within 28-days. At the Investigator's discretion, following dose interruption, patients may be considered for dose reductions. However, if upon re-challenging with AZD2281 at the lowest reduced dose, (for guidelines refer to Section 4.5.3), any CTCAE grade 3 or 4 adverse events recur, the patient must be discontinued.
- Bone marrow findings consistent with myelodysplastic syndrome/acute myeloid leukaemia
- Disease progression

Note: Patients may continue to receive study treatment following objective progression provided that, in the opinion of the Investigator, the patient is benefiting from the treatment and does not meet any other discontinuation criteria.

In the event that cisplatin is permanently discontinued on the basis of cisplatin related toxicity, treatment with AZD2281 alone may continue. If the patient does continue on AZD2281 alone, at the discretion of the PI and in consultation with AstraZeneca Study Team Physician, the patient may be dose escalated to receive the optimal monotherapy dose (i.e.: 400 mg bid).

4.4.6.2 Procedures for Discontinuation of a Patient from Investigational Product

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Sections 5.10.3 and 5.10.4); and all study drugs should be returned by the patient.

Any patient discontinuing investigational product should be seen at 30 days post discontinuation of study treatment for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal Investigator/Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the CRF the date of discontinuation, the reasons, manifestation and treatment at the time of discontinuation. If patients discontinue study treatment, the AstraZeneca monitor must be informed immediately. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up

(see Sections 5.10.3 and 5.10.4). All new AEs and SAEs occurring during the 30 calendar days after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 5.10.4) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study medication to collect and /or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study medication should also be reported as an AE.

4.4.6.3 Withdrawal from Study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Sections 5.10.3 and 5.10.4), diary cards and study drug should be returned by the patient.

Withdrawn patients will not be replaced

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Risk to patients as judged by the Investigator and /or AstraZeneca
- Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca
- Incorrectly enrolled patients i.e., the patient does not meet the required inclusion/exclusion criteria for the study
- The patient becomes pregnant
- Patient lost to follow-up

4.4.6.4 (PGx:) Procedures for Discontinuation from Genetic aspects of the Study

Patients who discontinue from the study should always be asked specifically whether they are withdrawing or continuing their consent for this linked genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic analyses in the future.
- Withdraws consent for the sample to be kept for genetic analysis in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is

traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The principal investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the investigator of the actions taken with the sample, which must be filed in the investigator study file.

4.5 Treatment(s)

4.5.1 Investigational product(s)

4.5.1.1 Identity of investigational product

AZD2281 is a white to off-white crystalline solid with a molecular weight of 434 Da. The molecular formula is $C_{24}H_{23}FN_4O_3$.

Micronised AZD2281 will be supplied as an oral capsule, with Gelucire 44/14 (Lauroylmacrogylcerides) as excipients (solubiliser).

Capsules will be Vcaps® Hydroxypropyl Methylcellulose Capsugel® Capsules which are not banded or enteric coated.

For this study, capsules are in one dosage strength: 50 mg, Size 0, coloured white.

Investigational product	Dosage form and strength	Manufacturer	Formulation Number	Batch number
AZD2281	50 mg	Patheon Inc on behalf of AstraZeneca	F13579	TBC[a]

[a] Batch numbers not currently available, these will be detailed in the Clinical Study Report

4.5.1.2 Labelling

AZD2281 will be supplied in High Density Polyethylene containers with a child-resistant cap. Patients will be given sufficient supplies for a dispensing visit, multiple capsules /bottles may be required to make up the dose.

The Investigator / site staff should dispense one or more bottles to the patient as required, in order to make up the assigned dose of AZD2281. Each container of AZD2281 will have an investigational-use label permanently affixed to the outside and will be labelled in accordance with Good Manufacturing Practice and local regulations, The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language stating that the drug is for clinical trial use only and should be kept out of reach of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at

the time of dispensing. Each label will also include a tear-off portion that should be applied to individual patient CRF/drug accountability forms, upon dispensing.

Centres will use their commercial supply of cisplatin for this trial. In situations where the cost of the drug is not covered by third party payment (ie, insurance) then centres will be reimbursed for the cost of the drug**.** Cisplatin should be stored, reconstituted and administered according to the manufacturers' recommendation. Details of each dose administered and the duration of infusion must be recorded in the Case Report Forms.

4.5.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. A description of the appropriate storage and shipment conditions are specified on the investigational product label.

4.5.1.4 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling trial treatments, including investigational medicinal products, so as to ensure that:

- deliveries of such products from AstraZeneca are correctly received by a responsible person
- such deliveries are recorded
- study treatments are handled and stored safely and properly
- study treatments are only dispensed to study patients in accordance with the protocol

4.5.2 Doses and treatment regimens

4.5.2.1 AZD2281

The doses of AZD2281 will be made up from 50 mg capsules to be taken twice daily either continuously or intermittently. Patients should swallow the medication whole with a glass of water in the morning and in the evening at the same time each day. This is to ensure approximately a 12-hour interval between doses. The dose of AZD2281 should be taken no sooner than 1 hour after food and patient should refrain from eating for 2 hours after dosing due to potential effect of food on absorption. The olaparib capsules should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the AZD2281 capsules are swallowed, the dose should only be replaced if all of the intact capsules can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the capsules or vomiting), the patient will be allowed to take the scheduled dose up to a maximum

of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Up to1 week before the start of combination treatment patients allocated to receive continuous dosing will attend the clinic to receive a single dose of AZD2281, PK samples over 12 hours will be obtained to get monotherapy PK information. PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort.

4.5.2.2 Cisplatin

Cisplatin should be prepared in accordance with the local prescribing guidelines. Cisplatin will be administered 2 hours (+/- 1 hour) after the first (morning) dose of AZD2281 every 3 weeks.

- **Dose:** cisplatin 75 mg/m^2 IV q3 weeks or cisplatin 60 mg/m^2 IV q3 weeks
- **Infusion Time:** 60 minutes.
- **Anti-Emetic Premedication**. Patients should receive prophylactic anti-nausea medications such as ondansetron 24 mg po/iv x 1, dexamethasone 10 mg –20 mg po/iv x 1, prochlorperazine 10 mg po x 1 prn, and/or lorazepam 1 mg iv/po x 1 prn prior to cisplatin therapy.
- **Pretreatment Hydration:** Hydration may be achieved by IV infusion of 1 litre of sodium chloride 0.9% over 1-2 hours prior to cisplatin infusion
- **Treatment:** Give 12.5 gm iv of mannitol 20% or mannitol 25% 30 minutes prior to cisplatin infusion. Mix cisplatin in 100-500 ml sodium chloride 0.9% and infuse IV over 60 minutes. Ensure there is adequate urine output averaging at least 100cc/hr prior to cisplatin infusion
- **Post treatment Hydration:** Patient should receive 1 litre of sodium chloride 0.9% iv over 1-2 hours after cisplatin administration.

In this phase I study, after patients have completed 4 cycles of cisplatin based therapy at the full dose of 75 mg/m^2, or a dose of 60 mg/m^2 for those patients that received the lower cisplatin dosing treatment cohort option, subsequent cycles of cisplatin may be administered at a reduced dose as low as and including 50 mg/m^2 at the investigator's discretion as long as the patient is continuing to derive clinical benefit and has not met the criteria for progressive disease or any other discontinuation criteria. (see section 4.4.6.1)

In this study, after patients complete 6 cycles of cisplatin based therapy, cisplatin may be discontinued and AZD2281 may be continued at the optimal monotherapy dose (i.e., 400 mg bid) at the investigators discretion, as long as the patient is continuing to derive clinical benefit and has not met the criteria for progressive disease or any other discontinuation criteria. See Table 5

Supplementation:

- **Magnesium supplementation:** Give prior to cisplatin, magnesium sulfate 2 g IV x 1. Patient to take 500 mg magnesium gluconate qd for 7 days. Magnesium level will be checked on day 7 and if <1.8 mg/dL, then magnesium supplementation should continue and adjusted at the physician's discretion.

- **Potassium supplementation:** give Potassium 30-40 mEq/day po for 7 days after each dose. Potassium level will be checked on day 7. If the measurement is <3.5 mmol/L, then potassium supplementation should be continued and adjusted at the physician's discretion.

4.5.3 Management of Toxicity

4.5.3.1 Management of Hematological Toxicity (cisplatin and AZD2281)

The following hematologic criteria must be met on Day 1 of each cycle to administer dosing of cisplatin and AZD2281:

- ANC $\geq 1.5 \times 10^9$/L

- Platelet count $\geq 100 \times 10^9$/L

If both of these criteria are not met, both cisplatin and AZD2281 should be held for up to a total of 14 days until neutrophils and platelets have recovered to meet the above criteria. If cisplatin and AZD2281 must be held for greater than 14 days and the above hematologic criteria are not met, the patient should be removed from the study. Growth factor is not to be used during cycle 1 (ie any time prior to the second dose of cisplatin). Growth factor can be administered as required after the second dose of cisplatin.

4.5.3.2 Management of Neutropenic Events

Cisplatin and AZD2281 may not be dosed until ANC $\geq 1.5 \times 10^9$/L

Filgrastim or PEG-filgrastim may be instituted at the investigator's discretion at any time following completion of cycle 1. Cycle 1 is defined as the time period up until the second dose of cisplatin dose is administered). Filgrastim or PEG-filgrastim may be used at the investigator's discretion during cycle 1 only in the event of febrile neutropenia occurring during cycle 1.

Filgrastim doses can be rounded to within (plus or minus) 10% of the contents of one commercial vial or combinations of the commercial products; i.e., 300 or 480 micrograms/vial.

Each of the following neutropenic events will be managed in a sequential fashion as described in Table 6.

1. ANC <1.0 $\times 10^9$/L on Day 1 of a cycle

2. Febrile neutropenia (ANC <1.0 x10^9/L with fever ≥38.5°C) at any time

3. CTCAE grade 4 neutropenia (ANC <0.5 x10^9/L) lasting longer than 5 days in the middle of a cycle

4.5.3.3 Management of Thrombocytopenic Events

Cisplatin and AZD2281 may not be dosed until Platelet count ≥ 100 x10^9/L

Each of the following thrombocytopenic events will be managed in a sequential fashion as described in Table 6.

1. CTCAE grade ≥3 thrombocytopenia (platelets <50 x10^9/L) at any point in the middle of a cycle

2. Platelet count <100x10^9/L on Day 1 of any cycle

4.5.3.4 Management of Hematologic NCI-CTCAE grade 3 or 4 AZD2281 Treatment Related Adverse Events

For the management for CTCAE grade 3 or 4 hematological toxicity, refer to Sections 4.5.3.1, 4.5.3.2, 4.5.3.3 and Table 6.

Table 6 Management of Hematologic (including Anaemic, Thrombocytopenic or Neutropenic) Grade 3 and 4 AZD2281 Treatment Related Adverse Events Whilst the Patient is Receiving Combination Therapy

Initial Dose Level[d]	1st Event Occurrence[abe] - Recommended Dose Reduction	2nd Event Occurrence[abe] – Recommended Dose Reduction	Dose Administration
100 mg bid	50 mg bid	No reduction allowed – withdraw patient	Continuous
200 mg bid	100 mg bid	50 mg bid	Continuous
400[c] mg bid	200 mg bid	100 mg bid	Continuous
50 mg bid	No reduction allowed – withdraw patient	Not applicable	Continuous
100 mg bid days 1-10 of a 21 day cycle	100 mg bid days 1-5 of a 21 day cycle	100 mg bid days 1-3 of a 21 day cycle	Intermittent
50 mg bid days 1-5 of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 60 mg/m^2	Intermittent

Table 6 Management of Hematologic (including Anaemic, Thrombocytopenic or Neutropenic) Grade 3 and 4 AZD2281 Treatment Related Adverse Events Whilst the Patient is Receiving Combination Therapy

Initial Dose Level[d]	1st Event Occurrence[abe] - Recommended Dose Reduction	2nd Event Occurrence[abe] – Recommended Dose Reduction	Dose Administration
50 mg bid <5 days dosing of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 60 mg/m^2	No reduction allowed – withdraw patient	Intermittent
50 mg bid days 1-5 dosing of a 21 day cycle with cisplatin dosed at 60 mg/m^2	50 mg bid days 1-3 of a 21 day cycle Cisplatin dose to remain at 60 mg/m^2	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 50 mg/m^2	Intermittent
Dose schedule advised by safety monitoring committee	Patients on other dose schedules should have their dose decreased as appropriate in line with the above guidance		

[a] Hold any remaining doses of AZD2281 in the current cycle
[b] Neutropenic events: Filgrastim or PEG-filgrastim may be implemented at the investigators discretion
[c] If 400 mg bid dose is explored
[d] Initial dose level includes cisplatin dosed at 75mg/m^2 unless stated otherwise
[e] At the investigators discretion, growth factor can be administered as required after the second dose of cisplatin

Note: The patient must be withdrawn if there is a third occurrence of any haematologic Grade 3 or 4 AZD2281 Treatment Related Adverse Events.

4.5.3.5 Management of non-hematological toxicity attributable to AZD2281

Grade 3-4 Non-hematological toxicities observed during the course of the study and attributable to AZD2281 will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 28 days. If an interruption of longer than 28 days is required, the patient should be withdrawn. When AZD2281 is interrupted, the patient must either recover completely or the toxicity must revert to NCI CTCAE ≤ grade 1 or to the baseline CTCAE grade before restarting treatment.

Where toxicity recurs following re-challenge with AZD2281, and where further dose interruptions are considered inadequate for management of toxicity, then the patient is to be considered for dose reduction or withdrawal.

See Table 7 for instructions on dose reductions for non-hematologic CTCAE grade 3 and 4 AZD2281 treatment related adverse events whilst the patient is on combination study treatment.

Please see Section 4.5.3.6 for further information on management of grade 3-4 non-hematologic toxicities, and Section 4.5.3.7 for management of grade ≤ 2 non-hematologic toxicity.

4.5.3.6 Management of Non-Hematologic NCI-CTCAE grade 3 or 4 AZD2281 Treatment Related Adverse Events

Treatment with AZD2281 must be interrupted for any non-hematologic CTCAE grade 3 or 4 adverse event which the Investigator considers to be related to administration of AZD2281. Repeated dose interruptions of up to a maximum of 28 days are allowed. Patients whose NCI CTCAE grade 3 or 4 event does not resolve to ≤ grade 1 or to the baseline CTCAE grade after a full 28 day dose interruption should be withdrawn from the study.

Upon appropriate resolution of the toxicity (i.e., to NCI CTCAE grade 1 or to baseline CTCAE grade), the patient should restart treatment with AZD2281 but with a 50% dose reduction (as per Table 7). The dose of AZD2281 should not be reduced to less than 50 mg bid daily for patients receiving continuous AZD2281 dosing or to less than 50 mg bd for days1-3 of a 21 day cycle for patients receiving intermittent AZD2281 dosing.

If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made where allowed.

Once a chemotherapy combination dose is reduced due to toxicity, combined chemotherapy dose re-escalation is not permitted.

Table 7 Management of Non-Hematologic[a] Grade 3 and 4 AZD2281 Treatment Related Adverse Events whilst the patient is receiving combination therapy

Initial Dose Level[c]	1st Event Occurrence - Recommended Dose Reduction	2nd Event Occurrence – Recommended Dose Reduction	Dose Administration
100 mg bid	50 mg bid	No reduction allowed – withdraw patient	Continuous
200 mg bid	100 mg bid	50 mg bid	Continuous
400[b] mg bid	200 mg bid	100 mg bid	Continuous
50 mg bid	No reduction allowed – withdraw patient	Not applicable	Continuous

Table 7 Management of Non-Hematologic[a] Grade 3 and 4 AZD2281 Treatment Related Adverse Events whilst the patient is receiving combination therapy

Initial Dose Level[c]	1st Event Occurrence - Recommended Dose Reduction	2nd Event Occurrence – Recommended Dose Reduction	Dose Administration
100 mg bid days 1-10 of a 21 day cycle	100 mg bid days 1-5 of a 21 day cycle	100 mg bid days 1-3 of a 21 day cycle	Intermittent
50 mg bid days 1-5 of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 60 mg/m^2	Intermittent
50 mg bid <5 days dosing of a 21 day cycle	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 60 mg/m^2	No reduction allowed – withdraw patient	Intermittent
50 mg bid days 1-5 dosing of a 21 day cycle with cisplatin dosed at 60 mg/m^2	50 mg bid days 1-3 of a 21 day cycle Cisplatin dose to remain at 60 mg/m^2	50 mg bid days 1-3 of a 21 day cycle Reduce cisplatin to 50 mg/m^2	Intermittent
Dose schedule advised by safety monitoring committee	Patients on other dose schedules should have their dose decreased as appropriate in line with the above guidance		

[a] With the exception of grade 3 or worse neurologic toxicity, in which case both cisplatin and AZD2281 should be discontinued, as per Section 4.5.3.8
[b] If 400 mg bid dose is explored
[c] Initial dose level includes cisplatin dosed at 75mg/m^2 unless stated otherwise

Note: The patient must be withdrawn if there is a third occurrence of any non-haematologic Grade 3 or 4 AZD2281 Treatment Related Adverse Events.

4.5.3.7 Management of Non-Hematologic NCI-CTCAE grade ≤2 AZD2281 Treatment Related Adverse Events whilst the patient is receiving combination therapy

For non-hematologic toxicities of CTCAE grade ≤2 that the investigator feels are related to the administration of AZD2281, the investigators should use their discretion in deciding whether dose interruptions are necessary and should also treat the events as medically appropriate based on signs and symptoms.

Except as noted above, the dose of AZD2281 must not be modified under any other circumstances unless prior agreement is given by AstraZeneca Pharmaceuticals.

Management of new or worsening pulmonary symptoms: If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in AZD2281 dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then AZD2281 treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

All dose reductions and/or interruptions (including any missed doses), and the reasons for the reductions and/or interruptions are to be recorded in the CRF.

4.5.3.8 Management of Non-hematologic treatment related adverse events attributable to cisplatin

Any cisplatin related toxicity, with the exception of ototoxicity, should resolve to ≤ Grade 1 prior to retreatment with cisplatin. Treatment with cisplatin may be continued on Day 1 of each cycle as long as each of the following criteria are met:

- ANC >1.5 x $10^{9/}$L
- Platelets >100 x $10^{9/}$L
- Creatinine ≤1.5 mg/dL
- CrCl >50 mg/mL (Creatinine Clearance should be calculated every cycle)
- Neurotoxicity ≤ CTCAE grade 1

Nephrotoxicity

The major dose-limiting toxicity of cisplatin is cumulative nephrotoxicity. Tubular necrosis of both proximal and distal renal tubules has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Renal function must meet the criteria described above before another dose of cisplatin can be given. Nephrotoxicity can be reduced by iv hydration and mannitol diuresis.

If creatinine clearance < 50 mL/min on Day 1 of each cycle;

- hydrate as indicated and hold cisplatin until CrCl is >50 mL/min;
- AZD2281 dose adjustment is not necessary.

Neurologic toxicity

Although symptoms and signs of cisplatin neuropathy may develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of cisplatin. Cisplatin should be discontinued if CTCAE ≥ grade 3 or functionally important neuropathy develops.

If Grade ≥3 neurotoxicity develops:

- Cisplatin should be discontinued
- AZD2281 should be discontinued
- Patient should be removed from study

Ototoxicity

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin (50 mg/m^2) and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz.) Decreased ability to hear normal conversational tones may occur occasionally. Ototoxicity can be more severe in children than in adults and more frequent and severe with repeated administration. Hearing loss can be unilateral or bilateral and is usually not reversible. During treatment with cisplatin, it is necessary to monitor hearing at each visit. Audiometric testing should be performed at baseline, at the end of the 2nd, 4th and 6th cycles of cisplatin and as clinically indicated thereafter. A final audiogram should be done at study completion. In the event that cisplatin is permanently discontinued, only the final audiometric test done at study completion is required, unless otherwise clinically indicated.

If Grade ≥2 ototoxicity develops:

If a patient had an initial dose level of 75 mg/m^2 cisplatin, reduce the cisplatin to 60 mg/m^2. If the patient had an initial dose level of 60mg/m^2 cisplatin, at the investigators discretion, the cisplatin can be reduced to 50 mg/m^2.

AZD2281 dose adjustment is not necessary

Management of hypersensitivity reactions to cisplatin

Reactions, possibly secondary to cisplatin therapy, have been occasionally reported in patients who were previously exposed to cisplatin. Patients who are particularly at risk are those with a prior history or family history of atopy. Facial oedema, wheezing, tachycardia, hypotension and skin rashes of urticarial non-specific maculopapular type can occur within a few minutes of administration. Any reactions should be managed (i.e. by iv adrenaline, corticosteroids or antihistamines) according to local practice. Patients may remain on study after hypersensitivity reactions at the discretion of the investigator providing desensitization protocols are available to the patient.

Nausea

For CTCAE grade ≥ 2 nausea and vomiting attributable to cisplatin and despite the use of optimised anti-emetics, if the patient was on an initial dose level of 75 mg/m^2 cisplatin, reduce cisplatin to 60 mg/m^2. If the patient had an initial dose level of 60mg/m^2 cisplatin, at the investigators discretion, the cisplatin can be reduced to 50 mg/m^2.

No dose modification is required for AZD2281 (as per Table 8).

Other non-haematologic toxicity attributed to cisplatin

Patients with grade 4 non-haematological toxicity attributed to cisplatin will have their cisplatin discontinued unless exception is given by one of the principal investigators and agreed with AstraZeneca. Prior to re-treatment, these non-hematological toxicities must resolve to less than or equal to grade 1. Cisplatin therapy should be delayed for up to 14 days until the toxicity has resolved to ≤ grade 1 or baseline if considered to be treatment related. If the toxicity fails to resolve within a two-week treatment delay, patients will be taken off protocol. For any other CTCAE grade 2 or 3 toxicities, no action should be taken for cisplatin.

Table 8 Cisplatin and AZD2281 dose adjustments for non-hematologic treatment and Cisplatin-related toxicities.

Non-Hematologic and Cisplatin Related Toxicities	Management of AZD2281 during cycle	Dose modification of Cisplatin in subsequent cycles[a]
Creatinine clearance < 50 mL/min	No modification	Hydrate as indicated and hold cisplatin until CrCl is >50 mL/min, administer cisplatin with a dose reduction to 60 mg/m^2
Grade ≥2 ototoxicity	No modification	Reduce cisplatin to 60 mg/m^2
Grade ≥3 neurotoxicity	Discontinue treatment; remove from study	Discontinue treatment; remove from study
Grade ≥2 nausea and vomiting despite the use of optimised anti-emetics	No modification	Reduce cisplatin to 60 mg/m^2

Table 8 Cisplatin and AZD2281 dose adjustments for non-hematologic treatment and Cisplatin-related toxicities.

Non-Hematologic and Cisplatin Related Toxicities	Management of AZD2281 during cycle	Dose modification of Cisplatin in subsequent cycles[a]
Other clinically significant grade ≥ 3 toxicities	Hold up to 28 days until recovery to ≤ grade 1 or baseline if considered possibly related; reduce dose as per Table 7. After resumption, if toxicity returns interrupt. If toxicity does not recover to ≤grade 1, discontinue AZD2281. The minimum dose of AZD2281 is 50 mg bid days 1-3 of a 21 day cycle for patients treated with intermittent dosing and 50 mg bid for patients treated with continuous dosing.	Hold up to 14 days until recovery to ≤ grade 1 or baseline if considered possibly related; may resume at current dose or with dose reduction, to a minimum of 60 mg/m^2, per the Investigator's discretion
Grade 4 non-hematologic toxicities attributable to cisplatin	No change unless cisplatin is discontinued. If cisplatin is discontinued, at the investigators discretion and if treatment criteria are met, dose of AZD2281 can be escalated to 400 mg bid continuously.	Discontinue cisplatin. If the investigator believes that the patient is benefiting from combination therapy then reducing cisplatin to 50 mg/m^2 and maintaining the dose of AZD2281 may be considered instead of the above after discussion with the Principal Investigator and agreed by AstraZeneca.

[a] The dose reductions advised in the table relate to patients who had an initial cisplatin dose of 75mg/m^2, for those patients that had their initial cisplatin dose administered at 60 mg/m^2, the dose modification of cisplatin should be a reduction to 50 mg/m^2 per the Investigator's discretion.

4.5.3.9 Management of toxicity of AZD2281 (monotherapy treatment)

Any toxicity observed during the course of the study could be managed by interruption of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. AZD2281 must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge with AZD2281, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment with AZD2281.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of AZD2281.

Management of leukopenia and/or anaemia:

An exception to the management of olaparib-related toxicity is the occurrence of leukopenia and/or anaemia. In this case, the AE should be managed as deemed appropriate by the investigator (eg G-CSF or blood transfusions), without interruption in study drug or change in dose. However, growth factors must be discontinued once the AE has recovered to CTCAE grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers.

Management of prolonged haematological toxicities including anaemia, neutropenia or thrombocytopenia whilst on study treatment:

If any study treatment is interrupted/delayed because of one or more of the following:

≥2 week interruption/delay in study treatment due to CTC grade >2 neutropenia

≥2 week interruption/delay in study treatment due to CTC grade >2 thrombocytopenia

≥2 week interruption/delay in study treatment due to CTC grade >2 anaemia and or development of blood transfusion dependence

Weekly blood counts should be performed during the study treatment interruption/delay. If the levels have still not recovered to CTC Grade ≤1 after 4 weeks of dose interruption, the patient should be referred to a haematologist for further investigations. Bone marrow analysis or blood cytogenetic analysis should be considered at this stage according to standard haematological practice. Development of myelodysplastic syndrome should be reported as an SAE and full reports must be provided by the Investigator for documentation on the Patient Safety database.

The dose of AZD2281 must not be adjusted under any other circumstances unless the AstraZeneca Study Physician gives prior agreement.

Management of new or worsening pulmonary symptoms: If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the CRF (up to the data cut-off).

AZD2281 should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of AZD2281 is required for any biopsy procedures.

AZD2281 should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

4.5.4 Method of assigning patients to treatment groups

Written informed consent will be obtained before enrolment and the patients identified with an enrolment number starting with E000NXXX. N being the centre number, XXX being the patient enrolment number at the centre. Enrolment numbers will start at 999 in each centre and go down.

Patients fulfilling the eligibility criteria will be assigned patient number and dose level by AstraZeneca. Patients will be entered strictly sequentially as they become eligible for enrolment. Patient numbers will begin at 001 and will be allocated sequentially across all study centres. If a patient discontinues from the study the patient number will not be re-used and the patient will not be allowed to re-enter the study.

Details on the process for allocation of study numbers to patients and contact details for the AstraZeneca coordinator will be supplied in a separate document.

4.5.5 Blinding and procedures for unblinding the study (Not applicable)

This is an open labelled study design, therefore blinding is not applicable.

4.5.6 AZD2281 and CYP3A4

The use of any herbal/natural products or other "folk remedies" should be discouraged, but use of those products, as well as the use of vitamins, nutritional supplements, and all other concomitant medications must be recorded in the CRF.

AZD2281 is an investigational drug, for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data AZD2281 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of AZD2281 is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving AZD2281.

Whilst this is not an exhaustive list, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions, and therefore a potential reduction in efficacy, the following CYP3A4 inducers should be avoided:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone nevirapine, modafinil and St John's Wort (*Hypericum perforatum*)

For patients taking any of the above, the required wash-out periods prior to starting olaparib are:

- phenobarbitone 5 weeks, and for any of the others, 3 weeks.

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the Principal Investigator and the AstraZeneca Medical Advisor, and a decision to allow the patient to remain on study will be made on a case-by-case basis.

4.5.7 Other Concomitant Medications

Any medications, with the exceptions noted in Section 4.5.10 below, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the CRF. All relevant concomitant medications, including those stopped within 6 weeks of first dose of AZD2281, should be recorded in the CRF, up until the 30 day follow up date

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the CRF.

Between study visits, in order to verify dosing compliance and times of administration of AZD2281, patients will be asked to complete details of any self -medication in a diary card, and during the study visits special attention will be paid to questioning patients in relation to any self-medication.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

Anti-emetics: Routine prophylactic anti-emetic therapy to be administered according to local practice guidelines.

Prophylaxis with granulocyte colony stimulating factor (G-CSF or Neulasta) / granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin are prohibited in any arm of the study during the first cycle of therapy. It should only be used during the study after a relevant AE has occurred. In this case, their use is permitted at the Investigator's discretion and according to local hospital guidelines. However, if the patient has an Absolute Neutrophil Count <500 for at least 7 days or fails to recover to the required neutrophil count within 14 days or has febrile neutropaenia, then the use of G-CSF or GM-CSF is permitted in accordance with local clinical practice.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF.

All medications (prescriptions or over-the-counter medications) continued at the start of the study or started during the study or until 30 days from the end of the last protocol treatment and different from the study medication must be documented.

4.5.8 Palliative radiotherapy

Palliative radiotherapy may be used for treatment of pain at the site of bony metastases that were present at baseline providing the investigator does not feel that these are indicative of clinical disease progression during the study period. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the CRF.

4.5.9 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease and corticosteroids. Full details of all of these treatments are recorded in the patient's notes and appropriate section of the CRF.

4.5.10 Medications that may NOT be administered

No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted during the course of the study for any patient.

Prophylactic cytokine administration should not be given in the first cycle.

4.5.11 Treatment compliance

The administration of all medication (including investigational products) should be recorded in the appropriate sections of the CRF.

Patients should be given clear instructions on how and when to take their study treatment. Patients will self-administer AZD2281. A member of the Investigative site's study team will query the patient for treatment compliance at each visit. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the CRF.

All patients must return their bottle of AZD2281 at the appropriate scheduled visit, when a new bottle will be dispensed. An assessment of compliance (capsule count) of any remaining capsules in the bottle will be performed in order to determine if the patient is following their treatment dose schedule. Compliance will be assessed by the capsule count and the information will be recorded in the appropriate section of the CRF. After the capsule count has been performed, the remaining capsules will not be returned to the patient but will be retained by the Investigative site until the study monitor completes reconciliation.

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

Any unused supply of AZD2281 will be returned to AstraZeneca Pharmaceuticals or its representative upon completion of the trial or destroyed at site following written approval from AstraZeneca.

The responsible pharmacist will track all cisplatin allotted to the study and administered to the study patients.

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

5. COLLECTION OF STUDY VARIABLES

A schedule for the tests and evaluations to be conducted in the study are presented in Table 4

5.1 Medical examination and demographic measurements

The Principal Investigator/Sub-Investigator should adhere to the study plan, procedures and perform tests/observations in accordance with the protocol.

5.1.1 Physical examination

A physical examination will be performed and findings will be recorded as normal, abnormal or not done. If any abnormal findings are reported, the abnormality must be specified.

5.1.2 Body weight

Body weight will be measured in kilograms (kg) using a standard scale. Patients should be weighed while wearing light indoor clothing without any footwear. Efforts should be made to use the same scales for each assessment to minimise equipment variability.

5.1.3 Audiometric testing

An audiogram will be performed at baseline and after every 2 cycles of cisplatin administration. Hearing should be monitored at each study visit. 3 audiograms should be performed while on treatment, beyond the baseline assessment and as clinically indicated thereafter. A final audiogram should be done at study completion, unless the audiogram immediately preceding was performed within 1 month of discontinuation. If the reason for discontinuation was hearing loss a final audiogram should be performed at study termination unless the prior audiogram was within 4 weeks of study withdrawal.

5.1.4 Height

Height, without any footwear, will be measured in centimetres (cm).

5.1.5 Performance status (ECOG)

The patient's ECOG performance status will be assessed (see Appendix F).

5.1.6 BRCA status (Optional)

Details of a patients BRCA1/2 mutation status will be collected for any patients who had received testing prior to enrolment on the study. If BRCA1/2 mutation status is not known at screening, but becomes known during the study, this will also be recorded. No BRCA1/2 testing is required for this study.

5.1.7 Post-study medical examination

Where possible, a follow up medical examination should be performed 30 days after the last dose of AZD2281 (as summarised in Table 4 or Table 5 for the monotherapy phase). Any new findings or any deterioration in existing abnormalities should be recorded as adverse events.

5.2 Assessment of Anti-Neoplastic activity

Only tumour assessments according to RECIST (Appendix D) should be performed at baseline (within 28 days before first dose) and according to the planned study assessments (Section 4.2). Scans that were performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and of sufficient quality. It is important to follow the assessment schedule as closely as possible.

Baseline contrast-enhanced CT of the chest, abdomen and pelvis should be performed for the assessment of measurable lesions. Where iodine contrast is contraindicated then contrast-enhanced MRI of the abdomen and pelvis is preferred. Other regions should be scanned at baseline and followed up where clinically indicated for the assessment of disease. Lesions must be assessed using the same method and technique on each occasion.

Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (e.g. computed tomography (CT), magnetic resonance imaging (MRI) or bone scan confirmed by X-ray), prompted by symptoms is considered disease progression and should be recorded as new lesions.

Categorisation of the objective tumour response assessments will be based on the RECIST criteria for target and non-target lesions (Appendix D). Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of longest diameter previously recorded since starting treatment)

Patients with non-measurable disease only are not excluded from this study. These patients should be followed up with the same assessment schedule as those with measurable disease at baseline, preferably using contrast enhanced CT or MRI where CT is not feasible (see Appendix D for methods). Patients with non-measurable disease only will be assessed according to RECIST criteria for non-target and new lesions (see Appendix D).

Lesion details will be recorded on the CRF page in the same order as they were recorded at screening. Details of any new lesions will also be collected.

Note:Patients will be assessed according to RECIST version 1.0

5.3 Pharmacokinetic Measurements - Continuous Dosing Only

For timing of individual samples refer to the study plan Table 4.

5.3.1 Determination of drug concentration in biological samples

Samples for measurement of drug concentration will be analysed by Covance Laboratories Ltd, Otley Road, Harrogate HG3 1PY. The methods used will be referred to in the clinical study report.

5.3.2 Collection of biological samples

Blood samples (4 mL) for determination of AZD2281 in plasma will be taken at the times presented in the study plan (Table 4). Blood samples will be collected, labelled and shipped as detailed in Appendix E. The date and time of collection will be recorded on the appropriate CRF.

Samples should be stored at -20°C and analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable. Results from analyses stored longer than the period stated will not be reported.

Samples will be disposed of after the clinical study report has been finalised.

5.4 Pharmacogenetic research sample (optional)

Patients will be requested to provide a blood sample to be stored frozen at -80°C for DNA extraction and potential pharmacogenetic analysis (see Section 5.7). Any genotyping performed will relate to the absorption, distribution, metabolism, elimination or mode of action of AZD2281 and any similar drugs, its related pathway and other oncogenic pathways. Patients do not have to consent to this sample in order to participate in the study

The blood sample for genetic research will be obtained from the patients at Screening or prior to first dose. 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 at prior to first dose it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume see Section 5.8.

Samples will be analysed by a laboratory approved by the investigative team.

5.5 Pharmacodynamics – Not applicable

5.6 Safety measurements

5.6.1 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the study plan). The date and time of collection will be recorded on the appropriate CRF.

The following laboratory variables will be measured:

Full haematology assessments for safety (haemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell haemoglobin concentration [MCHC], mean cell haemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated.

If absolute differentials are not available please provide the % differentials.

Coagulation [activated partial thromboblastin time {APTT} and international normalised ratio {INR}] will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase [GGT], alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT], urea or blood urea nitrogen [BUN], total protein, albumin and lactic dehydrogenase [LDH]) should be performed at each visit and when clinically indicated.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 4.5.3

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the CRF.

Table 9 Laboratory assessments

Clinical chemistry	Haematology
Calcium	Haemoglobin
Sodium	Red blood cell count (RBC)
Potassium	MCV
Magnesium	MCHC
Chloride	MCH
Glucose	Platelet count
Creatinine	White blood cells
Total bilirubin	Differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils)
Gamma glutamyltransferase (GGT)	Absolute neutrophil count
Alkaline phosphatase (ALP)	Activated partial thromboplastin time (APTT)
Aspartate transaminase (AST)	International normalised ratio (INR)
Alanine transaminase (ALT)	
Urea or BUN	
Phosphorus	
Total protein	**Urinalysis**
Albumin	Blood
Lactic dehydrogenase (LDH)	Protein
Amlyase	Glucose
Lipase	Human gonadotrophin[a]

[a]female premenopausal women pre-study only

5.6.2 Other Safety Assessments

5.6.2.1 Serum or urine pregnancy test

Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued

from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

5.6.2.2 Urinalysis

Urinalysis will be performed using a dipstick for blood, protein and glucose. Other abnormal results should be collected if appropriate. Microscopic analysis will be performed by the hospital's local laboratory if clinically indicated.

5.6.3 Electrocardiographic measurements

For timing of individual measurements refer to study plan (Table 4, and Table 5 for the Monotherapy phase

Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the patient has been lying down for 5 minutes in each case. ECGs will be recorded at 2.5 mm/sec. ECG data will be recorded on the appropriate CRF. At each time point 2 identical ECG copies will be taken (one for AstraZeneca, one to be retained by the site).

The investigator or a designated physician will review the paper copies of each 12-lead ECG and provide an overall clinical assessment. If there is a clinically significant abnormal finding this should be reported as an adverse event.

5.6.4 Vital signs

Blood pressure and pulse rate

For timing of individual measurements refer to study plan (Table 4, for and Table 5 for the Monotherapy phase

On each study day, semi supine blood pressure after 5 minutes of rest and pulse rate (PR) will be measured preferably using a semi-automatic blood pressure recording device with an appropriate cuff size. All date will be captured in the paper CRF (pCRF) and an overall clinical assessment will be made by the investigator.

5.6.5 Subjective symptomatology

Symptoms reported spontaneously by the patient will be recorded throughout the study period. Symptoms reported will be reviewed by the Investigator and recorded as adverse events on the patient's CRF. Patients will be assessed for the presence of adverse events approximately 30 days after the last administration of the study medication. Adverse events will be graded according to the National Cancer Institute Common Terminology (NCI CTC) Criteria version 3.0 for cancer clinical trials (CTCAE).

5.7 Genetic measurements and co-variables

This section refers to the pre-dose blood sample collected for retrospective genotyping only, which is optional for the patient and involves a separate consent procedure.

5.7.1 Collection of samples for genetic research (optional)

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample 10 mL will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials or date of birth) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the CRF.

Genotype is a stable parameter; therefore if for any reason the blood sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection and must remain frozen at all times.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment number and/or randomisation code and date of sample collection, should accompany the shipment.

5.8 Volume of blood sampling

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 10 Volume of blood to be drawn from each patient (4 cycles)

Assessment		Sample volume (mL)	n of samples	Total volume (mL)
Pharmacokinetic[a] (Continuous dosing only)		4	16	64
Pharmacogenetic Sample (optional)		10	1	10
Safety[b]	Clinical chemistry	6	12	72
	Haematology	9	12	108
Total				**254**

[a] PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort

[b] Safety blood assessments will continue to be taken for as long as the patient is in the study as detailed in the study plan Table 4 and Table 5. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

5.9 Handling, storage and destruction of biological samples

The samples will be used up or disposed of after analyses or retained for further use as described here.

Biological samples for future research will be retained at R&D Alderley Park on behalf of AstraZeneca for a maximum of 15 years following the Last Patient's Last Visit in the study. The results from future analysis will not be reported in the Clinical Study Report but separately in a Scientific Report or Scientific Publication.

5.9.1 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. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used 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.

5.9.2 Labelling and shipment of biohazard samples

The Principal Investigator 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 C '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 patient unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

5.9.3 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients 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 and keeps documentation of receipt of arrival.

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

5.9.4 Withdrawal of informed consent for donated biological samples

If a patient 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 the biological samples is an optional part of the study (eg pharmacogenetic sample), then the patient may continue in the study.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.

- Ensures that biological samples from that patient, 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/destroyed, the action documented and the signed document returned to the study site.

- Ensures that the patient 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

5.10 Adverse Events

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

The methods for collecting adverse events are described below.

5.10.1 Definition of Adverse Events

An adverse event 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, electrocardiogram). 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.

For cases where it could be suspected that a tissue derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

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

5.10.2 Definitions of Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the pharmaceutical product 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 or incapacity
- Is a congenital abnormality or birth defect
- Is another medically important condition (ie, one which may not be immediately life-threatening or result in death or hospitalisation, but is clearly of major clinical significance. It may jeopardise the patient, or may require intervention to prevent one of the other serious outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalisations; or development of drug dependency or drug abuse).

For further guidance on the definition of an SAE, see Appendix B to the Clinical Study Protocol.

5.10.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events will be collected from time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment (i.e., 30 day follow up visit) in the study must be followed until resolution unless, in the Investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 5.10.3 and 5.10.4). AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post Follow-up adverse events

After study treatment completion (i.e. after any scheduled post treatment follow-up period has ended) there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for survival but who have completed the post treatment follow up period (30 days). 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 causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and / or post study completion then as a minimum all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe (Section 5.10.4).

Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no), comparator/combination drug (yes/no)
- Action taken with regard to investigational product/combination agent
- 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
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug

Severity of AE

For each episode on an adverse event, all changes to the CTCAE grade attained as well as the highest attained CTC grade should be reported.

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 5.10.1. 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.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 3.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

A copy of the CTCAE version can be downloaded from the Cancer Therapy Evaluation program website (http://ctep.cancer.gov).

Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, 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 investigational product combination drug?"

For SAEs causal relationship will also be assessed for other medication and study procedures and additional drug. 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 B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the CRF. 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.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory

values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product and combination drug.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG 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.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product(s) is being studied. It may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should be considered as disease progression and not as an AE. Any events that are unequivocally due to disease progression should not be reported as an AE during the study.

New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 5.10.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 5.10.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death CRF'.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca within the usual timeframes.

5.10.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives within one day i.e., immediately but **no later than the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life threatening events **and within five calendar days** of initial receipt for all other SAEs.

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

Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the EU Summary of Product Characteristics (SmPC) for the active comparator product (including any AstraZeneca comparator). (required EU countries only)

6. STUDY MANAGEMENT

6.1 Pre-Study Activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator.

6.2 Monitoring

6.2.1 Monitoring of the Study

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document "Good Clinical Practice: Consolidated Guideline".

During the study, an AstraZeneca 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 (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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.

(***PGx:*** The specific requirements of the genetic part of the study will be discussed with the investigator(s) (and other personnel involved with the study)

6.2.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the patient's medical notes (permission from the patient will be sought as part of the consent process). Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

For this study original data recorded on the CRF and regarded as source data are as follows:

- Actual time and date of collection for PK samples

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

(PGx): Source verification of the genetic consent of participating patients will be performed and make sure that the investigational team is adhering to the specific requirements of the genetics aspects of the study.

6.3 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. 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 should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

6.4 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to

the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Pharmacogenetics: Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic testing with AstraZeneca personnel. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' samples will also be made clear.

6.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the principal investigator 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 Clinical Study Protocol).

The amendment is to be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal investigator(s). For distribution to Ethics Committee see Section 8.

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

6.6 Study timetable and end of study

The study is expected to start on November 2008 and to be completed by December 2012**.** Anticipated duration of the trial (recruitment of all patients to last patient last visit) is 49 months.

The study may be terminated at individual centres if the study procedures are not being performed according to 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 AZD2281.

Table 11 Study timetable

Activity / Milestone	Approximate Timings
FPI	[redacted]
LSI	[redacted]
Data Cut-off	[redacted]
Final LSLV	[redacted]
End of Study	[redacted]

The end of this study is defined as the date of the last visit of the last patient, occurring when all patients have completed study therapy.

If any patient has ongoing toxicities at this time, the data will continue to be collected in the patient's notes and any SAEs reported to AstraZeneca Patient Safety in accordance with Section 5.10.4. Additionally as stated in Section 5.10.3 (Handling unresolved adverse events/serious adverse events at withdrawal), any SAE or non-serious adverse event, that is ongoing at the end of the study, must be followed up to resolution or stabilization of the toxicity or until the patient starts another anticancer therapy or unless in the opinion of the investigator the condition is unlikely to resolve due to the patients underlying disease.

6.6.1 Patient Management Post Data cut-off

6.6.1.1 Patients continuing on AZD2281

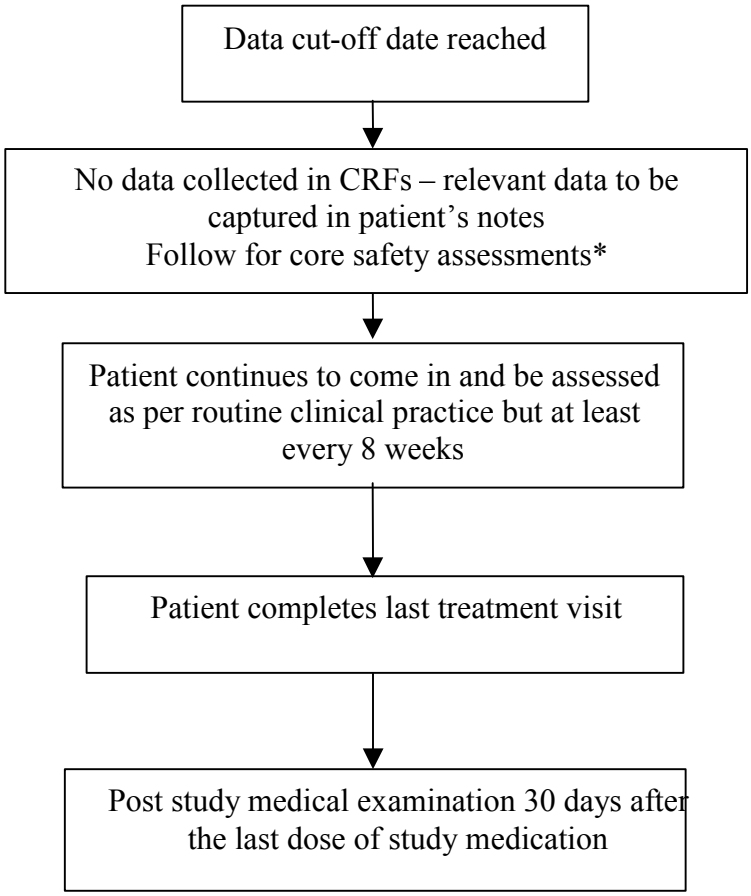
There will be a final data cut-off defined as the time when all patients receiving AZD2281 have been followed for a minimum of 3 months of monotherapy AZD2281 following combination treatment, or there are no more patients remaining on treatment in the study; whichever is the earlier date. At this time point, the clinical study database will close to new data. Patients are however permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment with AZD2281. Patients continuing on study treatment will be followed for core safety assessments only (haematology, clinical chemistry, AEs/SAEs and concomitant medications, IMP dosing details).

For patients who do continue to receive treatment beyond the time of this data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 5.10.4 (Reporting of Serious Adverse Events). Additionally as stated in Section 5.10.3 (Recording of adverse events), any SAE or non-serious adverse event that is ongoing at the time of this data cut-off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up.

Patients continuing on monotherapy AZD2281 at the data cut-off should attend visits according to routine clinical practice but at least every 8 weeks until they meet any discontinuation criteria as per Section 4.4.6.1.

Drug accountability should continue to be performed until the patient stops study treatment completely.

Figure 4 Flowchart to describe how to handle patients after the data cut-off date



* Core safety assessments - haematology, clinical chemistry, AE s, concomitant medications

6.7 Data Management

Data management will be performed by AstraZeneca Data Management Centre staff.

When the completed paper Case Report Forms have been scanned and indexed, the data are entered into the study database and proofread.

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 the Medical Coding Team at the AstraZeneca Data Management Centre.

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.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

6.7.1 Case report forms

Paper CRFs (pCRFs) will be used to record all data not captured electronically. Data should be recorded legibly onto the pCRFs in blue or black ballpoint pen. Correction fluid or covering labels must not be used.

The AstraZeneca Monitor will check data at the monitoring visits to the study site. The Investigator will ensure that the data in the pCRFs are accurate, complete and legible.

Data from the completed pCRFs will be entered onto AstraZeneca's clinical study database and validated under the direction of the Data Manager. Any missing, impossible or inconsistent recordings in the pCRFs will be referred back to the Investigator using a data query form and be documented for each individual patient before clean file status is declared.

6.7.2 Genetic data

In the case of genotypic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the CRF and database.

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the datasets from the main clinical study dataset may be duplicated within the AstraZeneca LIMS database or other appropriate system for exploratory analysis.

6.8 *(PGx)* Reporting of genotypic results

Results from any genetic research performed will be reported separately from the clinical study report. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

7. PHARMACOKINETIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

7.1 Pharmacokinetic evaluation

7.1.1 Calculation or derivation of pharmacokinetic variables

The pharmacokinetic analyses will be performed by [redacted]

All plasma concentration-time data will be analysed using non-compartmental methods by WinNonlin Version 4.1 Enterprise.

C_{max}, t_{max} and AUC_{0-t} for AZD2281 will be calculated for each patient directly from their plasma concentration-time profiles, and AUC0-t will be calculated by the linear trapezoidal rule.

7.2 Efficacy evaluation

7.2.1 Calculation or derivation of efficacy variables

ORR is defined as the percentage of patients who have at least one RECIST assessment response of CR or PR. Data obtained up until progression, or last evaluable assessment in the absence of progression will be included in the assessment of ORR. The ORR will be based on the investigator visit assessment of RECIST response and will not be derived programmatically by AZ. Depending on the number of patients with non-measurable disease, ORR may also be calculated for the subset of patients with measurable disease only

7.3 Safety evaluation

7.3.1 Calculation or derivation of safety variables – Not Applicable

7.3.2 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement,

significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs data will be performed for identification of OAEs.

Examples of these may be 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.

7.4 Statistical methods and determination of sample size

7.4.1 Statistical evaluation

Details of the statistical methods are provided in the following section. Any additional information will be documented in a comprehensive Statistical Analysis Plan (SAP), which will be prepared and finalised prior to database lock. All statistical analyses will be carried out under the direction the Biostatistics Group, AstraZeneca.

7.4.2 Description of variables in relation to hypotheses

The primary objective is to determine the safety and tolerability of twice-daily dosing of AZD2281 when administered in combination with cisplatin to patients with advanced solid tumours. This objective will be assessed by adverse events, vital signs (blood pressure and pulse rate), haematology, clinical chemistry, urinalysis and physical examination. The safety data will also be used to establish the desired dose or MTD of the combination therapy and identify the DLT of the combination of AZD2281 and cisplatin.

The secondary objective of comparing exposure to AZD2281 when given alone and in combination with cisplatin will be assessed using PK parameters C_{max}, t_{max}, AUC_{0-t}.

A secondary objective is to make an assessment of the anti-tumour activity of AZD2281 in combination with cisplatin and versus cisplatin alone. This will be made using ORR and summaries of Best Overall Response (CR, PR, SD or PD).

7.4.3 Description of analysis sets

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This is a subset of the Full Analysis Set (FAS) which includes all patients who received at least one dose of study medication. Treatment group summaries will be according to initial dose of study treatment actually received.

If a patient discontinues study medication and starts another anti-cancer therapy, all subsequent safety data for that patient after 30 days from discontinuation will be excluded from the assessment of safety.

Only PK-evaluable patients will be included in the analysis of PK parameters. Such patients are those with sufficient PK data available with no protocol violations or deviations likely to have a significant impact on the PK parameters.

A strategy for dealing with data affected by protocol violations or deviations will be agreed by the investigator, study team physician and statistician before any formal data summaries are produced.

7.4.4 Methods of statistical analyses

No formal statistical analyses will be performed on safety data (primary objective), PK data, and efficacy data. All data will be summarised descriptively and where appropriate, confidence intervals will be presented as measures of study precision

Categorisation of response rate will be based on the RECIST criteria (Therasse et al 2000) using the following response categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time up to and including the defined analysis cut-off point. ORR is the number of CR and PR divided by the number of enrolled patients evaluable for RECIST.

ORR will be analysed in the same way as described for the primary analysis. ORR and best overall objective response categories will be summarised at each assessment and overall by allocated study treatment. Conformed responses will be summarised where possible. The proportion of patients with responses will be presented along with corresponding 95% confidence intervals using the Wilson score method (Newcombe 1998).

Safety, tolerability and PK data will be summarised descriptively and with plots, further details of which will be provided in the SAP.

7.4.5 Determination of sample size

The primary objective of the study is safety and tolerability of ascending doses of AZD2281 in combination with cisplatin. The total number of patients has, therefore, been based on the desire to obtain adequate safety and tolerability data whilst exposing as few patients as possible to the study treatment and procedures. A patient will be defined as evaluable for safety review if they complete at least 1 cycle of cisplatin (3 weeks) and also receive at least 75% of either continuous or intermittent daily treatment of AZD2281 or they experience a DLT prior to completing 21 days of either continuous or intermittent treatment. If there are fewer than 3 evaluable patients in a given cohort then further patients will be recruited to the cohort until there are at least 3 evaluable patients. Once the dose or MTD has been determined (or the highest dose level has been explored) the cohort will be expanded to ensure that there are 6 evaluable patients who have completed four cycles of treatment.

7.5 Interim analyses

Safety, tolerability and PK data (if decided needed) from each cohort will be reviewed on an ongoing basis by the safety monitoring committee (see Section 7.6).

At least 3 evaluable patients in a given cohort must be treated, followed up and assessed for 21 days prior to recruiting patients into subsequent cohorts. In addition, the first patient in

each cohort will have to provide acceptable Day 7 safety data before further patients can be included.

7.6 Data monitoring committee

Once all evaluable patients within a dose cohort have completed 21 days treatment, a safety monitoring committee comprising the Investigator, the Study Team Physician, the Safety Physician, the study team pharmacokineticist (if needed) and the Study Team Statistician (or nominated deputy in each case) will meet to assess the safety and tolerability data. The committee must comprise of a minimum of 3 physicians but may also include other members of the study team and an independent physician. Escalation to the next dose cohort will only occur if the committee consider that the maximum well-tolerated dose has not yet been defined.

All dose escalation and scheduling decisions will be the responsibility of the safety monitoring committee. No formal statistical analysis will be performed in the safety reviews.

8. ETHICS

8.1 Ethics review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form(s) including biomarker and /or pharmacogenetic sample consents and any other written information and/or materials to be provided to the patients.

The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients 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 Ethics Committee annually.

Before enrolment of any patient 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, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

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

Where there is a genetic research, approval must be obtained for this genetic research and the associated genetic informed consent from the Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The investigator must submit written approval to AstraZeneca before any patient participates in this genetic research.

8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.3 Informed Consent

The principal investigator at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Informed Consent Form. A copy of the Informed Consent Form must be given to the patient.

The informed consent form will ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

The genetic research is optional and the patient may participate in 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 (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original 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 the genetic aspect of the study at any time.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient Data Protection

The Master 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. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by <<*randomisation code/study code/ initials*.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

(PGx): All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

(PGx): Reference to participation in this genetic research should not be recorded into the patients' general medical records. All notes should be kept within the clinical study records.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. 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, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the 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.

[redacted]

8.5 Study Agreements

The Principal Investigator at each centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

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

8.5.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such, see Section 5.10

[redacted]

Please call the number above and ask security to page the physician on call for AZD2281

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 5.10.**

9.3 Overdose

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established.

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 400 mg bid.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

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

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca 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 SAE, standard reporting timelines apply; see Section 5.10.4. For other overdoses, reporting should be done within 30 days.

9.4 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

9.4.1 Maternal exposure

If a patient becomes pregnant during the course of the study AZD2281 should be discontinued immediately.

The outcomes of any conception occurring from the date of the first dose of study medication until 3 months after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study medication 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 patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate AstraZeneca representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca 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 days for SAEs, see Section 5.10.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

9.4.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

The outcome of any conception occurring from the date of the first dose until 3 months *after the last dose* should be followed up and documented.

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Clinical Study Protocol Appendix B	
Drug Substance	AZD2281
Study Code	D0810C00021
Edition Number	1
Date	[redacted]

Appendix B
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

Out-patient 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.

<<Examples of such events are:

- *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

The following factors should be considered 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?

- Dechallenge 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.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C

Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00021
Edition Number	1
Date	[redacted]

Appendix C
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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** 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 **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**

- **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.

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Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281)
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Appendix D
Definitions of Measurable, Target and Non-target Lesions and Objective Response Criteria Based on the RECIST Criteria 1.0 – Part A only

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1. INTRODUCTION

This appendix details the implementation of RECIST v1.0 Guidelines for the D0810C00021 study Part A with regards to Investigator assessment of tumour burden including protocol specific requirements.

In this Phase I study, patients will be assessed using MRI/CT according to RECIST v1.0 with modification to include patients with non-measurable and measurable disease at base-line.

2. DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Patients with measurable and non-measurable disease will be included in this study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable: Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with spiral Computed Tomography (CT) scan or as ≥ 20mm with conventional techniques (Conventional CT, Magnetic Resonance Imaging (MRI), not previously irradiated.

Non-measurable: All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan)

Truly non-measurable lesions include the following: bone lesions; leptomeningeal disease; ascites; pleural / pericardial effusion; inflammatory breast disease; lymphangitis cutis/pulmonis; abdominal masses that are not confirmed and followed by imaging techniques; cystic lesions.

- Previously irradiated lesions*
- Skin lesions assessed by clinical examination

* Localised post-radiation changes may occur which affect lesion sizes. 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

Target lesions: A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved, should be identified as target lesions (TL) at baseline. The site and location of each TL

should be documented as well as the longest diameter (LD) of each TL.

Non-Target lesions All other lesions (or sites of disease) not recorded as target lesions should be identified as non-target lesions at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits.

3. METHODS OF MEASUREMENT

The same method of assessment should be used to characterize each identified and reported lesion at baseline and during follow-up.

All measurements should be recorded in metric notation by using a ruler, calipers or electronic calipers etc. A summary of the methods of assessment originally reviewed for RECIST is provided below and those excluded from tumour assessments for this study are highlighted with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-Target lesions & New Lesions
CT (preferred)	CT (preferred)
MRI	MRI
	Clinical examination
	X-ray, Chest x-ray
	Ultrasound
	Endoscopy

The specific details for the imaging modalities are outlined below.

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure target lesions selected for response assessment and to assess non-target and new lesions.

In the D0810C00021 study, it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess all the lesions at baseline and follow-up time points. CT examination with intravenous (i.v.) 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. For more details, please refer to the imaging acquisition guidelines from Section 5 of this Appendix.

3.2 Clinical examination

In the D0810C00021 study, all lesions detected clinically, selected as target lesions (TL) will be measured using CT or MRI scans, as these are the best currently available and reproducible methods. Clinical examination can be used to assess non-target and identify the presence of new lesions.

3.3 X-ray

Chest X-ray

In the D0810C00021 study, chest x-ray assessment will not be used as part of RECIST assessment for target lesions as they will be assessed by CT examination or MRI examination. Chest X-ray can however be used to assess non-target and identify the presence of new lesions.

Plain X-ray

In the D0810C00021 study, plain x-ray may be used as a method of assessment for bone non-target and for confirmation of new bone lesions.

3.4 Ultrasound

In the D0810C00021 study, ultrasound examination will not be used as part of RECIST assessment for target lesions as it is not a reproducible method and does not provide an accurate assessment of tumour size during the study. Ultrasound examination can however be used to assess non-target lesions and identify the presence of new lesions.

3.5 Endoscopy and laparoscopy

In the D0810C00021 study, these methods will not be used for assessing target lesions as part of the RECIST assessment as they are not validated in the context of tumour measurements. However, these methods can be used for assessment of non-target lesions and new lesions.

3.6 Tumour markers

In the D0810C00021 study, tumour markers will not contribute to the tumour response assessment.

In studies where tumour markers (e.g. CA-125 in ovarian cancer) are being collected for separate analysis these will not contribute to tumour response based on RECIST assessment.

3.6.1 Cytology and histology

In the D0810C00021 study, histology will not be used as part of the RECIST assessment.

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

effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed).

Where cytology findings are not available, any effusion that significantly worsens or appears during the study treatment will be considered to be progression of non-target lesions, or disease progression due to new lesions if regarded as clinically significant by the investigator.

3.7 Imaging techniques not covered in the RECIST guidelines and not used in studies using RECIST tumour assessment

Isotopic bone scan

In the D0810C00021 study, isotopic bone scans will not be used to assess bone lesions as these fall outside the RECIST framework due to insufficient specificity.

Bone lesions identified on an isotopic bone scan and confirmed by CT, MRI or x-ray at baseline should be recorded as non-target lesions and followed by the same method as per baseline assessment. If new bone lesions or worsening bone symptoms occur and a bone scan is performed then worsening of disease needs to be confirmed by x-ray, CT or MRI.

PET scan

In the D0810C00021 study, PET scans will be performed to determine inhibition of tumour glucose uptake. These scans will not be used for assessment of tumour response as PET evaluations do not form part of the RECIST framework.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

All baseline tumour assessments should be performed no more than 28 days before the start of study treatment and should ideally be performed as close as possible to the start of study of treatment. Baseline assessment must be able to adequately assess tumour burden disease and be in line with imaging requirements detailed in this Section 5.2. Any other sites at which new disease is suspected should also be adequately imaged at follow-up. Follow-up assessments will be performed according to the study plan(Table 3 and Table 4).

4.2 Target lesions

Documentation of target lesions

A maximum of 10 measurable lesions (with a maximum of 5 lesions per organ), representative of all lesions involved, should be identified as target lesions at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements. At baseline the sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. At follow-up visits the sum of the LD for all target lesions will be calculated and reported as the follow-up LD.

Special cases:

1. If a lesion splits into two or more parts, then the sum of the LDs of those parts is recorded.

2. If two or more lesions merge, then the LD of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion.

3. If a lesion becomes too small to measure accurately, then as close an estimate to the size as possible should be provided. The minimum size that can be recorded for a single lesion is 5 mm.

4. If a lesion cannot be measured accurately due to it being too large, provide as close an estimate as possible of the size of the lesion.

5. For lesions measurable in 2 or 3 dimensions, always report the longest diameter.

6. When a target lesion has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study the size of the target lesion should still be provided where possible and intervention recorded.

4.3 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for target lesions at the investigational site:

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all target lesions since baseline
Partial Response (PR)	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
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 the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention
Not applicable (NA)	Only relevant if there are no target lesions at baseline

4.4 Non-Target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as target lesions should be identified as non-target lesions at baseline. Non-target lesions should be followed using the same method

of assessment and technique throughout the study. At each visit an overall assessment of the non-target lesions response should be recorded by the Investigator at site. This section provides the definitions of the criteria used to determine and record overall response for non-target lesions at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline
Incomplete Response (IR)/ Stable Disease (SD)	Persistence of one or more non-target lesions
Progression (PD)	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 have not been assessed and in the Investigator's opinion they are not able to provide an evaluable overall NTL assessment
Not Applicable (NA)	Only relevant if there are no non-target lesions at baseline

4.5 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.

If the Investigator is in doubt as to whether a new lesion is present, it is advisable to pursue treatment until the next scheduled RECIST visit and then repeat the RECIST assessment. If the lesion is still present it should be recorded as a new lesion on the date it was first observed.

4.6 Evaluation of Overall Visit Response and Best Overall Response

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR (or NA)	No	CR
CR	IR/SD	No	PR
PR	CR, IR/SD (or NA)	No	PR
SD	CR, IR/SD (or NA)	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE

Table 4 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
Non-PD	NE	No	NE
NA	CR or IR/SD	No	SD
NA	NE	No	NE
NA	PD	Yes or No	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NA = not applicable

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

Overall visit response and Best overall response will be derived as part of the study analysis by the Sponsor from target lesion measurements, overall assessment of non-target lesions and presence/absence of new lesions.

4.7 Confirmation of response

According to RECIST Guidelines the main goal of confirmation of objective response is to minimize the risk of over-estimation of the response rate. This aspect of response evaluation is particularly important in non-randomized studies where response is the primary endpoint.

In the D0810C00021 study, the confirmation of response (CR or PR) is determined by study protocol to be performed at the next scheduled RECIST assessment (certainly no less than 4 weeks) following the date the criteria for response was first met.

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

These notes are recommendations for use in clinical studies. The use of standardized protocols for Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

5.1 CT Scan

CT scans of the neck, thorax, abdomen and pelvis should be contiguous throughout the anatomical region of interest.

The type of CT scanner is important regarding the slice thickness and minimum sized lesions. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous

reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

CT examination with intravenous (i.v.) contrast media administration is the preferred method. This is to accentuate vascular structures from adjacent lymph node masses and to help enhance liver and other visceral metastases. The method of administration of i.v. contrast agents is variable. Contrast agent timing should be aimed at the portal-venous phase of the liver. In subjects in whom the abdomen and pelvis have been imaged, oral contrast agents should be given to accentuate the bowel from other soft tissue masses. A consistent method should be used on subsequent examinations for any given subject.

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 chest examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the chest, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

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 target lesions 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.

5.2 MRI Scan

MRI is a complex issue. MRI is entirely acceptable and capable of providing images in different anatomical planes. It is important therefore that when it is used lesions must be measured in the same anatomical plane using the same imaging sequences on subsequent examinations. MRI scanners vary in the images produced. For a particular patient the same scanner should be used during the study assessment.

Moreover many subjects with advanced malignancy are in pain, so their ability to remain still for the duration of a scan sequence, in the order of 2-5 minutes is limited. Any movement during the scan time leads to motion artifacts, degradation of image quality such that the examination will probably be useless.

For these reasons, CT is the imaging modality of choice.

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Clinical Study Protocol Appendix E	
Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00021
Edition Number	2
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Appendix E
Handling and Shipment of PK Samples – Part A Continuous Dosing Schedule only

1. INSTRUCTIONS FOR HANDLING PHARMACOKINETIC SAMPLES

1.1 Collection and handling of pharmacokinetic blood samples

A full 12 hour PK profile for the determination of AZD2281 plasma concentration will be collected at the following time points:

Study day	Time point
1	Predose, 1, 2, 3, 4, 6, 8 and 12 hrs post AZD2281 dose*
2	*
3	*
4	*
5	
6	
7	
8	Predose, 1, 2, 3, 4, 6, 8 and 12 hrs post AZD2281 dose
9	

* Single dose monotherapy profile can be taken on any day between 1-4

PK blood draws will not be performed for patients enrolled into an intermittent dosing cohort.

Venous blood samples (4 mL) will be collected into pre-labelled tubes containing LITHIUM HEPARIN anticoagulant at the times shown in the study plan and thoroughly mixed. Pharmacokinetic sample tubes will be clearly labelled with the compound name, protocol number, subject enrolment code (or centre and patient number), study day, date of sample collection and nominal time-point. The date and time of sample collection will be recorded on CRFs.

Venous blood samples taken into LITHIUM HEPARIN anticoagulant will be centrifuged at 2000G for 10 minutes at room temperature within 30 minutes of collection, to provide plasma for analysis of AZD2281. Following centrifugation, each plasma sample should be transferred to a separate individually labelled cryo vial and stored at –20ºC within 1 hour of blood collection. Plasma samples should be stored at -20ºC or below at all times until analysis.

1.2 AZD2281 PK sample handling, storage and shipment

Plasma samples should be stored at -20°C until the AstraZeneca CRA advises on shipment (approximately once each cohort of 3 patients has been completed). Samples will only be shipped once there are complete profiles for patients.

Plasma samples must be kept at a temperature of –20 ºC or below (using a freezer or dry ice) whilst being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples will remain frozen for at least 72 hours to allow for delays in shipment. Arrival at Covance at the weekend and public holidays must be avoided.

The primary contact at Covance and the AstraZeneca Monitoring Scientist [redacted] must be notified, by e-mail, of the shipment details (including an electronic copy of the sample manifest) before the samples are shipped. The samples should be addressed as follows:

URGENT
(D0810C00021 samples)

[redacted]

Clinical Study Protocol Appendix F

Drug Substance	Olaparib (AZD2281)
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Edition Number	2
Date	[redacted]

Appendix F
Example of Performance Status (ECOG/Karnofsky Scale)

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Description	ECOG Grade	Karnofsky Equivalent	
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature ie, light housework, office work	1	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.