AstraZeneca

Revised Clinical Study Protocol	
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A Phase II, Open-Label, Randomised, Comparative, Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin Versus Paclitaxel and Carboplatin Alone in Patients with Platinum Sensitive Advanced Serous Ovarian Cancer

[redacted]

AstraZeneca Research and Development site representative

[redacted]

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PROTOCOL SYNOPSIS

A Phase II, Open-Label, Randomised, Comparative, Multicentre Study to Compare the Efficacy and Tolerability of Olaparib in Combination with Paclitaxel and Carboplatin and Versus Paclitaxel and Carboplatin Alone in Patients with Platinum Sensitive Advanced Serous Ovarian Cancer

Study centre(s) and number of patients planned

Approximately 150 platinum sensitive advanced serous ovarian cancer patients will be randomised at approximately 50 sites worldwide. Additional sites may be added dependant on recruitment rates.

Study period		Phase of development
Estimated date of first patients enrolled	[redacted]	II
Estimated date of last patients completed	[redacted]	II

International Co-ordinating Investigator

[redacted]

Objectives

The primary objective of this study is:

- To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone, by assessment of Progression Free Survival (PFS). (Independent Central Review)

The secondary objectives of this study are:

- To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone, by assessment of Overall Survival (OS), percent change in tumour size, Objective Response Rate (ORR), Ovarian Cancer Response Rate (a composite of CA-125 Response Rate [Gynecologic Cancer InterGroup {GCIG} criteria] and/or RECIST Response Rate), and CA-125 response rate (GCIG criteria).

- To compare the safety and tolerability of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone.

The exploratory objective of this study is:

- To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses.

Study design

This study is a phase II, open-label randomised study in platinum sensitive advanced serous ovarian cancer patients.

150 patients will be randomised in a 1:1 ratio to the following treatment arms:

Arm A Olaparib p.o. (200 mg bid days 1 –10 of a 21 day cycle), in combination with paclitaxel i.v. (175 mg/m^2 day 1 of a 21 day cycle) and carboplatin i.v. (AUC 4 day 1 of a 21 day cycle) for 6 cycles. Followed by olaparib monotherapy (400 mg bid continuous dosing, days 1-21).

versus:

Arm B Paclitaxel i.v. (175 mg/m^2 day 1of a 21 day cycle) and carboplatin i.v. (AUC 6 day 1 of a 21 day cycle) for 6 cycles.

Patient randomisation will be stratified (using an IVR system) based on the following baseline prognostic variables:

- Number of prior platinum-containing treatment lines received (1 or >1)

- Time to disease progression following completion of the previous platinum containing therapy (>6 to $\leq$12 months or >12 months)

Following randomisation, patients in both treatment arms will attend weekly clinic visits for the first 6 weeks of treatment, and then upon completion of cycle 2, every 3 weeks thereafter, until completion of paclitaxel and carboplatin. At the end of the last cycle of paclitaxel and carboplatin all patients will attend a clinic visit.

Upon completion of cycle 6 (ie, 21 days after last dose of chemotherapy), patients randomised to the olaparib arm (Arm A) will continue to receive olaparib at the maintenance dose of 400 mg bid continuously. *Note: Patients who prematurely discontinue the combination of olaparib, carboplatin and paclitaxel are permitted to participate in the olaparib maintenance phase as long as they have completed at least 4 cycles of study treatment in the combination phase of the study and have not received any other anti-cancer therapy between completion of the combination phase and commencing olaparib maintenance.* 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 and 22.

For patients in Arm A only, an additional clinic visit for safety assessments between olaparib maintenance day 22 and week 24 (relative to randomisation) is recommended for patients who have only completed 4 cycles of the chemotherapy phase, but are eligible to continue into the olaparib maintenance phase per the criteria described above. This recommended additional visit for safety assessments should be timed to ensure there are no more than 6 weeks between clinic visits.

Patients randomised to Arm A who have not completed at least 4 cycles of chemotherapy (therefore not eligible for olaparib maintenance phase) and Arm B patients have they not completed 6 cycles of chemotherapy (therefore not eligible for post completion phase), shall return to the clinic for the chemotherapy discontinuation visit and a final follow up visit 30 days after the last dose of study medication. Following this final 30 day follow up visit, patients will continue to be followed for objective disease progression and survival but will not receive any further study treatment. Further treatment options will be at the discretion of the Investigator.

Arm A patients who have completed at least 4 cycles of chemotherapy and Arm B patients who have completed 6 cycles of chemotherapy shall return to the clinic at week 24, week 30, and every 6 weeks thereafter relative to date of randomisation until objective disease progression as per RECIST version 1.1 criteria (assessed every 12 weeks), unless any other discontinuation criteria are met.

Patients in both treatment arms will have tumour assessments according to RECIST v1.1 at baseline, week 9, week 18 and every 12 weeks thereafter, until objective disease progression as per RECIST v1.1 criteria. Any patient who discontinues from study treatment for reasons other than objective progression per RECIST v1.1 should continue, where possible, to undergo scheduled radiological tumour assessments according to the study plan. Following objective disease progression per RECIST v1.1, all patients will be contacted every 12 weeks relative to the date of progression to establish survival status until the final analysis of OS. No crossover is permitted. All patients should be followed regardless of whether they have stopped treatment or received other cancer treatment.

Following discontinuation from study treatment and following objective disease progression as per RECIST v1.1, patients may receive any cancer treatment at the Investigators discretion, which must be captured in the web-based data capture (WBDC) system.

Assessments of PFS will be made on the basis of CT or MRI scans by independent radiographic central review.

A preliminary analysis of the emerging tumour size data (as assessed by Investigator review) and safety data will take place after approximately 50 patients have completed their 9 week tumour assessments (Interim I). An interim analysis of PFS will occur when approximately 38

progression events have occurred (Interim II) as assessed by independent central review using RECIST v1.1 of Computerized Tomography (CT)/Magnetic Resonance Imaging (MRI) scans.

The primary PFS analysis will occur when at least 70 progression events have occurred and will be based on an independent central review using RECIST (v1.1) of CT/MRI scans. The primary PFS analysis will include analysis of all secondary objectives (including an interim analysis of OS) if there are sufficient events for meaningful analysis).

A post-primary PFS analysis will occur after approximately 60% maturity (approximately 90 progression events) and will be based on an independent central review, using RECIST (v1.1) of CT/MRI scans. The post-primary PFS analysis will include analysis of all secondary objectives (including an interim analysis of OS, if there are sufficient events for meaningful analysis).

If any of the three PFS analyses (interim, primary or post-primary) fall very close together in time then they may not all be performed. If the primary (70 event) analysis is not performed the post-primary analysis will become the primary analysis.

Following the point at which approximately 60% maturity (approximately 90 progression events) is reached no further scanning for study RECIST assessments would be required.

The planned final OS analysis will be performed at approximately 60% maturity and an interim OS analysis will be performed when at least 30% deaths have occurred. If there is insufficient evidence of an effect on OS at the time of this interim analysis, then a decision may be made not to continue to 60% OS maturity.

For a summary of analyses please see Table 14.

Following the final OS analysis the study database will be closed, however, patients still receiving study treatment may continue to do so until disease progression or for as long as receiving clinical benefit.

An archived paraffin embedded tumour sample will be collected from all patients, if available.

Target patient population

Female patients with platinum-sensitive, histologically or cytologically diagnosed advanced ovarian cancer with a serous histology or a serous component (including primary peritoneal and fallopian tube cancer).

Patients must have measurable disease and have received no more than three previous platinum containing regimens, and have been progression free for at least 6 months following completion of their last platinum containing regimen, prior to randomisation in this study.

Investigational product, dosage and mode of administration

Olaparib p.o. (200 mg bid on day 1 –10 of a 21 day cycle), in combination with paclitaxel i.v. (175 mg/m^2 on day 1 of a 21 day cycle) and carboplatin i.v. (AUC 4 day 1 of a 21 day cycle).

Olaparib will be in capsule form. Following 6 cycles of combined treatment, patients may continue on olaparib monotherapy 400 mg bid continuous dosing, days 1-21.

Comparator, dosage and mode of administration

Paclitaxel i.v. (175 mg/m^2 on day 1 of a 21 day cycle) and carboplatin i.v. (AUC 6 day 1 of a 21 day cycle) for 6 cycles.

Duration of treatment

It is expected all patients will receive 6 cycles (18 weeks) of paclitaxel and carboplatin. Following cycle 6, patients randomised to receive olaparib in combination (Arm A) will continue on olaparib monotherapy at a dose of 400 mg bid continuously, days 1-21. Patients will continue to receive treatment until objective disease progression as per RECIST v1.1 or for as long as receiving clinical benefit.

Outcome variable(s):

Efficacy

- **Primary outcome variable:**
  - Progression Free Survival (PFS) evaluated by RECIST v1.1 (Independent Central Review)
- **Secondary outcome variables:**
  - Overall Survival (OS)
  - Percentage change in tumour size
  - Objective Response Rate (ORR)
  - Ovarian Cancer Response Rate (a composite of CA-125 Response Rate [Gynecologic Cancer InterGroup {GCIG} criteria] and/or RECIST Response Rate)
  - CA-125 response rate (GCIG criteria)
  - Adverse events
  - Laboratory findings (clinical chemistry, haematology)
  - Vital signs (BP, pulse rate)
  - Cardiology (ECG)
  - Physical examination

- **Exploratory outcome variable**
  - Candidate predictive biomarkers for olaparib efficacy.

Statistical methods

The primary objective of this study is to assess the efficacy of olaparib in combination with paclitaxel and carboplatin to the efficacy of paclitaxel and carboplatin alone. This objective will be assessed by the primary variable of Progression Free Survival (PFS).

The efficacy analysis population will include all randomised patients following the Intention-To-Treat (ITT) principle (Full Analysis Set). It will compare the treatment groups on the basis of randomised treatment, rather than actually received. All patients who received at least one dose of therapy will be included in the safety population.

The primary analysis will be performed after approximately 70 PFS events, and provides 80 % power to detect a HR of 0.6 based on a one-sided 10% significance level.

The primary outcome variable PFS will be based on an independent central review of the RECIST v1.1 data, blinded to randomised treatment. The treatment groups will be compared using a stratified log-rank rest with strata defined for number of prior platinum-containing treatment lines (1 or >1) and time to disease progression following previous platinum containing therapy (>6 to ≤12 months versus >12 months). The adjusted hazard ratio and associated 80% and 95% confidence interval (CI) will be calculated. Kaplan-Meier plots of PFS will be presented by treatment group.

The secondary endpoints will be analysed using the following methods: the analysis of overall survival will use the same stratified log-rank test as described for the primary PFS analysis; the percentage change in tumour size will be analysed using an analysis of covariance; for ORR, Ovarian Cancer Response Rate and CA-125 Response Rate the proportion of responding patients will be analysed by logistic regression.

The safety data will be summarised descriptively and will not be formally analysed.

The potential retrospective analysis for biomarker research will be reported outside the CSR.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
bid	Twice daily
BP	Blood Pressure
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
DoR	Duration of Response
DUS	Disease under Study
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
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.
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-Treat
iv	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IA	Interim Analysis
LIMS	Laboratory Information Management System
LLOQ	Lower Limit of Quantification

Abbreviation or special term	Explanation
LSLV	Last Patient Last Visit
mg	Milligram
MRI	Magnetic Resonance Imaging
OAE	Other Significant Adverse Event (see definition in Section 6.4.2)
OS	Overall Survival
ORR	Objective Response Rate
PFS	Progression Free Survival
PGx	Pharmacogenetic research
PI	Principal Investigator
po	By mouth
SAE	Serious adverse event (see definition in Section 6.4.4).
SO	Serous Ovarian
TMZ	Temozolomide
WBDC	Web Based Data Capture

1. INTRODUCTION

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

1.1 Background

Although major improvements in oncologic treatments have been made, ovarian cancers frequently recur after primary treatment. At recurrence, these cancers are incurable. With currently available treatment, survival may be improved but this is usually for a short duration and may be associated with long periods of toxic chemotherapy. In addition, the causes of resistance to specific therapies remains poorly understood. Rational therapies directed to specific targets, and a clearer understanding of the mechanism of resistance is needed to provide effective therapies to those who will benefit most.

1.1.1 Ovarian cancer

Ovarian cancer is the fourth most common cancer in women and accounted for an estimated 114,000 deaths worldwide in 2000 (Parkin et al 2001). Due to late presentation, (usually at stage III-IV) the prognosis is not good for these patients. Treatments for the disease have improved over the last 30 years, with advances in surgery and platinum based chemotherapy, but most women with ovarian cancer still develop recurrent disease and die within 5 years of diagnosis. The two-drug combination of carboplatin plus paclitaxel is the current standard regimen for advanced cancer in the first line setting. However, despite clinical complete remission following surgery and chemotherapy in approximately 75% patients, responses are generally short-lived and the clinical outcome is still unsatisfactory with median progression free survival rates from 16 to 21 months (Ozol 2006).

Based on their response to previous platinum therapy, patients treated at relapse are categorised into platinum sensitive, resistant or refractory groups. Patients that have responded to platinum therapy, with a progression free interval with a duration greater than 6 months after completing platinum therapy, are termed platinum sensitive, whereas patients with disease recurrence within 6 months or less are termed platinum resistant and patients who progressed during treatment are termed platinum refractory (Markman et al 1991). Platinum resistant patients are not usually considered for further platinum therapy and are often offered other chemotherapeutics, including topotecan, doxorubicin or paclitaxel alone (Markman et al 2000).

Patients that are platinum sensitive are frequently considered candidates for further treatment with carboplatin plus paclitaxel (Fung-Kee et al 2007). However, as in the first line setting, despite significant response rates, patients often subsequently progress and in the second line setting this occurs even sooner, with progression free survival rates 11-12 months (Gadducci et al 2005). Therefore there is a great need for a treatment to improve response rates and prolong duration of response with platinum therapy, ultimately leading to increased progression free survival times in these patients.

1.1.2 Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation (PARP)

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 display 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. They include: 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 et al 2002).

Of the various members of the PARP enzyme family, only PARP 1 and PARP 2 have been shown to 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 utilised to synthesise 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-KB, DNA-dependant protein kinase, p53, topoisomerase I, lamin B and PARP 1 protein itself.

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. Like PARP1, PARP 2 also responds to DNA damage and is similarly involved in 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 has confirmed that in combination an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents occurs (Virag et al 2002; Nguewa et al 2005).

1.1.3 Homologous recombination deficiency and PARP

Olaparib (AZD2281, KU-0059436) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination pathway, which includes cells with the BRCA1-/- and BRCA2-/- genotype. Due to the molecular targeting of olaparib 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. For further information please refer to the current version of the olaparib Investigator's Brochure.

1.1.4 Homologous recombination deficiency in ovarian cancer

Studies in ovarian cancer have demonstrated a strong hereditary component. Numerous genes have been linked with susceptibility to develop ovarian cancer (Lux et al 2006). Among the most common are the BRCA1 and BRCA2 genes. Germline mutations in BRCA 1/2 genes have been detected in studies at rates ranging from 8-18% in ovarian cancer patients (Risch et al 2001; Malander et al 2004; Menkiszak et al 2003; Pal et al 2005; Parikh et al 2007). The frequency of these BRCA 1/2 mutations is markedly increased in Jewish populations, particularly Ashkenazi Jews who have a carrier rate of 2.5% vs <0.5% in the general population (Szabo et al 1997).

In addition to germline BRCA 1/2 mutations, there are many other mechanisms that affect BRCA 1/2 function and hence affect homologous recombination (Turner et al 2004). Deleterious somatic mutations can occur in both BRCA1 and BRCA2 in approximately 5% of ovarian cancers. In addition aberrant expression of BRCA 1/2 can also occur through epigenetic mechanisms, such as promoter hyper-methylation, which has been noted in 11-35% of ovarian cancer patients (Yang et al 2006; Press et al 2008). Finally, other proteins involved in the homologous recombination pathway, including Fanconi anaemia proteins, ATM, MRE-11 and EMSY are affected in a significant proportion of ovarian cancer patients estimated to be between 17% to 60% (Taniguchi et al 2003; Hughes-Davies et al 2003; Parikh et al 2007).

Genetic studies on different histology subgroups indicate that the majority of BRCA 1/2 mutations are detectable within the serous ovarian cancer subgroup, with estimates ranging from 62% and 93% of all mutations being identified in serous ovarian cancer patients rather than other histological subgroups (Risch et al 2001; Malander et al 2004; Pal et al 2005).

1.1.5 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib Investigator's Brochure. Key findings are summarised below.

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

Distribution of olaparib is typical for an orally administered foreign compound, in the gastrointestinal 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.

Olaparib is a potent inhibitor of PARP-1. Olaparib shows significant monotherapy activity in tumour cells with defective components of homologous recombination, which includes cells with the BRCA1$^{-/-}$ and BRCA2$^{-/-}$ genotype. Inhibition of PARP activity using olaparib also sensitises the cells to the cytotoxic effects of ionising radiation and certain chemotherapies, notable camptothecins and alkylating agents like DTIC and temozolomide

Data has been published regarding the potentiation of platinum agents such as cisplatin and carboplatin in combination with olaparib (Evers et al 2008, Rottenberg et al 2008). These studies were conducted in vitro and in vivo using BRCA mouse mammary tumour models. BRCA2-deficient mouse mammary tumour cell lines were analysed in combination studies and showed a synergistic potentiation of cisplatin cytotoxicity with olaparib against BRCA2-deficient cells whereas the interaction was only additive against BRCA2-proficient control cells (Evers et al 2008). Studies with BRCA1-deficient orthoptically transplanted in vivo mouse tumour models showed that, in addition to single agent activity of olaparib, combination with platinum agents increased the recurrence-free and overall survival, suggesting that olaparib potentiates the effect of these DNA-damaging agents in vivo as well as in vitro (Rottenberg et al 2008).

1.1.6 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g. 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 conductd exposing human bone marrow cells to olaparib, which has confirmed that olaparib 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 myelosupression in n=4 human donors compared with 0.1 μM 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 olaparib in rat and dog have given similar results, with the drug being well tolerated and no drug-related mortality.

Potential combination therapies have been studied. In the rat, the combination of topotecan and olaparib or of temozolomide (TMZ) and olaparib were tolerated at doses that would support therapeutic dosage ranges. Findings in the combination studies have been typical of anticancer agents and there have been indications of a synergistic effect of olaparib with both topotecan and TMZ. There was also evidence of recovery with both combinations. A publication by Rottenberg et al also reports potentiation of cisplatin induced toxicity as well as improved recurrence-free and overall survival in a mouse xenograft model (Rottenberg et al 2008).

Importantly, oncology clinics are well used to monitoring for the onset of such effects and are expert in their management.

Olaparib 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 olaparib to male rates 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 males with 5 mg/kg/day caused no significant effects.

In the embryofoetal development study in the rat, administration of olaparib 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. In addition the occurrence of major eye and vertebrean/rib malformations and increased incidences of several minor visceral and skeletal minor abnormalities and variants were noted. Dosing with 0.05 mg/kg/day had no effect on pregnant animals but was associated with an increased incidence in minor visceral abnormalities and skeletal variants. 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

1.1.7 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 appears to be generally well tolerated in patients with various solid tumours at doses up to and including 400 mg twice daily, as monotherapy.

Administration of olaparib has been associated with cases of:

- Laboratory findings and/or clinical diagnoses of:
  - Anaemia, generally mild to moderate (CTC grade 1 or 2)
  - Neutropenia, predominantly mild to moderate (CTC grade 1 or 2)
  - Thrombocytopenia, generally mild to moderate (CTC grade 1 or 2), sometimes severe (CTC grade 3 or 4)
- Nausea and vomiting, generally mild to moderate (CTC grade 1 or 2), intermittent and manageable on continued treatment.
- Fatigue, generally intermittent, of mild to moderate intensity (CTC grade 1 or 2).
- Pneumonitis events with no consistent clinical pattern have been reported in a small number of patients.

Phase I dose escalation studies of olaparib in combination with various chemotherapy agents are ongoing. Consistent with the pre-clinical data, the degree of bone marrow suppression observed in some patients in these ongoing studies has been greater than would be expected with the chemotherapy agent alone. The principal haematological toxicities observed have been thrombocytopenia and neutropenia and have been clinically managed by dose-delays and

dose reductions together with routine supportive care measures, including growth factor support.

Preliminary data from an ongoing Phase I study investigating the combination of olaparib, carboplatin and paclitaxel showed that carboplatin AUC 4/paclitaxel 175 mg/m^2 with olaparib 200 mg bid on days 1-10 was associated with an acceptable safety profile. The main toxicity seen was neutropenia but this could be managed with supportive treatment and occasional dose delays.

At present, the number of patients exposed to olaparib either given alone or in combination with other agents is small. These events will continue to be monitored to assess frequency and severity as patient exposure increases.

Events observed to date, suggest an emerging safety profile for olaparib that supports further studies in cancer patients.

1.2 Research hypothesis

The primary hypothesis is that the efficacy of olaparib in combination with paclitaxel plus carboplatin is superior to that of paclitaxel plus carboplatin alone by assessment of Progression Free Survival (PFS).

1.3 Rationale for conducting this study

Despite significant response rates in patients with ovarian cancer to platinum containing regimens, relapse is common soon after completion of treatment. Therefore, the identification of new treatments or treatment combinations in this setting, which increase responses rates, progression-free and overall survival is an important area for further development.

Study D0810C00002 has illustrated that olaparib can effectively inhibit the PARP enzyme. Inhibition of PARP affects the repair of DNA damage. Whilst the ability to repair DNA is desirable in normal cells, following cancer therapy it may enable tumour cells to recover from chemotherapy thus preventing effective treatment.

The potential to effectively inhibit the DNA repair in tumour cells following cytotoxic agents may potentiate the effects of chemotherapy and lead to better responses in some tumours. This concept is supported by pre-clinical and clinical studies with both olaparib and other PARP inhibitors.

Olaparib monotherapy has demonstrated significant anti-tumour activity at doses of 100 mg, 200 mg and 400 mg bid for ovarian cancer patients (previously treated with platinum agents) harbouring mutations in BRCA1 or BRCA2. Many studies have indicated BRCA 1/2 mutations and other BRCA 1/2 defects (eg, epigenetic changes affecting BRCA, or other genetic changes in the same HRD pathway) are predominantly found within the serous subset of ovarian cancer patients (Risch et al 2001; Malander et al 2004; Pal et al 2005).

Carboplatin exerts its cytotoxic and therapeutic effect primarily by forming intrastrand and DNA adducts with adjacent guanine residues in tumour cell DNA, leading to DNA damage and strand breaks, thereby inhibiting tumour growth. It is known that PARP inhibition can selectively kill cells with homologous recombination defects, and contribute to increased cell death associated with the treatment of these cells with agents that cause DNA damage and strand breaks. Therefore the combination of olaparib with carboplatin may be an effective anti-cancer combination and warrants further clinical investigation. The paclitaxel/carboplatin doublet is standard treatment for advanced ovarian cancer. It is therefore expected that the addition of olaparib to the carboplatin and paclitaxel combination may potentially lead to a significant improved clinical outcome for these patients.

A key question is to what extent the addition of olaparib to the paclitaxel/carboplatin doublet chemotherapy regimen potentiates the cytotoxic effect of these agents. Experimental animal models suggest that olaparib may enhance the therapeutic effect of platinum chemotherapy in a synergistic way, and an ongoing Phase I study has shown that the proposed combination is tolerable for patients at the doses proposed for this clinical trial. Therefore there is a strong rationale for investigating this combination further in a randomised phase II clinical trial of patients with relapsed platinum sensitive advanced ovarian cancer.

1.4 Benefit/risk and ethical assessment

Platinum-based therapy and particularly the paclitaxel/carboplatin doublet is considered a widely used treatment for patients with recurrent platinum sensitive ovarian tumours (defined as disease progression >6 months after completion of platinum containing therapy). However, responses are generally short lived and the clinical outcome is still unsatisfactory (Fung-Kee et al 2007). There is a clear clinical need to improve response rates and extend the progression free and overall survival for these patients.

Pre-clinical studies using olaparib in combination with platinum agents have shown that addition of olaparib potentiates the DNA-damaging effects of these agents in both BRCA1 and BRCA2 deficient tumours in a synergistic way. Safety and tolerability data from an ongoing Phase I study investigating olaparib in combination with carboplatin/paclitaxel has demonstrated that using carboplatin AUC 4/paclitaxel 175 mg/m^2 on day 1 plus olaparib 200 mg bid for 10 days of a 21 day cycle has an acceptable tolerability profile.

Treatment with the doublet of carboplatin/paclitaxel is an accepted standard of care in the relapsed platinum-sensitive serous ovarian cancer population (Aebi et al 2008). Therefore, investigating the addition of a PARP-inhibitor, olaparib to this chemotherapy combination is considered appropriate for this patient population.

Although AUC 5 or 6 is often considered to be the standard dose of carboplatin in ovarian cancer, available data suggests that the difference in efficacy resulting from increasing doses of carboplatin may not be significant (Jakobsen et al 1997). In particular, the addition of new agents often requires some reduction in standard doses. For example, the combination of gemcitabine with carboplatin AUC 4 led to a significant improvement in PFS and response rates compared to carboplatin AUC 5 (Pfisterer et al 2006).

Thus the potential efficacy of the combination is theoretically justified, and has been demonstrated in both in vitro and in vivo pre-clinical studies. The clinical safety of the specific proposed combination has been demonstrated in an ongoing phase I combination study (KU36-96). In addition the comparator arm is considered standard of care for this population of patients. The trial is therefore considered to offer an appropriate benefit/risk ratio for this group of patients and to be ethically justified.

There is strong preclinical evidence that deficiencies in homologous recombination are associated with susceptibility to PARP inhibition (Section 1.1). Potential biomarker research on archival tumour tissue, from patients in this study, may contribute to the understanding of this hypothesis clinically and ultimately ensure that AstraZeneca will be able to prospectively identify patients most likely to benefit from treatment with olaparib.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is:

- To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone, by assessment of Progression Free Survival (PFS).

2.2 Secondary objectives

The secondary objectives of this study are:

- To compare the efficacy of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone by assessment of Overall Survival (OS), percent change in tumour size, Objective Response Rate (ORR), Ovarian Cancer Response Rate (a composite of CA-125 Response Rate [Gynecologic Cancer InterGroup {GCIG} criteria] and/or RECIST Response Rate), and CA-125 response rate (GCIG criteria).

- To compare the safety and tolerability of olaparib when given in combination with paclitaxel and carboplatin to paclitaxel and carboplatin alone.

2.3 Exploratory objectives

The exploratory objective of this study is:

- To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses.

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This study is a phase II, open-label randomised study in platinum sensitive advanced serous ovarian cancer patients.

150 patients will be randomised in a 1:1 ratio to the following treatment arms:

Arm A Olaparib p.o. (200 mg bid days 1 –10 of a 21 day cycle), in combination with paclitaxel i.v. (175 mg/m^2 day 1 of a 21 day cycle) and carboplatin i.v. (AUC 4 day 1 of a 21 day cycle) for 6 cycles. Followed by olaparib monotherapy (400 mg bid continuous dosing, days 1-21).

versus:

Arm B Paclitaxel i.v. (175 mg/m^2 day 1of a 21 day cycle) and carboplatin i.v. (AUC 6 day 1 of a 21 day cycle) for 6 cycles.

Patient randomisation will be stratified (using an IVR system) based on the following baseline prognostic variables:

- Number of prior platinum-containing treatment lines received (1 or >1)
- Time to disease progression following completion of the previous platinum containing therapy (>6 to ≤12 months or >12 months)

Following randomisation, patients in both treatment arms will attend weekly clinic visits for the first 6 weeks of treatment, and then upon completion of cycle 2, every 3 weeks thereafter, until completion of paclitaxel and carboplatin. At the end of the last cycle of paclitaxel/carboplatin all patients will attend a clinic visit.

Upon completion of cycle 6 (ie, 21 days after last dose of chemotherapy), patients randomised to the olaparib arm (Arm A) will continue to receive olaparib at the maintenance dose of 400 mg bid continuously. *Note: Patients who prematurely discontinue the combination of olaparib, carboplatin and paclitaxel are permitted to participate in the olaparib maintenance phase as long as they have completed at least 4 cycles of study treatment in the combination phase of the study and have not received any other anti-cancer therapy between completion of the combination phase and commencing olaparib maintenance.* 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 and 22.

For patients in Arm A only, an additional clinic visit for safety assessments between olaparib maintenance day 22 and week 24 (relative to randomisation) is recommended for patients who have only completed 4 cycles of the chemotherapy phase, but are eligible to continue into the olaparib maintenance phase per the criteria described above. This recommended additional visit for safety assessments should be timed to ensure there are no more than 6 weeks between clinic visits.

Patients randomised to Arm A who have not completed at least 4 cycles of chemotherapy (therefore not eligible for olaparib maintenance phase) and Arm B patients have they not completed 6 cycles of chemotherapy (therefore not eligible for post completion phase), shall return to the clinic for the chemotherapy discontinuation visit and a final follow up visit 30 days after the last dose of study medication. Following this final 30 day follow up visit, patients will continue to be followed for objective disease progression and survival but will not receive any further study treatment. Further treatment options will be at the discretion of the Investigator.

Arm A patients who have completed at least 4 cycles of chemotherapy and Arm B patients who have completed 6 cycles of chemotherapy shall return to the clinic at week 24, week 30, and every 6 weeks thereafter relative to date of randomisation until objective disease progression as per RECIST version 1.1 criteria (assessed every 12 weeks), unless any other discontinuation criteria are met.

Patients in both treatment arms will have tumour assessments according to RECIST v1.1 at baseline, week 9, week 18 and every 12 weeks thereafter, until objective disease progression as per RECIST v1.1 criteria. Any patient who discontinues from study treatment for reasons other than objective progression per RECIST v1.1 should continue, where possible, to undergo scheduled radiological tumour assessments according to the study plan. Following objective disease progression per RECIST v1.1, all patients will be contacted every 12 weeks relative to the date of progression to establish survival status until the final analysis of OS. No crossover is permitted. All patients should be followed regardless of whether they have stopped treatment or received other cancer treatment.

Following discontinuation from study treatment and following objective disease progression as per RECIST v1.1, patients may receive any cancer treatment at the Investigators discretion, which must be captured in the web-based data capture (WBDC) system.

Assessments of PFS will be made on the basis of CT or MRI scans by independent radiographic central review.

A preliminary analysis of the emerging tumour size data (as assessed by Investigator review) and safety data will take place after approximately 50 patients have completed their 9 week tumour assessments (Interim I). An interim analysis of PFS will occur when approximately 38 progression events have occurred (Interim II) as assessed by independent central review using RECIST v1.1 of Computerized Tomography (CT)/Magnetic Resonance Imaging (MRI) scans.

The primary PFS analysis will occur when at least 70 progression events have occurred and will be based on an independent central review using RECIST (v1.1) of CT/MRI scans. The primary PFS analysis will include analysis of all secondary objectives (including an interim analysis of OS if there are sufficient events for meaningful analysis).

A post-primary PFS analysis will occur after approximately 60% maturity (approximately 90 progression events) and will be based on an independent central review, using RECIST (v1.1) of CT/MRI scans. The post-primary PFS analysis will include analysis of all secondary objectives (including an interim analysis of OS, if there are sufficient events for meaningful analysis).

If any of the three PFS analyses (interim, primary or post-primary) fall very close together in time then they may not all be performed. If the primary (70 event) analysis is not performed the post-primary analysis will become the primary analysis.

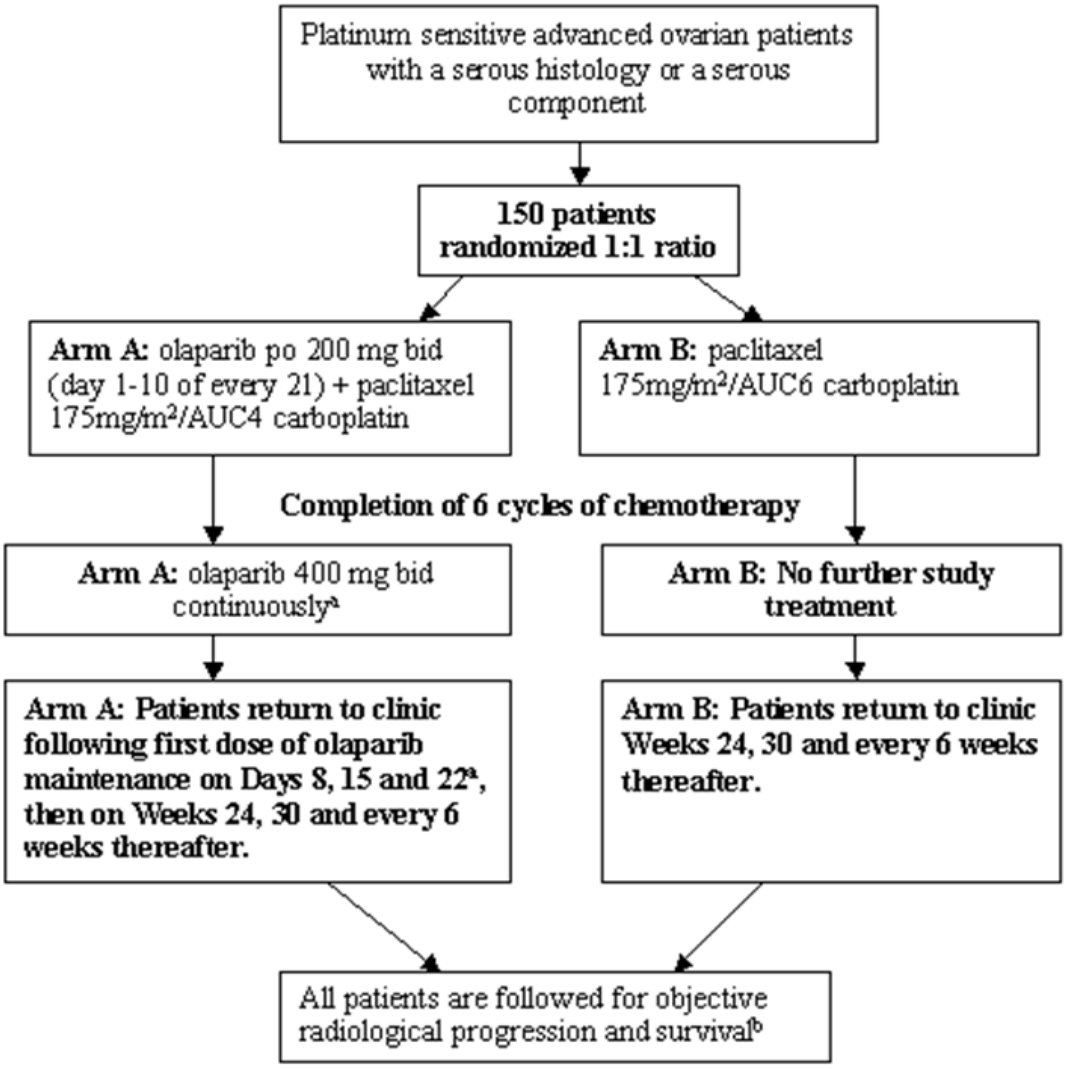
Following the point at which approximately 60% maturity (approximately 90 progression events) is reached no further scanning for study RECIST assessments would be required.

The planned Final OS analysis is planned at approximately 60% maturity and an interim OS analysis will be performed when at least 30% deaths have occurred. If there is insufficient evidence of an effect on OS at the time of this interim analysis, then a decision may be made not to continue to 60% OS maturity.

For a summary of analyses please see **Table 14.**

Following **the** final OS analysis the study database will be closed, however, patients still receiving study treatment may continue to do so until disease progression or for as long as receiving clinical benefit.

Figure 1 Study Flow Chart



a Upon completion of cycle 6 (ie, 21 days after last dose of chemotherapy), patients randomised to the olaparib arm (Arm A) will continue to receive olaparib at the maintenance dose of 400 mg bid continuously. Note: Patients who prematurely discontinue the combination of olaparib, carboplatin and paclitaxel are permitted to participate in the olaparib maintenance phase as long as they have completed at least 4 cycles of study treatment in the combination phase of the study and have not received any other anti-cancer therapy between completion of the combination phase and commencing olaparib maintenance. Patients randomised to Arm A who have not completed at least 4 cycles of chemotherapy will receive no further study treatment, and other treatment options will be at the discretion of the investigator.

b Following confirmed objective disease progression as per RECIST v1.1 criteria, patients will continue to be contacted to assess survival status until final analysis of OS and to collect subsequent cancer therapy details including best response (unless patient withdraws consent).

Table 1 Study plan: Screening (all patients)

Day	-28 to -1	-7 to -1
Informed consent	X	
Demographics	X	
Medical and surgical history	X	
Inclusion/exclusion criteria	X	
Physical examination	X	
Vital signs, body weight (Includes BP, pulse and temperature)	X	
ECOG performance status	X	
ECG		X
Haematology / clinical chemistry	X	
Pregnancy test [a]	X	
Tumour Assessment (CT or MRI according to RECIST v1.1)[b]	X	
CA-125 Blood Sample		X
Adverse Events (from time of consent)	X	X
Concomitant medications	X	
BRCA status (if known, not required for enrolment) [c]	X	

a Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 28 days prior to starting treatment and a confirmatory test before study treatment. In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately

b RECIST v1.1 assessments will be performed using CT or MRI scans of abdomen and pelvis. Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, and ideally should be performed as close as possible to the start of study treatment.

c If BRCA 1/2 mutation status is known or becomes known for a patient during the study this information will be recorded in the eCRF either at screening or at later visits. No BRCA1/ 2 testing is required for this study

Table 2	**Study plan: Paclitaxel/carboplatin phase (all patients)**									
Visit type	**Paclitaxel/carboplatin phase (6 cycles/18 weeks)**							**Chemotherapy Discontinuation visit**	**30-day follow -up**	**Survival follow-up[j]**
Cycle(s)	**1**			**2**			**3-6[b]**	**End of the last cycle of paclitaxel/ carboplatin[h]**	**30-days after last dose of study medication[i]**	**N/A**
Day of Cycle	1	8	15	1	8	15	1	N/A		**N/A**
Visit Window	N/A	± 2 d	±2d	± 2 d	± 2 d	±2d	±3d	±3d	±3d	**±4d**
Physical exam	X[a]			X			X	X		
Vital signs, body weight (Includes BP, pulse and temperature)	X[a]	X	X	X	X	X	X	X		
ECOG performance status	X[a]			X			X	X		
ECG[c]								X		
Haematology /clinical chemistry	X[a]	X	X	X	X	X	X	X		
Pregnancy test before treatment	X									
CA-125 blood sample	X			X			X	X		
Tumour Assessment (CT or MRI according to RECIST v1.1)[d]	Tumour assessments at weeks 9 and 18 (± 1 week) and every 12 weeks thereafter relative to date of randomisation until disease progression									
Adverse Events	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Randomisation	X									

Table 2	**Study plan: Paclitaxel/carboplatin phase (all patients)**									
Visit type	**Paclitaxel/carboplatin phase (6 cycles/18 weeks)**							**Chemotherapy Discontinuation visit**	**30-day follow -up**	**Survival follow-up[j]**
Cycle(s)	**1**			**2**			**3-6[b]**	**End of the last cycle of paclitaxel/ carboplatin[h]**	**30-days after last dose of study medication[i]**	**N/A**
Day of Cycle	1	8	15	1	8	15	1	N/A		**N/A**
Visit Window	N/A	± 2 d	±2d	± 2 d	± 2 d	±2d	±3d	±3d	±3d	**±4d**
Archival tumour sample (if available)[e]	X									
Olaparib dispensed/ returned[f]	X			X			X	X[g]		
Paclitaxel/ carboplatin infusion	X			X			X			
Subsequent cancer therapy								**X**	**X**	**X**
Survival Status										**X**

a If assessed within 7 days before randomisation and meets the stated eligibility criteria (if applicable), it need not be repeated on Day 1 of cycle 1 unless investigator believes that it is likely to have changed significantly.

b Upon completion of cycle 2, and unless more frequent assessments are required, vital signs, performance status, haematology, and clinical chemistry assessments may be performed at the beginning of each 21 day cycle.

c ECG performed at baseline and completion of chemotherapy, 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 v1.1 assessments will be performed using CT or MRI scans of abdomen and pelvis and other areas as clinically indicated. Mandatory tumour assessments will be performed at baseline, 9 weeks and 18 weeks and every 12 weeks thereafter relative to date of randomisation until disease progression.

e Archival paraffin embedded tumour sample, where available.

f For patients in Arm A only: At each visit in the treatment period, 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.

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

h Applies to all patients, regardless of the number of chemotherapy cycles completed.

[i] Visit to be performed 30 days after last dose of study medication, for Arm A patients not eligible for olaparib maintenance and Arm B patients not eligible for post completion phase. Following this visit, patients are still to be followed until disease progression, but will receive no further study treatment.

[j] Following disease progression, patients will be contacted every 12 weeks relative to the date of progression to assess survival status and to collect any subsequent cancer therapy data including best response. In addition, patients will be contacted in the week following the primary and post-primary data cut-off for any survival analysis to ensure availability of complete survival data. Following the point at which approximately 60% maturity (approximately 90 progression events) is reached no further scanning for study RECIST assessments would be required.

Table 3 Study plan: Olaparib maintenance phase - Arm A only

Visit type	**Olaparib maintenance phase[a] (patients who have completed at least 4 cycles)**						Olaparib Treatment Discontinuation	Post discontinuation follow-up	Survival Follow-Up[e]
Timing of visit	Maintenance Day 8	Maintenance Day 15	Maintenance Day 22	Week 24	Week 30	Every 6 weeks	N/A	30 days post discontinuation	Every 12 weeks
Visit Window	±2 days	±2 days	±2 days	± 4 days	± 4 days	±4 days	±3 days	±3 days	±4 days
Physical exam				X	X	X	X		
Vital signs, body weight (Includes BP, pulse and temperature)				X	X	X	X	X	
ECOG performance status				X	X	X	X	X	
ECG[b]							X		
Haematology / clinical chemistry	X	X	X	X	X	X	X	X	
CA-125 blood sample				X	X	X	X	X	
Tumour Assessment (CT or MRI according to RECIST v1.1)[c]					X	Mandatory tumour assessments will be performed at baseline, 9 weeks and 18 weeks and every 12 weeks **(± 1** week**)** thereafter relative to date of randomisation			
Adverse Events	X	X	X	X	X	X		X	

Table 3 Study plan: Olaparib maintenance phase - Arm A only

Visit type	**Olaparib maintenance phase[a] (patients who have completed at least 4 cycles)**						Olaparib Treatment Discontinuation	Post discontinuation follow-up	Survival Follow-Up[e]
Timing of visit	Maintenance Day 8	Maintenance Day 15	Maintenance Day 22	Week 24	Week 30	Every 6 weeks	N/A	30 days post discontinuation	Every 12 weeks
Visit Window	±2 days	±2 days	±2 days	± 4 days	± 4 days	±4 days	±3 days	±3 days	±4 days
Concomitant medications	X	X	X	X	X	X		X	
Olaparib dispensed/returned[d]				X	X	X	X		
Subsequent cancer therapy							**X**	**X**	**X**
Survival status									X

a The first dose of olaparib maintenance (Day 1 of olaparib maintenance phase) is the day after the chemotherapy discontinuation visit. All patients should attend study visits until objective disease progression according to RECIST v1.1 (assessments are performed every 12 weeks). An additional clinic visit for safety assessments between olaparib maintenance day 22 and week 24 (relative to randomisation) is recommended for patients who have only completed 4 cycles of the chemotherapy phase, but are eligible to continue into the olaparib maintenance phase. This recommended additional visit for safety assessments should be timed to ensure there are no more than 6 weeks between clinic visits.

b 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.

c RECIST v1.1 assessments will be performed every 12 weeks using CT or MRI scans of abdomen and pelvis and other areas as clinically indicated. Mandatory tumour assessments will be performed (± 1 week) at baseline, 9 weeks and 18 weeks and every 12 weeks thereafter relative to date of randomisation, until disease progression. At the time of approximately 60% maturity (approximately 90 progression events) all patients remaining on olaparib who have not progressed will continue to be assessed for safety (see Table 5). However, no further scanning for study RECIST assessments would be required.

d 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.

e Following disease progression, patients will be contacted every 12 weeks relative to the date of progression to assess survival status and to collect any subsequent cancer therapy data including best response. In addition, patients will be contacted in the week following the data cut-off for any survival

analysis to ensure availability of complete survival data.

Table 4	**Study plan: Post completion of chemotherapy phase - Arm B only**			
Visit type	**Post completion of chemotherapy phase[a] (patients who have completed 6 cycles)**			Survival Follow-Up[d]
Timing of visit	Week 24	Week 30	Every 6 weeks	Every 12 weeks
Visit Window	±4 days	±4 days	±4 days	±4 days
Physical exam	X	X	X	
Vital signs, body weight (Includes BP, pulse and temperature)	X	X	X	
ECOG performance status	X	X	X	
ECG[b]				
Haematology / clinical chemistry	X	X	X	
CA-125 blood sample	X	X	X	
Tumour Assessment (CT or MRI according to RECIST v1.1)[c]	Performed every 12 weeks thereafter relative to date of randomisation			
Adverse Events	X	X	X	
Concomitant medications	X	X	X	
Subsequent cancer therapy	X	X	X	X
Survival status				X

a. Patients must have completed 6 cycles of chemotherapy to be eligible for this post completion phase. All patients should attend study visits until objective disease progression according to RECIST v1.1 (assessments are performed every 12 weeks).

b ECG performed at baseline and completion of chemotherapy, 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.

c RECIST v1.1 assessments will be performed using CT or MRI scans of abdomen and pelvis and other areas as clinically indicated. Mandatory tumour assessments will be performed at baseline, 9 weeks and 18 weeks and every 12 weeks thereafter relative to date of randomisation. At the time of approximately 60% maturity (approximately 90 progression events) all patients remaining on olaparib who have not progressed will continue to be assessed for safety (see Table 5). However, no further scanning for study RECIST assessments would be required.

d Following disease progression, patients will be contacted every 12 weeks relative to the date of progression to assess survival status and to collect any subsequent cancer therapy data including best response. In addition, patients will be contacted in the week following the data cut-off for any survival analysis to ensure availability of complete survival data.

Table 5 Study plan: Follow up of patients after the post-primary PFS analysis [a]

Visit Type	Follow up (Arm A patients on treatment and Arm B patients who have not yet progressed)	Treatment discontinuation visit (Arm A only)	Post discontinuation follow-up (Arm A only)	Survival Follow-Up [c]
Timing of Visit	Every 12 weeks	N/A	30 days post discontinuation	Every 12 weeks
Visit Window	±4 days	±3 days	±3 days	±4 days
Physical exam	X	X		
Vital signs, body weight (Includes BP, pulse and temperature)	X	X	X	
ECOG performance status	X	X	X	
Haematology / clinical chemistry	X	X	X	
Adverse Events	X	X	X	
Concomitant medications	X	X	X	
Olaparib dispensed/returned [b]	X	X		
Subsequent cancer therapy		X	X	X
Survival status				X

a At the time of approximately 60% maturity (approximately 90 progression events) all Arm A patients remaining on olaparib and Arm B patients who have not progressed will continue to be assessed for safety. However, no further scanning for study RECIST assessments will be required from this point in the study.

b For Arm A patients, when all other procedures have been performed, olaparib will be dispensed (sufficient for an appropriate number of days). Used and unused olaparib should be accounted for and compliance checked. At the discontinuation visit, no olaparib will be dispensed.

c Following disease progression, patients will be contacted every 12 weeks relative to the date of progression to assess survival status and to collect any subsequent cancer therapy data including best response. **This will continue until the final analysis of OS when data collection will stop and the database will be closed.**

3.2 Rationale for study design, doses and control groups

Platinum containing regimens are considered the treatment of choice for advanced ovarian cancer patients, both in the first and second line setting (if the patient is platinum sensitive). Unfortunately, studies demonstrate that the progression free survival times for patients are relatively short after treatment (Ozol 2006) and hence there is a need to find new treatments or treatment combinations that will prolong this interval and overall survival for this patient population.

The use of carboplatin AUC 6 in combination with paclitaxel 175 mg/m^2 on day 1 of a 21 day cycle as the control group is justified since this is an accepted standard of care with demonstrated efficacy in the relapsed platinum-sensitive serous ovarian cancer population.

The combination of carboplatin AUC 4 plus paclitaxel 175 mg/m^2 on day 1 and olaparib 200 mg bid on days 1-10 of a 21 day cycle in the investigational arm was chosen based on safety and tolerability data from an ongoing Phase I study. In addition pre-clinical investigations, clinical studies with other PARP inhibitors and clinical studies investigating the carboplatin dose support this choice of combination for further investigation in a randomised phase II setting.

Due to the different dose of carboplatin being administered to patients in the two treatment arms, the study will be conducted using an open-label design and patients will be randomised to a 1:1 ratio. To reduce the potential bias caused by use of an open-label design, efficacy analysis of the RECIST v1.1 data will be based on outcomes assessed by an external independent central review panel of experts who are blinded to treatment allocation and adverse events experienced.

4. PATIENT SELECTION CRITERIA

The patient population should be selected without bias.

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

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.

4.1 Inclusion criteria

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

1. Provision of fully informed consent prior to any study specific procedures

2. Patients must be > 18 years of age.

3. Histologically or cytologically diagnosed ovarian cancer with a serous histology or a serous component, including primary peritoneal and fallopian tube cancer.

4. Patients who have received no more than 3 previous platinum containing regimens and were progression free, in the opinion of the Investigator, for a minimum of 6 months following completion of their last platinum containing regimen, prior to randomisation in the study.

5. At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

6. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

   – Haemoglobin ≥ 9.0 g/dL

   – Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

   – White blood cells (WBC) > 3x10^9/L

   – Platelet count ≥ 100 x 10^9/L

   – Total bilirubin ≤ 1.5 x institutional upper limit of normal

   – 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 x institutional upper limit of normal (ULN)

   – Creatinine clearance (using Cockcroft-Gault) within normal range (> 50 mL/min)

7. ECOG performance status ≤ 2 (see Appendix F)

8. Patients must have a life expectancy ≥ 12 weeks.

9. Evidence of non-childbearing status for women of childbearing potential, or postmenopausal status: negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on day 1.

   Postmenopausal is defined as one of the following:

   – Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments,

- LH and FSH levels in the post menopausal range for women under 50,
- radiation-induced oophorectomy with last menses >1 year ago,
- chemotherapy-induced menopause with >1 year interval since last menses,
- or surgical sterilisation (bilateral oophorectomy or hysterectomy).

10. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

4.2 Exclusion criteria

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

1. Patients receiving any systemic anticancer chemotherapy, radiotherapy (except for palliative reasons), within 2 weeks from the last dose prior to study treatment (or a longer period depending on the defined characteristics of the agents used). The patient can receive a stable dose of bisphosphonates for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment.

2. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, Ductal Carcinoma in Situ (DCIS), stage 1 grade 1 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years.

3. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.

4. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

5. Patients with severe hypersensitivity reactions to paclitaxel, macrogolglycerol ricinoleate (polyoxyl castor oil) or to any of the excipients in paclitaxel.

6. Patients with a known hypersensitivity to olaparib or any of the excipients of the product.

7. Patients with a history of severe allergic reaction to carboplatin or other platinum containing compounds. Patients who require desensitisation procedures for further platinum-based treatment should not be included.

8. Hypersensitivity to pre-medications required for treatment with paclitaxel/ carboplatin.

9. Any previous treatment with a PARP inhibitor, including olaparib.

10. Patients receiving the following classes of inhibitors of CYP3A4 (see Section 5.6.1 for guidelines and wash out periods).

    – Azole antifungals

    – Macrolide antibiotics

    – Protease inhibitors

11. Persisting toxicities (>CTCAE grade 2) caused by previous cancer therapy.

12. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.

13. Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

14. Breast feeding women.

15. Known immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus (HIV).

16. Patients with known active hepatic disease (ie, Hepatitis B or C).

17. Patients with uncontrolled seizures.

18. Previous randomisation in this study.

19. Participation in another clinical study with administration of an investigational product during the last 14 days.

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

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

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 (eg, hormone implants)
- Placement of an intra-uterine device (see Appendix E as consideration should be given to the type of device/system used)

Appendix E provides details of acceptable birth control methods to be used within the study.

Other Concomitant treatment

- No other chemotherapy, hormonal therapy (HRT is acceptable) or other novel agent is to be permitted during the treatment portion of the study for any patient (patients 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.
- 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.
- Patients receiving olaparib concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity (see Section 5.6.1) 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, although the contribution of metabolic clearance to total drug clearance in man is currently unknown this restriction is required to ensure patient safety.

- Paclitaxel should be used with caution with medicines known to inhibit or induce cytochrome P450 isoenzymes CYP2C8 and CYP3A4.

- Caution should be exercised in the concomitant use of amino glycosides with carboplatin, as this may result in increased renal and/or audiologic toxicity.

5.2 Patient enrolment and randomisation and initiation of investigational product

The Principal Investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Determine patients' eligibility. See Sections 4.1 and 4.2

3. The unique enrolment number (beginning with 'E#') and randomisation code (patient number) will be obtained through IVRS/IWRS.

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (eg, the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient's unique identifier and is used to identify the patient on the eCRFs.

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

5.2.1 Procedures for randomisation

Randomisation codes will be assigned strictly sequentially, as patients become eligible for randomisation.

Eligible patients will be randomised in a 1:1 ratio to either olaparib in combination with paclitaxel/carboplatin or paclitaxel/carboplatin alone.

Patient randomisation will be stratified based on the following baseline prognostic variables:

- Number of prior platinum-containing treatment lines received (1 or >1)

- Time to disease progression following completion of the previous platinum containing therapy (>6 to ≤12 months or >12 months)

The actual treatment given to individual patients will be determined by a randomisation scheme that has been loaded into the Interactive Voice Response System (IVRS) database. The randomisation scheme will be produced by a computer software program called GRand

(AZ Global Randomisation system) that incorporates a standard procedure for generating randomisation numbers.

It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days.

A blocked randomisation will be generated and all centres will use the same list in order to minimise any imbalance in the number of patients assigned to each treatment group.

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS Centralised Randomisation Centre by telephone for allocation of randomised therapy. Patients will be identified to the Centralised Randomisation Centre using patient initials, E-code and date of birth. If a patient discontinues participation in the study, then their enrolment/randomisation code cannot be reused.

5.3 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 Delivery 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 Delivery 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.

5.4 Blinding and procedures for unblinding the study – Not applicable

5.5 Treatments

5.5.1 Identity of investigational product(s)

The Investigational Products Supply (IPS) section of AstraZeneca will supply olaparib to the investigator as white, size 0, capsules.

Investigational product[a]	Dosage form and strength	Manufacturer
olaparib	50 mg capsule	AstraZeneca

a Descriptive information for olaparib can be found in the Investigator's Brochure

5.5.2 Doses and treatment regimens

For all centres, olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Paclitaxel and carboplatin is commercially available and supplied locally.

Olaparib 200mg bid will be taken on Day 1 through day 10 for each 21 day cycle of treatment until completion of study treatment (expected to be 6 cycles/18 weeks). On Day 1 of each treatment cycle, olaparib should be taken at least 1 hour prior to the administration of paclitaxel and carboplatin.

Four 50mg olaparib capsules should be taken at the same time each day, morning and evening, approximately 12 hours apart, with a glass of water. In the olaparib monotherapy treatment phase (commencing following completion of paclitaxel/ carboplatin), patients will be instructed to take eight 50 mg capsules bid continuously (days 1- 21).

Patients will be instructed to take their doses of olaparib at least 1 hour after food, and the patient 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.

If vomiting occurs shortly after the olaparib 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 (eg, 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.

5.5.3 Additional study drug

Paclitaxel and carboplatin treatment should be given at least 1 hour after the patient has taken their olaparib morning dose. Patients will receive prophylactic anti-emetic therapy before carboplatin administration according to local practice (ie, 5HT3 antagonist plus dexamethasone). In addition all patients should be pre-medicated prior to paclitaxel dosing in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20mg PO administered approximately 12 and 6 hours before paclitaxel dosing, diphenhydramine (or its equivalent) 50mg i.v. 30-60 minutes before paclitaxel dosing, and cimetidine 300mg or ranitidine 50mg i.v. 30-60 minutes before paclitaxel.

Paclitaxel will be administered at a dose of 175 mg/m^2 on day 1 of a 21 day cycle.

Carboplatin dosing of AUC 4 or 6 is calculated using the Calvert formula based on creatinine clearance using Cockcroft-Gault (Calvert et al 1989) as follows:

Dose (mg) = (GFR + 25) x AUC.

If any investigational site is unable to adhere to the specified method of dose calculation, it is essential that any alternative is approved by the AstraZeneca physician prior to any patient being dosed.

5.5.4 Labelling

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

Investigational Product Supplies (IPS), AstraZeneca, will label each bottle of olaparib. Each bottle will have a label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach of children.

The label will include blank lines for the following information:

- number of capsules to be taken
- enrolment code (E-code)
- date of dispensing
- Instructions stating that the olaparib should be taken at approximately the same time each morning and evening.

5.5.5 Storage

All study drugs must be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The investigational product label on the bottle and the Investigator Brochure specifies the appropriate storage and shipment conditions.

5.5.6 Management of toxicity on the investigational arm

During the study, consideration may be given to dose reduction of olaparib, paclitaxel and carboplatin, based on the following guidelines.

For drug associated toxicities the following will apply:

Initially delay all study treatment until the toxicity has recovered (based on the guidance in Sections 5.5.6.1 and 5.5.6.3 below), followed by a maximum of two dose reductions of the olaparib dose

- First reduction to 100 mg bid for 10 days of a 21 day cycle
- Second reduction to 100 mg bid for 5 days of a 21 day cycle.

Dose adjustments of paclitaxel and/or carboplatin may be considered after dose reduction of olaparib following consultation with the sponsor.

In the event of neutropenia (<500 x 10^6/l) and/or thrombocytopenia (<50,000 x 10^6/l) safety assessments must be taken more often than listed in the Study Schedule, Table 2, to establish the duration and nadir of neutropenia and thrombocytopenia.

Doses, which have been reduced for toxicity, must not be re-escalated.

If permanent discontinuation of any of the 3 treatments is indicated, then the combination of olaparib, AUC4 carboplatin and paclitaxel must be discontinued. Any further chemotherapy treatment may be given at the discretion of the investigator. Note: Patients who prematurely discontinue the combination of olaparib, carboplatin and paclitaxel, and subsequently receive alternative chemotherapy, are not permitted to receive olaparib monotherapy following completion of that chemotherapy.

Should a delay of >14 days be required then the patient should be discontinued from study treatment.

All dose modifications must be recorded in the eCRF.

5.5.6.1 Dose modifications for pneumonitis

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption of the combination of paclitaxel, carboplatin and 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 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 Delivery Physician.

5.5.6.2 Dose modifications for neutropenia/thrombocytopenia

In the event of haematological toxicity (described below) all three drugs should be withheld until recovery from toxicity. The absolute neutrophil count (ANC) must be ≥1,500 x 10^6/l and the platelet count must be ≥100,000x 10^6/l in order to administer paclitaxel, carboplatin and olaparib and administration is to be delayed until counts recover to those values. Table 6 and Table 7 summarise the required initial dose modifications or delays for patients who experience haematological toxicity that may be treatment related.

Table 6 Dose modifications for thrombocytopenia

Toxicity	Action Taken
Platelet Count <100,000 x 10^6/l on the day of scheduled treatment.	Delay the combination of paclitaxel, carboplatin and olaparib until platelet count ≥100,000 x 10^6/l.
If treatment delay of >7 days	At the start of the next cycle reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days.
At any time following a dose of carboplatin: platelet count <50,000 x 10^6/l	No dose reduction. Delay the combination of paclitaxel, carboplatin and olaparib until platelet count ≥100,000 x 10^6/l.
platelet count <25,000 x 10^6/l	Delay all treatment until platelet count ≥100,000 x 10^6/l and at the start of the next cycle reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days.

Table 7 Dose modifications for neutropenia

Toxicity	Action Taken
ANC of <1,500 x 10^6/l on any day of scheduled treatment.	Delay the combination of paclitaxel, carboplatin and olaparib until ANC ≥1,500 x 10^6/l.
If treatment delay of >7 days	At the start of the next cycle reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days.
At any time following a dose of carboplatin:	
• ANC of <1,000 x 10^6/l associated with hospitalisation or an emergency room visit for neutropenic fever or documented infection.	Delay all treatment until ANC ≥1,500 x 10^6/l and at the start of the next cycle reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days.
• ANC of <500 x 10^6/l, which lasts at least 5 days.	Delay all treatment until ANC ≥1,500 x 10^6/l and at the start of the next cycle reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days.

5.5.6.3 Dose modifications for other toxicities

Table 8 Dose modifications for other toxicities

Toxicity	Action Taken
Grade 2, 3 or 4 toxicity (excluding nausea, vomiting, alopecia and grade 2 diarrhoea, if not judged as clinically significant by the investigator) considered by the Investigator to be related to study treatment present on the day of scheduled treatment.	For grade 2 toxicity, delay all treatments until resolution to grade 1 or baseline. For grade ≥3 toxicity, delay all treatments until resolution to grade 1 or baseline, then reduce olaparib by 50% first to 100mg bid for 10 days or secondly to 100mg bid for 5 days. Dependent on the specific toxicity, alterations in carboplatin and paclitaxel may be considered after consultation with the sponsor.

5.5.7 Carboplatin dosing modifications for hypersensitivity reactions

All patients will be carefully monitored for clinical features of hypersensitivity reactions. Should a hypersensitivity reaction of carboplatin occur during infusion, this must be discontinued and an attempt at desensitisation may be made subsequently if deemed appropriate by the Investigator in discussion with the patient. The timing of this will be at the discretion of the Investigator.

Dexamethasone 8mg bid (total of 3 oral doses) should be given starting on the morning prior to administration, (ie, morning, evening, morning). In addition, dexamethasone 8mg i.v. should be given 2 hours prior to carboplatin administration. Antiemetics should be given as usual (including dexamethasone 8mg i.v. and granisetron 1mg i.v.), together with chlorphenhydramine 10mg i.v. or clemastine 2mg immediately prior to administration

Table 9 Dose modifications for hypersensitivity reactions

Time (mins)	Dilution of full dosage	Diluted in	Example of amount of carboplatin administered at each level (based upon planned dose of 500mg)
0	1/500	100 ml 5% dextrose	1mg
+30	1/100	100 ml 5% dextrose	5mg
+60	1/10	100 ml 5% dextrose	50mg
+90	Remainder of planned dosage	500 ml 5% dextrose	444mg

The desensitisation procedure should take place with resuscitation facilities within easy access with regular observations and a trained nurse present throughout. If at any point during the

dose escalation allergic signs or symptoms are documented, the carboplatin infusion must be discontinued.

All subsequent cycles should then be given using this procedure.

5.5.8 Paclitaxel dose modifications

In the event paclitaxel-related toxicities occur, paclitaxel dosing alone should be delayed until recovery of the toxicity to grade 1 and subsequently a dose reduction to 135 mg/m^2 may be required for all subsequent cycles. If the toxicity continues after this reduction in paclitaxel, treatment with paclitaxel, carboplatin and olaparib must be discontinued.

5.5.9 Paclitaxel dosing modifications for hypersensitivity reactions

Severe hypersensitivity reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema, or generalised urticaria require the immediate discontinuation of paclitaxel and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged. Treatment with paclitaxel, carboplatin and olaparib should be discontinued.

5.5.9.1 Management of toxicity on the comparator arm

Management of toxicity for patients in the comparator arm (paclitaxel plus carboplatin) should be as per standard clinical practice.

All dose modifications must be recorded in the eCRF.

5.5.10 Dose modifications during olaparib monotherapy

Any toxicity observed during olaparib monotherapy should be managed by interruption of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are to be allowed as required, for a maximum of 4 weeks (28 days) on each occasion. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 3) grade 1 or less.

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

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 olaparib. If this has not resolved to at least NCI-CTCAE grade 1 during the maximum 4 weeks (28 days) dose interruption period, and/or the patient has already undergone a maximum of two dose reductions already, (to a minimum dose of 100 mg bid), the patient must permanently discontinue treatment with olaparib. If toxicity is appropriately resolved, then the patient should restart treatment with olaparib, but with a 50% dose reduction according to Table 1. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further 50% dose

reduction made. If, on re-starting treatment, the event continues to occur, the patient must permanently discontinue olaparib.

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 (growth factor, transfusions), without interruption in study drug or change in dose. However, growth factors must be discontinued once the AE has recovered to grade 1 or better. They may be resumed, if necessary, if leukopenia/anaemia develops again and discontinued once it recovers.

If new or worsening pulmonary symptoms (eg, 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 Delivery Physician.

The dose of olaparib must not be adjusted under any other circumstances unless the AstraZeneca physician gives prior agreement. Once the dose of olaparib has been reduced under no account should it be re-escalated.

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

Table 10 Dose reductions for olaparib monotherapy

Reduction	Dose Level [a]
Initial Dose Level	400 mg bid
1st dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	200 mg bid
2nd dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	100 mg bid
3rd dose reduction due to NCI-CTCAE grade 3 or 4 treatment related SAE/AEs	No reduction allowed – withdraw patient[a]

a olaparib is not to be decreased below 100 mg bid

5.6 Concomitant and post-study treatment(s)

5.6.1 Olaparib and CYP3A4

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

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, olaparib 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 olaparib 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 olaparib.

While this is not an exhaustive list, it covers known potent CYP3A4 inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- ketoconazole, itraconazole, ritonavir, indanavir, saquinavir, erythromycin, telithromycin, clarithromycin, nefazodon and nelfinavir.

For patients taking any of the above, the required wash-out periods prior to starting olaparib is one week.

In addition, to avoid potential reductions in exposure to olaparib due to drug interactions, the concomitant use of CYP3A4 inducers should be avoided. Though not all-inclusive, the following list refers to some commonly used CYP3A4 inducers:

- phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil, corticosteroids, efanirenz, pioglitazone, troglitazone and St. John's Wort.

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 the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient’s safety and welfare, the Investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

5.6.2 Other Concomitant Medications

Any medications, with the exceptions noted in Section 5.6.5 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 eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the comments section of the corresponding Adverse Event report.

Anticoagulant Therapy: Patients who are taking warfarin may participate in this trial; 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-diarrhoeals: Prophylactic anti-diarrhoeals should not routinely be given. Should a patient develop diarrhoea, which, in the Investigator's opinion, is considered related to the study medication, then appropriate prophylactic treatment may be given.

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 eCRF.

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

There are a number of medications which may interact with paclitaxel and/or carboplatin. Please refer to local full prescribing information for more details.

5.6.3 Palliative radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period.

5.6.4 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 provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

5.6.5 Medications that may NOT be administered

No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted while the patient is receiving study medication.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

5.7 Treatment compliance

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

Patients should be given clear instructions on how and when to take their study medication. Patients will self-administer olaparib. Compliance of the first dose and dose taken on the day

of any study visit of olaparib will be assured by supervised administration by the Investigator or delegate. Study site pharmacy staff will make capsule counts at regular intervals during treatment. Compliance will be assessed by the capsule count and the information will be recorded in the appropriate section of the eCRF. 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 reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

Patients must return all containers and any remaining capsules at the end of the study.

5.7.1 Accountability

The study drug provided for this study is for use only as directed in the study protocol. It is the Investigator/institution's responsibility to establish a system for handling study 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 as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol.

The study personnel will account for all study medications dispensed and returned. Certificates of delivery and return should be signed.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed/returned stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity and date of dispensing and unused study treatment returned to the Investigator. This record is in addition to any drug accountability information recorded on the eCRF. Any discrepancies must be accounted for on the appropriate forms. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist, and copies retained in the investigator site file.

5.8 Discontinuation of investigational product

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
- Objective progression according to RECIST v1.1 criteria:

Patients may continue to receive study treatment as long as they are receiving benefit, in the opinion of the Investigator. All patients who discontinue study treatment prior to objective disease progression, should continue to be followed until progression **and death,** according to the study schedule.

5.8.1 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) for discontinuation and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). For Arm A patients, adverse events will be followed up through the 30 day follow up period.

Any patient discontinuing investigational product should be seen at the end of the last cycle of paclitaxel/carboplatin and a final 30-day follow up visit for the evaluations outlined in Table 3. 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 eCRF 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 6.4.3 and 6.4.4). All new AEs and SAEs must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4.4) 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.

Any patient who discontinues study treatment for reasons other than objective disease progression as per RECIST v1.1 criteria should continue to be followed for radiological progression as described in Section 6.3. Any subsequent cancer therapies that are initiated after study medication is discontinued should be recorded in the CRF, including details of best response.

All patients will be followed for survival status until the final analysis of OS, unless they withdraw consent.

If a patient is withdrawn from study, see Section 5.9

5.9 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 6.4.3) and study drug should be returned by the patient.

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 ie, the patient does not meet the required inclusion/exclusion criteria for the study
- The patient becomes pregnant
- Patient lost to follow-up

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

6.2 Data collection and enrolment

6.2.1 Screening

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment. For details of the schedule and nature of the assessments, see below.

- Signed informed consent for the study
- Date of birth, race and ethnicity

- Menopausal status; serum or urine pregnancy test for women of childbearing potential (within 28 days prior to study treatment start and confirmatory test day 1 prior to starting study treatment)
- *BRCA*1/2 mutation status, if known from previous testing (not required for enrolment)
- Medical and surgical history
- ECG within 7 days prior to starting study treatment
- Current and concomitant medications including previous cancer therapies
- Physical examination; ECOG performance status, vital signs (blood pressure and pulse, body temperature), body weight, and height.
- Haematology, clinical chemistry
- Tumour assessment (scans of the abdomen/pelvis/other sites as clinically indicated for assessment of disease) by CT/MRI. To be performed within 28 days prior to starting treatment.
- Tumour marker (CA-125) will be assessed locally (within 7 days of starting treatment)
- Adverse events must be captured from time of consent

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

6.2.2 On trial assessments

Olaparib is self administered by the patient twice daily as instructed on days 1- 10 of a 21 day cycle. The visit schedule is based on 21 day cycle. Following randomisation, patients in both treatment arms will attend weekly clinic visits for the first 6 weeks of treatment, and then upon completion of cycle 2, every 3 weeks, or more often if clinically indicated. Paclitaxel and carboplatin treatment will be administered on day 1 of each 21 day cycle and given at least 1 hour after the patient has taken their olaparib morning dose. The following assessments are to be performed:

- Physical examination including ECOG performance status (day 1 of each 3 week cycle) and vital signs
- ECG (at discontinuation of chemotherapy from treatment and discontinuation of olaparib monotherapy)
- Haematology and clinical chemistry

- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day of first treatment)
- AE and concomitant medications
- Tumour marker (CA-125) will be assessed locally from blood samples taken at the beginning of each cycle prior to the patient receiving treatment
- Tumour assessments [scans of the abdomen/pelvis and other areas as clinically indicated (CT/MRI)] at week 9, week 18, and every 12 weeks thereafter.

Upon completion of cycle 6 (ie, 21 days after last dose of chemotherapy), patients randomised to the olaparib arm (Arm A) will continue to receive olaparib at the maintenance dose of 400 mg bid continuously. *Note: Patients who prematurely discontinue the combination of olaparib, carboplatin and paclitaxel are permitted to participate in the olaparib maintenance phase as long as they have completed at least 4 cycles of study treatment in the combination phase of the study and have not received any other anti-cancer therapy between completion of the combination phase and commencing olaparib maintenance.* 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 and 22.

For patients in Arm A only, an additional clinic visit for safety assessments between olaparib maintenance day 22 and week 24 (relative to randomisation) is recommended for patients who have only completed 4 cycles of the chemotherapy phase, but are eligible to continue into the olaparib maintenance phase per the criteria described above. This recommended additional visit for safety assessments should be timed to ensure there are no more than 6 weeks between clinic visits.

Patients randomised to Arm A who have not completed at least 4 cycles of chemotherapy (therefore not eligible for olaparib maintenance phase) and Arm B patients who have not completed 6 cycles of chemotherapy (therefore not eligible for post completion phase), shall return to the clinic for the chemotherapy discontinuation visit and a final follow up visit 30 days after the last dose of study medication. Following this final 30 day follow up visit, these patients will continue to be followed for objective disease progression and survival but will not receive any further study treatment. Further treatment options will be at the discretion of the Investigator.

Arm A patients who have completed at least 4 cycles of chemotherapy and Arm B patients who have completed 6 cycles of chemotherapy shall return to the clinic at week 24, week 30, and every 6 weeks thereafter relative to date of randomisation until objective disease progression as per RECIST version 1.1 criteria (assessed every 12 weeks), unless any other discontinuation criteria are met.

Any patient who discontinues study treatment for reasons other than objective disease progression as per RECIST v1.1 criteria should continue to be followed for radiological

progression as described in Section 6.3. Any subsequent cancer therapies that are initiated after study medication is discontinued should be recorded in the CRF, including details of best response.

6.2.2.1 Patient reported outcomes (PRO) – Not applicable

6.2.2.2 Pharmacokinetics – Not applicable

6.2.2.3 Pharmacodynamics – Not applicable

6.2.2.4 Pharmacogenetics - Not applicable

6.2.2.5 Health economics – Not applicable

6.2.2.6 Archival tumour tissue for biomarker analysis (if available)

These samples will be collected from the site pathologist during the screening period. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from resection or a core biopsy from the primary tumour or metastases should be provided. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, sections mounted on glass slides prepared from the block can be provided. This material may be used for, but not restricted to, the elucidation of mechanism of response, understanding the mode of action of olaparib and improving the understanding of disease progression. Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage. These samples will be collected from the site pathologist at the randomization visit.

6.2.3 Follow-up procedures

6.2.3.1 Treatment discontinuation visit

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled, see Section 5.8. The assessments to be carried out at the visit are detailed in Table 2.

6.2.3.2 Final follow-up visit

A final follow-up visit should be conducted 30 days after the last dose of study medication, with the exception of Arm B patients that have completed 6 cycles of chemotherapy. Arm B patients, who have completed 6 cycles of chemotherapy will continue to be followed for safety assessments, including Adverse Events/SAEs and laboratory assessments until objective disease progression.

Any serious and/or non-serious AEs ongoing at the time of the Discontinuation Visit or which have occurred during the defined 30-day follow-up period must be followed-up (in accordance with Sections 6.4.3 and 6.4.4). 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. If the patient is lost to follow-up, then this should be noted in the eCRF.

6.2.3.3 Survival follow-up

Assessments for survival status should be made every 12 weeks following objective disease progression as per RECIST v1.1 criteria. Survival information may be obtained via telephone contact with the patient, patient's family or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, including details of best response, after discontinuation of treatment, will be collected.

In addition, to determine survival status for all patients at the time of the data cut-off date, patients should be contacted in the week following the data-cut-off date for all PFS and OS analyses.

6.2.3.4 CT or MRI scans (RECIST v1.1)

The imaging modalities used for RECIST v1.1 assessment will be CT or MRI scans of the abdomen and pelvis or other sites as clinically indicated for assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged. The radiological examinations performed in the conduct of this study should be retained at the site as source data and be available for collection for the external independent central review. Assessments of PFS will be made on the basis of CT or MRI scans by independent radiographic central review.

6.3 Efficacy

6.3.1 Efficacy variables

Table 11 Efficacy and variables

Objective	Variable
Primary To compare the efficacy of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone.	Progression Free Survival (PFS)
Secondary To compare the efficacy of olaparib in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone.	Overall Survival (OS) Percentage change in total tumour size Objective Response Rate (ORR) Ovarian Cancer Response Rate (a composite of CA-125 Response Rate [Gynecologic Cancer InterGroup {GCIG} criteria] and/or RECIST Response Rate) CA-125 response rate (GCIG criteria)

6.3.2 Tumour evaluation

RECIST v1.1 criteria will be used to assess patient response to treatment by determining PFS, percentage change in total tumour size and ORR. The RECIST v1.1 guidelines for

measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix D.

The methods of assessment of tumour burden used at baseline (CT or MRI scans) of abdomen and pelvis and other areas as clinically indicated must be used at each subsequent assessment.

Tumour assessments are to be performed within 28 days of starting study treatment, week 9, week 18, and then every 12 weeks thereafter (+/-1 week) until objective disease progression as per RECIST v1.1 criteria. Any other sites at which new disease is suspected should also be appropriately imaged.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST v1.1.

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

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

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

It is important to follow the tumour assessment schedule as closely as possible. Please refer to the study plan and Appendix D.

Central reading of scans

An independent review of all scans used in the assessment of tumours using RECIST v1.1 will be conducted. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. Results of this independent review will not routinely be communicated to Investigators, and the management of patients will be based solely upon the

results of the RECIST v1.1 assessment conducted by the Investigator. The **PFS** analyses for this study will be based on data from the independent central review.

6.4 Safety

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

6.4.1 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, 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.

6.4.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, screening, run-in, treatment, washout, follow-up), at any dose of the study drugs 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 an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse Events/SAEs will be collected from time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period. However, Arm B patients, who have completed 6 cycles of chemotherapy, will continue to be followed for safety assessments, including Adverse Events/SAEs and laboratory assessments until objective disease progression.

Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated (see section 5.8.1). 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 (ie, 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. 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 6.4.4)

Variables

The following variables will be collected for each AE;

- AE (verbatim)
- the date *and time* when the AE started and stopped
- the maximum NCICTCAE grade attained
- whether the AE is serious or not
- investigator causality rating against the Investigational Product (yes or no), combination drugs (yes/no), comparator drug (yes/no) and study procedures/other medications
- action taken with regard to investigational product/combination drug(s) and comparator agent(s)

- AE caused patient's withdrawal from study treatment *(*yes or no*)*
- 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

Severity of AE

The grading scales found in the revised NCI-CTCAE version 3.0 will be utilized for all events with an assigned NCI-CTCAE grading. For those events without assigned NCI-CTCAE grades, the recommendation is the NCI-CTCAE criteria that convert mild, moderate, severe, life-threatening/disabling and fatal events into NCI-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)

For each event, the highest severity grade attained 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 6.4.2. 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.

Causality collection

The investigator will assess causal relationship between the study drugs 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(s)/comparator drug(s)?"

Causal relationship will also be assessed for other medication and study procedures. Note that for AEs 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?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately

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 and other safety variables 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, combination drug(s) and comparator agents.

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 6.4.2). 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 in serous ovarian, 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 eCRF 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 6.4.4 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 eCRF'.

- 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.

6.4.4 Reporting of serious adverse events

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

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

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by fax.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

6.4.5 Laboratory safety assessment

Blood samples for determination of clinical chemistry, haematology and coagulation will be taken at the times indicated in the Study Schedule (see Table 2, Table 3, Table 4 and Table 5).

The following laboratory variables will be measured:

Full haematology assessments for safety (haemoglobin, red blood cells [RBC], platelets, mean corpuscular volume [MCV], mean corpuscular haemoglobin concentration [MCHC], mean corpuscular haemoglobin [MCH], white blood cells [WBC], differential white cell count and absolute neutrophil count should be performed at each visit and when clinically indicated. Coagulation [activated partial thrombplastin time {APTT} and international normalised ratio {INR}]) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin (see Section 5.6.2).

Biochemistry assessments for safety (sodium, potassium, calcium, magnesium, 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, lactic dehydrogenase [LDH]) amylase and lipase will be performed.

Urinalysis should be performed if clinically indicated.

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 eCRF.

For blood volumes see Section 7.1.

6.4.6 Physical examination

For timing of individual measurements refer to study schedule (see Table 2, Table 3, Table 4 and Table 5).

Complete physical examinations will be performed including an assessment of the following:

Height (screening only), BP, pulse, and temperature at the screening visit and as outlined in the study schedule. Weight will be measured according to the study schedule.

Performance status will be assessed using the ECOG scale (reference Appendix F) at baseline and as outlined in the study schedule. The same observer should assess performance status each time.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting study treatment and at chemotherapy discontinuation of study treatment and discontinuation of continuous olaparib monotherapy treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. All 12-lead ECGs should be recorded while the patient is in the supine position. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected.

ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine BP and pulse rate will be measured using a semi-automatic BP recording device with an appropriate cuff size, after patient has rested for at least 10 minutes. For the timing of assessments refer to the study plan (see Table 1, Table 2, Table 3, Table 4 and Table 5). The date of collection and measurement will be recorded on the appropriate eCRF.

6.4.9 Other safety assessments

6.4.9.1 Serum or urine pregnancy test

Two pregnancy tests on either 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.

6.5 Personalized medicine biomarkers

6.5.1 Summary of objectives and analysis

To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses.

6.5.2 Collection of samples for personalised medicine biomarker research

Details of sample collection, processing, shipping and storage will be described further in the Investigators Laboratory Manual and in the following sections.

The samples and data for analysis in this research will be coded and will not be labelled with any personal details. Each sample will be identified with the study number and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the case of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient.

The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development drug project. However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties, except as required by law.

6.5.3 Collection of archival tumour sample

All consented patients will be asked to supply a sample of their archival tumour blocks. These samples will have been taken prior to the clinical trial and donation of samples involves no further biopsy procedures, as the sample has been previously taken as part of their standard care.

The tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site) or if this is not possible as slides (prepared unstained 5 micron sections from the archival tumour block). If providing sections it is important that a new disposable microtome blade is used for each patient to prevent any contamination between patient samples and sections floated in molecular grade water prior to mounting. Sections should be mounted on to clean 'SuperFrost' glass slides as described in the laboratory manual.

These slides are produced commercially and are ready treated (electrostatically charged).

All samples should be shipped at ambient temperature as per Investigator's Laboratory Manual. Samples will be collected from the site pathologist during the screening period and analysed for markers such as components of the homologous recombination pathway which may be predictive of patient benefit from olaparib.

6.5.4 Management of personalised medicine biomarker data

The biomarker data will not be generated in real time during the study and will have unknown clinical significance. AstraZeneca will not provide biomarker research 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 samples 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 research 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. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 12 Volume of blood to be drawn from each patient (Arm A only)

Assessment		Sample volume (mL)	No. of samples[a]	Total volume (mL)
Safety	Clinical chemistry	6[b]	24[c]	144
	Haematology	10[b]	24[c]	240
Biomarker	CA-125	4[b]	**18**[d]	**72**
Total				**456**

a Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments
b These are approximate volumes that are subject to site-specific change
c Based on baseline, 6 cycles of chemotherapy (18 weeks), chemotherapy discontinuation visit, olaparib maintenance (Days 8, 15, 22; weeks 24 through 66), maintenance discontinuation visit and 30-day follow-up.
d Based on baseline, cycles 1-6, chemo discontinuation, week 24, week 30, every 6 weeks until week 66, and treatment discontinuation **and 30-day follow up visit.**

Table 13 Volume of blood to be drawn from each patient (Arm B only)

Assessment		Sample volume (mL)	No. of samples[a]	Total volume (mL)
Safety	Clinical chemistry	6[b]	19[c]	114
	Haematology	10[b]	19[c]	190
Biomarker	CA-125	4[b]	16[d]	64
Total				368

a Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments
b These are approximate volumes that are subject to site-specific change
c Based on baseline, 6 cycles of chemotherapy (18 weeks), chemotherapy discontinuation visit, week 24 (safety follow-up), and weeks 30 through 66.
d Based on baseline, cycles 1-6, chemo discontinuation, week 24, week 30, and every 6 weeks until week 66.

7.2 Handling, storage and destruction of biological samples

For sample processing, handling and shipment see the Investigators Laboratory Manual.

7.2.1 Archival tumour samples

For sample processing, handling and shipment see the Investigators Laboratory Manual.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

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

8.2 Patient data protection

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

8.2.1 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 and keeps documentation of receipt of arrival.

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

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.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the 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 (EC)/ Institutional Review Board (IRB) should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The EC/IRB 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 EC/IRB 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, EC/IRB and Principal investigators with safety updates/reports according to local requirements.

AstraZeneca will be responsible for informing the regulatory authorities of SAEs/SUSARs as per the EU clinical trial directive and/or local country regulations and guidelines

For the US and Canada (may also be applicable to other countries), each Principal investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions (Investigator Safety Letters [ISLs]) from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal investigator (ISLs) so that he/she can meet these reporting requirements.

The Principal Investigator is responsible for sending their EC/IRB all serious adverse events that occur at their own site.

8.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- 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.

Patients will consent (as part of the main study consent) for the sourcing of their archival tumour specimen (taken at diagnosis). In the event that no archival tumour sample can be sourced, the patient will still be able to continue on the study.

8.4.1 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated the samples will be disposed/destroyed, if not already analysed and documented.

The principal investigator:

- Ensures patients withdrawal of informed consent is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed/destructed and the action documented.

- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destructed and the action documented returned to the study site.

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

In the event that analysis/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.

AstraZeneca ensures that any biological samples remaining after analysis have been performed may be repatriated upon request or kept until the end of the period specified in the informed consent.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating 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 should be approved by each EC/IRB and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, 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, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any

applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 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 patient 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.

9.2 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 (IVRS) system(s) utilised.

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

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

9.3 Monitoring of the study

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 on the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that investigational product accountability checks are being performed.

- Perform source data verification (a comparison of the data on the eCRFs 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 (eg, 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.

9.3.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, 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.

9.4.1 Archiving of study documents

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

9.5 Study timetable and end of study

There will be a final data cut-off defined as date of the final OS analysis of the data, at approximately 60% maturity (approximately 90 deaths). **At the time of the interim OS analysis, should it be decided not to continue the study to the planned final 60% maturity OS analysis, the interim OS analysis will become the final data cut-off**. 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 olaparib.

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 6.4.4 (Reporting of serious adverse events). Additionally as stated in Section 6.4.3 (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.

The end of this study is defined as the date of the last visit of the last patient, occurring when the last patient has discontinued study therapy.

The study is expected to start in 1Q2010 and to end by 4Q2013.

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 olaparib.

10. DATA MANAGEMENT BY [redacted]

Data will be entered in the Web Based Data Capture (WBDC) system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. Site personnel will enter the data in the eCRFs. The data will then be Source Data Verified (SDV), reviewed/ queried and updated as needed. The principal investigator will then sign the eCRF electronically. Clean file occurs when all data have been declared clean and signed by the investigator. The data will be frozen and then locked to prevent further editing. A copy of the eCRF will be archived at the study site when the study has been locked.

Dictionary coding

Medical coding is done using the most current version of MedDRA and AstraZeneca Drug Dictionary.

Management of external data

Data Management determines the format of the data to be received from external vendors and coordinates the flow of data to an external environment or clinical database (if applicable). Data Management will ensure that the data collection tool (for eg, eDiary, IVRs etc) will be tested / validated as needed. External data reconciliation will be done with the clinical database as applicable.

Serious Adverse Event (SAE) Reconciliation

SAE Reconciliation Reports are produced and reconciled with Patient Safety database and/or the Investigational Site.

Biological Samples

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca. Potential analyses will be reported outside of the CSR.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

At each visit patients will be programmatically assigned a RECIST visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments.

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

For TL measurements, if ≤ 1/3 of the TL sizes are missing then a scaling up rule will be applied as follows:

- If ≤ 1/3 of lesions recorded at baseline are missing then the results will be scaled up (based on the baseline sizes) to give an estimated sum of diameters and this will be used in calculations (this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the baseline sum of diameters excluding the lesions that are missing and determining at what rate the lesions are changing)

- If > 1/3 of lesions recorded at baseline are missing then the target lesion response will be NE. However, if the sum of non-missing target lesion diameters would result in PD (ie, if using a value of 0 for missing lesions the sum of diameters has still increased by > 20% or more compared to the smallest sum of diameters on study and has an absolute increase ≥ 5mm) PD takes precedence over NE

- A visit response of CR will not be allowed if any of the TL data is missing

11.1.1 Primary endpoint

Progression Free Survival (PFS) is defined as the time from randomisation until objective disease progression as defined by RECIST v1.1 or death (by any cause in the absence of progression).

Patients who have not progressed or died at the time of the statistical analysis will be censored at the time of their last evaluable RECIST assessment. If a patient has no RECIST follow up assessments or has no evaluable baseline assessment and is still alive at the time of the analysis then they will be censored at 0 days for PFS. Symptomatic deterioration will not be regarded as a progression event.

If a patient discontinues treatment prior to progression and/or receives a subsequent therapy prior to progression then these patients will continue to be followed until evidence of objective disease progression as defined by RECIST v1.1 and their PFS time will be derived as defined above.

PFS will be assessed via an independent central review of radiological data.

Agreement between the investigational site and central review will be assessed and discussed in the CSR.

11.1.2 Secondary endpoints

Overall Survival (OS)

Overall survival is defined as the time from randomisation until death by any cause. Patients who have not died at the time of the statistical analysis of OS will be censored at the time they were last known to be alive.

Percentage Change in Total Tumour Size

The total tumour size is defined as the sum of the longest diameters of the target lesions. For each post-baseline tumour assessment, the percentage change in tumour size will be calculated from the ratio of the post-baseline size over the baseline total tumour size for each patient.

Objective Response Rate (ORR)

ORR is defined as the percentage of patients who have at least one visit response of CR or PR prior to any evidence of progression (as defined by RECIST v1.1).

A visit response of CR is defined when all TL and NTL lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10mm to be considered non-pathological) and no new lesions have developed since baseline. A visit response of PR is defined when the sum of diameters of the TLs has decreased by 30% or more compared to baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

Ovarian Cancer Response Rate

Ovarian Cancer Response Rate will be defined as the proportion patients with a response based on either the RECIST criteria (PRs or CRs only) or CA-125 response criteria.

CA-125 response (GCIG criteria; http://ctep.cancer.gov/resources/gcig/respdef_nov2005.doc)

Patients will be evaluable for CA-125 response if:

- a pre-treatment CA-125 level (taken within 2 weeks prior to starting treatment) is at least twice the upper limit of normal, and

- there is no more than a 10% fall in CA-125 between the two pre-treatment samples
- the same assay method is used for each sample from the same patient

A response according to CA-125 will be considered to have occurred if there is at least a 50% reduction in CA-125 levels from the last pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. Note the GCIG criteria is not validated for this trial population.

11.2 Calculation or derivation of safety variable(s)

11.2.1 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 other data (eg, labs, vital signs) will also 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.

11.3 Calculation or derivation of patient reported outcome variables – Not applicable

11.4 Calculation or derivation of health economic variables – Not applicable

11.5 Calculation or derivation of biomarker variables

11.5.1 Biomarker data

In relation to the exploratory objective to enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses, these biomarker analyses will be reported outside the CSR and details of any analyses will be specified in a separate statistical analysis plan.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

12.1.1 Efficacy analysis set

The efficacy analysis population will include all randomised patients following the intention-to-treat (ITT) principle (Full Analysis Set). It will compare the treatment groups on the basis of randomised treatment rather than treatment actually received.

12.1.2 Safety analysis set

All patients who received at least one dose of study treatment and for whom any post-dose data are available will be included in the safety population (Safety Analysis Set). Throughout the safety results sections, erroneously treated patients (eg, those randomised to treatment A but actually given treatment B) will be accounted for in the actual treatment group.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set.

12.2 Methods of statistical analyses

For the primary efficacy analysis the null hypothesis is that there is no difference in treatment effects between olaparib in combination with paclitaxel and carboplatin compared with paclitaxel and carboplatin alone. The primary assessment of efficacy will be based on an independent central review of the RECIST v1.1 data, blinded to randomised treatment.

Analysis of Primary Endpoint

The primary outcome variable PFS is defined in Section 11.1.1 and will be based on the central review of the RECIST data. The treatment groups will be compared using a stratified log-rank rest with strata defined for number of prior platinum-containing treatment lines (1 or >1) and time to disease progression following previous platinum containing therapy (>6 to ≤12 months versus >12 months). The adjusted hazard ratio and associated 80% and 95% confidence interval (CI) will be calculated. Kaplan-Meier plots of PFS will be presented by treatment group.

Full details of the analysis methodologies, including testing of assumptions and sensitivity analyses will be provided in the Statistical Analysis Plan (SAP).

Analysis of Secondary Endpoints

Overall Survival (OS)

The analysis of Overall Survival (OS) will use the same stratified log-rank test as describe for the primary PFS analysis. The adjusted hazard ratio and associated 80% and 95% CI for the treatment effect will be calculated and Kaplan-Meir plots of overall survival will be presented by treatment groups. In addition to the final OS analysis **and the interim analysis of OS at a**

minimum of 30% OS maturity, an interim analysis of OS may be performed at the time of the primary and post-primary PFS analyses if there are sufficient events, eg, at least 20, for a meaningful analysis.

Percentage change in tumour size

The percentage change in tumour size at scheduled tumour assessments will be calculated for each patient based on the change in sum of Target Lesion longest diameters from baseline. The percentage change in tumour size will be analysed at scheduled assessments using an analysis of covariance allowing for baseline sum of longest diameters as a continuous covariate and two level covariates for the number of prior platinum therapies (1 or > 1) and time to progression on previous platinum containing therapy as well as a term for treatment group.

ORR, Ovarian Cancer Response Rate and CA-125 Response Rate

For the ORR, Ovarian Cancer Response Rate and CA-125 response rate, the proportion of responding patients will be analysed by logistic regression, adjusting for the number of prior platinum therapies (1 or > 1) and the time to progression on prior therapy stratification factor. The effect of treatment will be estimated using the adjusted odds ratio and its corresponding two-sided 80% and 95% confidence intervals. The denominator for summaries of response rates will be the number of patients evaluable for the response.

Safety

The safety analyses will consist of assessment of the safety and exposure profiles in terms of AEs/SAEs, laboratory data, vital signs and ECG that will be collected for all patients. Appropriate summaries of laboratory data, vital signs and AEs/SAEs will be produced for all patients in the safety analysis set. There will be no formal analyses of safety endpoints.

12.2.1 Interim analyses

The objective of the early tumour size and 38 PFS event interim analyses is to determine whether there is sufficient efficacy to trigger Phase III studies in this patient population. The study will continue until the primary and post-primary analysis of PFS irrespective of the efficacy results of the earlier analyses. If any of the three PFS analyses (interim, primary or post-primary) fall very close together in time then they may not all be performed. If the primary (70 event) analysis is not performed the post-primary analysis will become the primary analysis. An interim analysis of OS may be performed at the time of the primary and post-primary PFS analyses if there are sufficient events for a meaningful analysis**.**

Additionally, an interim OS analysis will be performed when at least 30% deaths have occurred. If there is insufficient evidence of an effect on OS at the time of this interim analysis, then a decision may be made not to continue to 60% OS maturity.

Table 14 Summary of Analyses

Analysis	Description
Interim I	Preliminary assessment of the emerging safety and efficacy (tumour size) after the first 50 patients have been on study for at least 9 weeks
Interim II*	38 PFS events
Primary PFS*	At least 70 PFS events
Post-primary PFS*	60% mature PFS (approximately 90 progression events)
Interim OS	**At least 30% mature OS**
Final OS	60% mature OS (approximately 90 deaths)

* Assessment of PFS will be made on the basis of CT or MRI scans by independent radiographic central review. If any of the three PFS analyses (interim, primary or post-primary) fall very close together in time then they may not all be performed. If the primary (70 event) analysis is not performed the post-primary analysis will become the primary analysis.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

An interim analysis (Interim II) of PFS is planned when approximately 38 PFS events have occurred. Approximately 38 PFS events will be required to provide 80% power to detect a true hazard ratio (HR) of 0.5 at the 1-sided 10% significance level. No adjustment for multiple testing will be used.

The primary PFS analysis will be performed when at least 70 PFS events have occurred. At least 70 PFS events will be required to provide 80% power to detect a true hazard ratio (HR) of 0.6 at the 1-sided 10% significance level. Assuming exponential event times, a HR of 0.6 corresponds to a 67% increase in median PFS from 9 to 15 months.

To provide information on whether the primary analysis result remains consistent when the data reaches a maturity similar to a typical Phase III study in this setting, the post-primary PFS analysis will be performed after approximately 60% maturity (approximately 90 PFS events). 90 PFS events will provide 80% power to detect a true hazard ratio (HR) of 0.639 at the 1-sided 10% significance level. Assuming exponential event times, a HR of 0.639 corresponds to a 56% increase in median PFS from 9 to 14.1 months. Ninety PFS events will also provide 87% power to detect the true hazard ratio of 0.6 used in the sample size calculation of the primary PFS analysis at 70 events.

It is intended that a total of 150 patients (75 patients in treatment group) will be randomized to the study. If patients are recruited over 9 months, and the median PFS for paclitaxel + carboplatin alone is 9 months, it is predicted that 70 PFS events will occur approximately 17 months after the first patients has been recruited.

The **planned** final analysis of OS is scheduled to take place at around 60% maturity (approximately 90 deaths). As an example of the precision of the final OS analysis, 90 deaths will provide 80% power to demonstrate superior overall survival at the 1-sided 10% level if the true HR is 0.639 (approx medians 24 months vs 38 months). Assuming a median survival of 24 months in the carboplatin/paclitaxel treatment arm, the final data cut-off for OS is expected to occur approximately 46 months after the first subject was randomised.

In addition to the planned final OS analysis at approximately 60% maturity, an interim OS analysis will be performed when at least 30% deaths have occurred. If there is insufficient evidence of an effect on OS at the time of this interim analysis, then a decision may be made not to continue to 60% OS maturity.

12.4 Data monitoring committee

No formal data monitoring committee will be set up during this Phase II study.

AstraZeneca will routinely monitor the safety data, and if any emerging clinically important events related to olaparib are identified then investigators will be informed in accordance with ICH guidelines.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

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 6.4.4.

In the case of a medical emergency the investigator may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the responsible physician as below.

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]

Name	Role in the study	Address & telephone number
[redacted]	[redacted]	[redacted]

13.2 Overdose

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

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 eCRF 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, ie, 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, complete the Overdose, AE and SAE module, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

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

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.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the 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 ie, 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 6.4.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure – Not applicable

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Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00041
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

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

Important medical event or medical intervention

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

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

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.

AstraZeneca

Clinical Study Protocol Appendix C	
Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00041
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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.

Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00041
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Appendix D
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer 2009) for study D0810C00041 with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

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

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Measurable: A lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis at baseline*).

Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

Previously irradiated lesions**

Skin lesions assessed by clinical examination

Brain metastasis

* Nodes with <10mm short axis are considered non-pathological and should not be recorded or followed as NTL.

**Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as Non-Target Lesions (NTL) at baseline and followed up as part of the NTL assessment.

Special Cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions.

Target lesions: A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as target lesions (TL) at baseline.

Non-Target lesions: All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline.

3. METHODS OF ASSESSMENT

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

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 1 Summary of Methods of Assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest x-ray	X-ray, Chest x-ray
		Ultrasound
		Bone Scan
		FDG-PET

3.1 CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TL selected for response assessment and to assess NTL and identification of any new lesions.

In D0810C00041, it is recommended that CT examinations of the abdomen, pelvis and other areas as clinically indicated will be used to assess tumour burden at baseline and follow-up visits. 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.

3.2 Clinical examination

In D0810C00041, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as target lesions if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

3.3 X-ray

3.3.1 Chest X-ray

In D0810C00041, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In D0810C00041, plain x-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

3.4 Ultrasound

In D0810C00041, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D0810C00041 study, endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

3.6 Tumour markers

In the D0810C00041 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study the following marker, CA-125, is being collected for separate analysis. However, the results will not contribute to tumour response based on RECIST 1.1 assessment.

3.7 Cytology and histology

In the D0810C00041 study histology will not be used as part of the tumour response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or

stable disease. In such circumstances, the cytology is necessary to differentiate between response / 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 (from trace to large) or appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTL, or disease progression due to new lesions.

3.8 Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In the D0810C00041 study isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

3.9 FDG-PET scan

In the D0810C00041 study FDG-PET scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake* not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

* A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment (See Study Plan). Other assessments will be performed at 9 weeks (+/- 1 week) (Interim Analysis), and 18 weeks (+/- 1 week) after randomisation. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

4.2 Target lesions (TL)

4.2.1 Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TL merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL.

Table 2 Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

Table 3 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. 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.

Table 3 Evaluation of Non-Target Lesions

Not Evaluable (NE)	Only relevant when one or some of the non-target lesions were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall non-target lesion assessment at this visit. Note: For patients without target lesions at baseline, this is relevant if any of the non-target lesions were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

4.4 New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

4.5 Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

4.6 Evaluation of Overall Visit Response

The overall visit response will be derived using the algorithm shown in Table 4.

Table 4 Overall Visit Response

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

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

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

5.1 CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of

scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvis MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax, abdomen and pelvis examination. For brain lesions assessment, MRI is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

5.2 MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope appendix to prescribe specific MRI pulse

sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

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

5.3 FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of patients with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all patients and serial scans in the clinical trial.

5.3.1 PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

6. REFERENCES

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Clinical Study Protocol Appendix E

Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00041
Edition Number	1
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Appendix E
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high foetal risk.

Patients of childbearing 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).

Acceptable Non-hormonal birth control methods include

- Total sexual abstinence. Abstinence must be for the total duration of the trial 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
- IUD plus male condom + spermicide. Provided coils are copper-banded

Acceptable hormonal methods

- Etonogestrel implants (e.g., Implanon, Norplan) + male condom with spermicide
- Normal and low dose combined oral pills + male condom with spermicide
- Norelgestromin / EE transdermal system + male condom with spermicide
- Intravaginal device + male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Clinical Study Protocol Appendix F

Drug Substance	Olaparib (AZD2281)
Study Code	D0810C00041
Edition Number	1
Date	[redacted]

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

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Table 1 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.