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Clinical Study Protocol

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00042
Edition Number	1

[redacted]

A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation

Sponsor: [redacted]

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

AstraZeneca

PROTOCOL SYNOPSIS

A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic BRCA1 And/Or BRCA2 Mutation

International Co-ordinating investigator

[redacted]

Study centre(s) and number of patients planned

Recruitment period 12 months.

Up to approximately 150 patients will be recruited.

It is intended that a minimum of 20 patients in each of the prostate and pancreatic tumour types will be recruited. The recruitment of patients with other tumour types (ie, breast, ovarian and any other) will be capped at a maximum of 110 patients. If, at an appropriate time, it is evident that recruitment to the prostate and pancreatic groups will not be achieved in a suitable timeframe, then study will be closed to further recruitment.

Patients will be recruited from clinical sites in Israel, USA and Australia.

Study period	Phase of development
[redacted]	

Objectives

Primary Objective

- To assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of tumour response.

Secondary objectives

- To assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of objective

response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR).

- To determine the safety and tolerability of oral olaparib in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation.

Study design

A phase II, open-label, non-randomised, non-comparative multicentre study to assess the efficacy and safety of olaparib given orally twice daily in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation.

Up to approximately 150 patients with a BRCA mutation are to be recruited. Tumour types expected, but not limited to, include ovarian, breast, prostate and pancreatic. It is intended that a minimum of 20 patients in each of the prostate and pancreatic tumour types will be recruited. The recruitment of patients of all other tumour types will be capped at a maximum of 110 patients.

The analysis of all primary and secondary objectives will occur 6 months after the last patient has commenced study treatment (data cut-off). The analyses will be based on the assessment of response based on RECIST 1.1. Following this analysis (at data cut-off) the study will be closed. However, patients may continue to receive olaparib for as long as they are receiving clinical benefit in the opinion of the investigator (until progression or other olaparib discontinuation criteria are met). During this time, serious adverse events (SAEs) must still be collected and reported until 30 days after the patient finally stops taking olaparib.

Target Study Population

Patients who have histologically and/or cytologically confirmed malignant solid tumours which are refractory to standard therapy and for which no suitable, effective/curative therapy exists. Patients must also have a confirmed genetic *BRCA1* and/or *BRCA2* mutation prior to enrolment in the study. This will have been determined according to local practice.

Investigational product, dosage and mode of administration

Patients will self-administer olaparib orally twice daily at 400 mg bd. Eight 50 mg olaparib capsules should be taken at the same time each day, morning and evening, with a glass of water.

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.

Comparator, dosage and mode of administration (Not Applicable)

Not applicable. This is a non-comparative study.

Duration of treatment

After starting study treatment, patients will attend periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression according to RECIST. Following confirmed disease progression patients will discontinue olaparib treatment, but may receive any cancer treatment at the investigator's discretion. All patients will continue to be contacted to assess survival status until death or the data cut-off for the primary analysis, whichever is the sooner. The analysis of all primary and secondary objectives will occur 6 months after the last patient has commenced study treatment (data cut-off).

Outcome variable(s):

Efficacy

- **Primary outcome variable**
  - Tumour response (assessed using the principles of RECIST 1.1, based on confirmed response).
- **Secondary outcome variables**
  - Efficacy: ORR, PFS, OS, DOR and DCR.
  - Safety: Adverse events (AEs), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.

Statistical methods

Up to 150 patients will be recruited to the study. It is intended that there will be at least 20 patients in each of the breast, ovarian, prostate and pancreatic tumour type groups and up to 110 others (including breast and ovarian as well as other tumour types), which will provide descriptive information on the effect of olaparib treatment on tumour response in a variety of tumour types in patients with *BRCA* mutations.

The primary objective is to assess the effect of olaparib treatment on tumour response. In all patients, the RECIST 1.1 guidelines for determining if a patient has a tumour response will be used. A response must be confirmed by a subsequent RECIST scan. Patients with measurable disease at baseline will be considered a responder if they meet the visit criteria for complete response (CR) or partial response (PR). Patients with non-measurable disease at baseline will only be considered a responder if they meet the visit criteria for CR. The tumour response rate will be summarised, and 95% confidence interval (CI) for the response rate will be calculated using a binomial distribution. The tumour response rate will also be summarised in breast, ovarian, prostate, pancreatic tumour types, and any other tumour types where sufficient patients are recruited.

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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
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
BER	Base excision repair
BP	Blood pressure
BRCA	Breast cancer gene
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
CI	Confidence interval
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
E-code	Enrolment code
ECOG	Eastern Co-operative Oncology Group

Abbreviation or special term	Explanation
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GMP	Good Manufacturing Practice
HRD	Homologous recombination deficiency
IB	Investigators' Brochure
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
INR	International normalised ratio
IP	Investigational Product
ITT	Intention-to-treat
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulator Activities
MRI	Magnetic Resonance Imaging
NAD	Nicotine adenine dinucleotide
NCI	National Cancer Institute
NE	Non-evaluable
NTL	Non-target lesion(s)
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective response rate
OS	Overall Survival
PAR	Poly-(ADP-ribose)
PARP	Poly- (ADP-ribose) polymerase
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
po	Per os (by mouth)
PR	Partial response

Abbreviation or special term	Explanation
prn	As needed (Pro re nata)
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2).
SAS	Safety Analysis Set
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SD	Stable disease
TL	Target lesion(s)
ULN	Upper limit of normal
WBDC	Web-based data capture

1. INTRODUCTION

Investigators should be familiar with the olaparib (AZD2281) Investigators' Brochure (IB).

1.1 Background

Although major improvements in oncology treatment have been made, many cancers frequently recur after primary treatment. At recurrence, these cancers are incurable. With specific targeted therapies, 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 remain poorly understood. Rational therapies directed to specific targets, and a clearer understanding of the mechanisms 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) and, despite aggressive surgery and chemotherapy, the prognosis is not good for these patients, with an overall 5-year survival rate of approximately 50% (Chetrit et al 2008). 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 median overall survival time for women with ovarian cancer is estimated to be 3.13 years (38 months) and the median survival time for patients with advanced ovarian cancer, following failure of treatment with platinum-based chemotherapy, is approximately 14 months (Gordon et al 2001; Gordon et al 2004). Ovarian cancer is a rare life-threatening disease and the EMEA has granted Orphan Drug Designation to several compounds for this indication, including olaparib(EU/3/07/501 in the Community Register of Orphan Medicinal Products). In Europe, there are approximately 40,000 new cases of ovarian cancer each year (Ferlay et al 2007).

Clinically, familial breast and ovarian cancer have been recognised for many years and led to the identification and sequencing of the "*BRCA*" genes, breast cancer susceptibility gene 1 and 2 respectively (*BRCA1* and *BRCA2*) (Miki et al 1994, Wooster et al 1995). Between 5% and 10% of cases of ovarian cancer are believed to be attributable to genetic factors (Kasprzak et al 1999) and the majority of genetic ovarian cancer is accounted for by germ line mutations in the *BRCA1* and *BRCA2* genes (Pal et al 2005). These patients therefore represent a small, well-defined, medically recognised sub-population comprising less than 4000 new cases per year in Europe.

Women who have ovarian cancer due to an inherited mutation tend to have a better prognosis (treatment outlook and survival rate) than women with ovarian cancer and no family history, particularly if they receive platinum-based chemotherapy (Foulkes 2006). A nationwide case-control study of ovarian cancer conducted in Israel between 1994 and 1999 confirmed that survival was significantly longer for *BRCA* mutation carriers than for non-carriers

(53.7 months vs 37.9 months, respectively; p=0.002; Chetrit et al 2008) This finding is consistent with literature evidence (Kauff 2008; Rubin et al 1996; Ben-David et al 2002).

1.1.2 Breast Cancer

Breast cancer is the most common malignancy and the second most common cause of cancer-related death in Western European and North American women. In the year 2006, there were over 214,000 cases of breast cancer in the U.S., 22,000 cases in Canada and 430,000 new cases in Europe and over 41,000, 5300 and 85,000 deaths, respectively, from breast cancer (Canadian Cancer Society; Jemal et al 2007). Recurrent or metastatic breast cancer is an incurable malignancy with a median survival of 20-24 months (Hortobagyi 1998) which has not changed significantly over the last decade with fewer than 20% of patients still alive at 5 years after a diagnosis of recurrence. The goals of treatment for recurrent breast cancer are to improve survival, prolong progression-free survival and promote good quality of life. Although initial treatments did not achieve these goals, in the last decade, a number of studies have shown an overall survival benefit. Population based studies have suggested that with the introduction of new contemporary agents, women are living longer after a diagnosis of advanced cancer (Chia et al 2007).

Recent microarray studies have confirmed that a number of subtypes of breast cancer exist including those with hormonal sensitivity (luminal A, B, etc) and those with HER2 over-expression. The identification of a group with no expression of hormone receptors nor HER2 has been increasingly discussed as their outcome is particularly poor despite a generally good response to chemotherapy initially (Carey et al 2007, Dent et al 2007). Within this group are those with a basal-like phenotype and those with inherited *BRCA* mutations. The basal group is estimated to be approximately 11-19% of invasive breast cancer cases and has been called "basal-like" because its gene expression profile is similar to the basal epithelial cells of the normal mammary gland with CK5/6 and CK17 expression (van de Rijn et al 2002). This group has also been reported in one study to have *BRCA1* mRNA expression that is lower than other non-basal like controls (Turner et al 2004). Over 75% of patients with *BRCA1* mutations have a similar breast cancer that also has a high rate of p53 mutations (Sorlie et al 2001), and amplification of c-myc and EGFR.

Candidates for such treatment are agents that target DNA repair mechanisms. In vitro testing of *BRCA1*-associated breast cancers suggests increased sensitivity to platinum drugs and these drugs have been tested in mutation carriers with some promising response rates in the neoadjuvant setting. Indeed larger randomised studies with platinum agents are ongoing.

1.1.3 Prostate cancer

Prostate cancer is the most common non-cutaneous cancer in men. An estimated 782,600 new cases and 254,000 deaths caused by the disease occurred in 2007. The mortality rates have been decreasing in many developed countries (eg, the United States, the United Kingdom, and Canada), which has been attributed to improved treatment and early detection. In contrast, the mortality has been increasing in some Asian countries (eg, Japan, Singapore). The list of likely causes includes increased consumption of animal fat, obesity, and physical inactivity (Crawford 2009).

Nearly 90% of all patients with metastatic prostate cancer initially respond to chemical or surgical castration. Unfortunately, the response only lasts for a median duration of 18 to 24 months. Until recently, few treatment options were available to men with hormone-refractory prostate cancer (HRPC), and no single agent or combination therapy had been proven to prolong survival in these patients once the disease became refractory to androgen ablation therapy (Petrylak 2005). However, recently, the results of the Southwest Oncology Group (SWOG) 99-16 and TAX 327 studies, demonstrating a survival benefit in men with HRPC-treated with docetaxel-based therapy, have changed the expectations of treatment outcome in these patients from solely palliative to improved survival (Petrylak 2005; Tannock et al 2004).

Although breast and ovarian cancer are the most common cancers occurring in women with *BRCA1* and *BRCA2* mutations, recent studies have suggested an increased incidence of prostate cancer in men with these mutations. A large linkage study based on 11,847 individuals from families with *BRCA1* mutations demonstrated an increased risk of prostate cancer in individuals under the age of 65 (RR = 1.82, 95% CI = 1.01 to 3.29, P = .05), but not those over the age of 65 (Thompson and Easton 2002). A similar study of 3,728 individuals from families with *BRCA2* mutations also demonstrated an increased risk, with a RR for prostate cancer for men below the age of 65 years of 7.33 (95% CI = 4.66–11.52) (The Breast Cancer Linkage Consortium 1999).

1.1.4 Pancreatic cancer

Pancreatic cancer is an aggressive malignant disease whose incidence has risen in the last two decades, with approximately 37,000 estimated new cases in USA in 2007 in both sexes, and is currently the fourth cause of death from cancer in the western world (Pierantoni et al 2008). There has been little improvement in prognosis over the past 20 years, with a survival of 4–6 months for metastatic disease and an overall 5-year survival <4%. Radical surgery increases median overall survival (OS) to 13–15 months with a 5-year survival rate of approximately 10% (Longo et al 2008). Unfortunately, systemic chemotherapy still relies on few drugs and has produced unsatisfactory results. Gemcitabine, the most active single cytotoxic drug in advanced disease, induces clinical benefit and symptom improvement in 20-30% of patients and a 1-year survival rate of 18% (Verslype et al 2007).

The studies discussed in the previous section also showed an increase with the large linkage study on *BRCA1* showing an increased risk of pancreatic cancer (RR = 2.26, 95% CI = 1.26 to 4.06, P = .004) and the large linkage study on *BRCA2* also showing an increased risk (RR = 3.51; 95% CI = 1.87–6.58) (Thompson and Easton 2002;The Breast Cancer Linkage Consortium 1999).

1.1.5 Identification of patients with genetic *BRCA* mutations

Patients with genetic *BRCA1* and *BRCA2* mutations may be routinely identified in the clinic through specific referral, counselling and molecular testing networks. However, there are major differences in the organization of *BRCA* genetic testing, the uses of genetic tests and the follow-up with patients across countries (Lowy and Gaudilliere 2008). Myriad Genetics own the intellectual property for *BRCA* analysis, and in the US they dominate the *BRCA* testing

market (Parthasarathy 2005). However, in most non-US territories, *BRCA* testing is performed by multiple laboratories in accordance with local clinical practice. For example, at present, ovarian cancer patients may not be routinely screened for *BRCA1* and *BRCA2* mutations, as currently the therapy for patients with *BRCA* mutations is identical to that of sporadic ovarian cancer. Therefore, the primary purpose of identifying heritable mutations in patients is to facilitate risk management in unaffected family members and potentially to recommend prophylactic surgical procedures.

The likelihood of an ovarian cancer patient carrying a *BRCA1* and/or *BRCA2* mutation is dependent on a number of factors including age-of-onset of disease, family history and ethnicity. During initial consultations the patient's risk of carrying a mutation is assessed and patients with characteristics consistent with *BRCA1* and/or *BRCA2* mutations will undergo confirmation of their *BRCA* status by molecular testing to identify loss-of-function mutations. Due to the cost, complexity and time required to complete molecular testing, it is not routinely performed in patients without predefined risk.

Identification of patients at risk, through family history/age-of-onset, is performed using a scoring system, such as the Manchester Scoring System (Evans et al 2005) which estimates the probability of a patient having a mutation in *BRCA1* and *BRCA2*. The score is then used to aid the decision as to which patients will undergo molecular testing to confirm *BRCA1* and *BRCA2* mutations.

In Jewish high-risk individuals of Ashkenazi (East European) descent, three mutations - 185delAG and 5382insC (BRCA1) and 6174delT (BRCA2) – account for a substantial proportion of germline mutations and represent a founder mutation within the Jewish people (Abeliovich et al 1997, Szabo and King 1997). In all Ashkenazi breast cancer patients in Israel, for example, 10.4% are BRCA1/2 carriers.

In the UK, National Institute for Clinical Excellence (NICE) clinical guideline 41 recommends that women from families with a 20% or greater chance of carrying a mutation should have access to molecular testing (NICE 2006) whereas in other EU regions (France and Germany) a threshold of 10% is routinely used.

Loss-of-function mutations result from either small-localised changes in the DNA sequence or as a result of larger-scale genomic rearrangements and can occur throughout *BRCA1* and *BRCA2*. The majority of loss-of-function mutations in *BRCA1* and *BRCA2* in ovarian cancer are the result of small localised changes in the DNA sequence, with large-scale genomic rearrangements accounting for ~13% of mutations (Evans et al 2008).

Due to the diversity of mutations present, genetic testing for *BRCA* mutations usually employs a phased process using a suite of testing methodologies. In cases where there is prior knowledge of a specific mutation in a family or the patient is from a population with founder mutations, where one or a few mutations are relatively common (such as Ashkenazi Jews), targeted testing that focuses on a small region of the *BRCA1* and/or *BRCA2* genes is normally undertaken first. If these tests prove negative, and for all patients where there is no a *priori* rationale for targeted mutation analysis, the entire sequence of the *BRCA1* and *BRCA2* genes

is screened for small alterations. As indicated above, larger rearrangements do occur and these normally cannot be detected by DNA sequencing or related screening tests. Hence, when no small alterations are identified, a final step is to employ techniques that can detect large-scale alterations, such as the deletion of one or more exons. It is clear, therefore, that since a large number of mutations in *BRCA1* and *BRCA2* have already been detected and these vary in position along the length of the genes and extent to which they alter the nucleotide sequence, no single test or methodology can detect all of the mutations that might be present (Hogervorst et al 2003). It is therefore common to run two methodologies to screen the entire *BRCA1* and *BRCA2* genes to confirm the presence of loss-of-function mutations.

1.1.6 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 and Szabo 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 leading 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 PARP 1, 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, when used in combination with radiation and DNA-damaging cytotoxic agents, an enhancement of the anti-tumour activity of the latter agents occurs (Virag and Szabo 2002; Nguewa et al 2005).

1.1.7 Homologous recombination deficiency and PARP

Olaparib is a targeted anticancer agent that exploits a cancer cell's inability to repair DNA.

Olaparib (AZD2281, KU-0059436) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination (HR) 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 IB.

The inhibition of PARP leads to persistence of DNA lesions normally repaired by the homologous recombination (HR) pathway (Farmer et al 2005). Although PARP is not required for HR itself, it regulates the process through its involvement in the repair of DNA single-strand breaks (SSBs). When only one of the two strands of a double helix has a defect, the other strand can be used as a template to guide the correction of the damaged strand. Inactivation of PARP results in the persistence of SSBs in DNA that, after DNA replication, will result in the generation of double strand breaks (DSBs). DSBs, in which both strands in the double helix are severed, are particularly hazardous to the cell because they can lead to chromosomal instability, cell cycle arrest and cell death.

BRCA1 and *BRCA2* are important proteins in the HR pathway that is responsible for the repair of DNA DSB. A number of proteins involved in the HR pathway, including *BRCA1* and *BRCA2*, have a strong disease linkage to a number of cancers when they are deficient. Individuals who inherit mutations in *BRCA1* and *BRCA2* are heterozygous and develop normally in the presence of a single mutant allele (Narod and Foulkes 2004). However, these individuals have a significant lifetime risk of developing breast and ovarian cancer as a consequence of having only one functional BRCA1 and/or BRCA2 gene. Subsequent loss of the functional inherited allele leads to BRCA-deficiency and tumourgenesis. Loss of *BRCA* in patients with inherited mutations is the best-known example of homologous recombination deficiency (HRD). Tumours with DNA repair defects, such as those arising from mutations in *BRCA*, are more sensitive to PARP inhibition(Pierantoni et al 2008). PARP inhibition is

effective in killing *BRCA*-deficient cells, but does not affect their heterozygous counterparts indicating that normal tissues in *BRCA* carriers are unlikely to be at risk of excess toxicity (Farmer et al 2005).

1.1.8 Pre-clinical experience

The pre-clinical experience is fully described in the current version of the olaparib IB.

1.1.9 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised 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.

Further information can be found in the current version of the olaparib IB.

1.1.10 Clinical experience

The clinical experience with olaparib is fully described in the current version of the olaparib IB.

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

At present, the number of patients exposed to olaparib is small. These events will continue to be monitored to assess frequency and severity as patient exposure increases.

These events suggest an emerging safety profile for olaparib that supports further studies in cancer patients.

1.2 Rationale for conducting this study

Olaparib is a poly-ADP-ribose polymerase (PARP) inhibitor. PARP enzymes are involved in the recognition and detection of single strand DNA breaks which if left unrepaired, are converted to double-strand breaks. If the optimal double-strand break (DSB) repair pathway known as homologous recombination (HR) is deficient in the cell, then the DSBs are not repaired or are repaired incorrectly using the error prone non-homologous end-joining pathway which ultimately leads to cell death.

BRCA1 and BRCA2 are proteins involved in the HR pathway, and pre-clinical studies have shown cell lines deficient in these to be hypersensitive to olaparib both in vitro and in vivo. Within certain cancers eg, ovarian, breast, prostate, pancreatic etc, there are sub-populations of patients with a mutation in the *BRCA1* and/or *2* gene and therefore these patient sub-populations may benefit from PARP inhibitor treatment.

A phase I study (D0810C00002) in patients with advanced tumours (enriched with patients with *BRCA1* and *BRCA2* mutations) and two phase II proof of concept studies (D0810C00008 and D0810C00009) in patients with *BRCA*-associated breast and ovarian cancer respectively demonstrated significant activity when dosed continuously with olaparib at doses ranging from 100 mg bd to 400 mg bd. Complete and partial responses have been seen at doses of 100 mg, 200 mg bd and 400 mg bd with numerically higher response rates at the higher dose levels. For example in studies D0810C00008 and D0810C00009, in the intention to treat (ITT) set, the confirmed RECIST ORR overall was 11/27 (40.7%) and11/33 (33.3%) respectively at 400 mg bd and 6/27 (22.2%) and 3/24 (12.5%) at 100 mg bd**.**

Therefore the rationale for the study is to provide additional data to support that initially reported. And to test the hypothesis that tumours in BRCA1/2 mutation carriers are responsive to PARP inhibition treatment, regardless of the tumour type involved.

1.3 Benefit/risk and ethical assessment

Olaparib as monotherapy has demonstrated significant anti-tumour activity in breast and ovarian cancer patients with identified genetic *BRCA* mutations. In patients with ovarian cancer, responses have been seen in all patient groups including platinum-resistant and refractory disease. In addition, olaparib as monotherapy was generally well tolerated, with mainly mild to moderate (CTCAE Grade ≤2) toxicities at doses up to and including 400 mg bd for prolonged periods of time. Based on the available data on efficacy and safety, AstraZeneca believes that olaparib will be of significant benefit for the treatment of cancer patients with other tumours where genetic *BRCA* mutations can occur eg, pancreatic, prostate, gastrointestinal. The risk-benefit assessment therefore strongly favours the proposed study.

In view of the potential for olaparib to have anti-tumour activity in cancer patients with genetic *BRCA* mutations in tumour types other than ovarian and breast, the current study is designed to allow for patients to continue on olaparib therapy for as long as they are receiving

clinical benefit in the opinion of the Investigator. However, patients may stop treatment at any time if they choose to do so or if the investigator believes it is in the best interest of the patient. Additionally, in the event of unmanageable toxicity, directions for reducing or stopping olaparib are provided.

2. STUDY OBJECTIVES

2.1 Primary objective

To assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation by assessment of tumour response.

2.2 Secondary objectives

To assess the efficacy of oral olaparib in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR).

2.3 Safety objective

To determine the safety and tolerability of oral olaparib in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation.

2.4 Exploratory objectives (Not Applicable)

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 is a phase II, open-label, non-randomised, non-comparative, multicentre study to assess the efficacy and safety of olaparib given orally twice daily in patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation.

The dose of olaparib to be used is 400 mg bd.

Up to approximately 150 patients with a BRCA mutation are to be recruited. Tumour types expected, but not limited to, include ovarian, breast, prostate and pancreatic. It is intended that a minimum of 20 patients in each of the prostate and pancreatic tumour types will be recruited. The recruitment of patients of all other tumour types will be capped at a maximum of 110 patients.

The analysis of all primary and secondary objectives will occur 6 months after the last patient has commenced study treatment (data cut-off). The analyses will be based on the assessment of response based on RECIST 1.1. Following this analysis (at data cut-off) the study will be closed. However, patients may continue to receive olaparib for as long as they are receiving clinical benefit in the opinion of the investigator (until progression or other olaparib discontinuation criteria are met). During this time, serious adverse events (SAEs) must still be collected and reported until 30 days after the patient finally stops taking olaparib.

After starting study treatment, patients will attend periodic clinic visits for assessment of safety and efficacy until confirmed objective disease progression according to RECIST. Following confirmed disease progression patients will discontinue olaparib treatment, but may may receive any cancer treatment at the investigator's discrection. All patients will continue to be contacted to assess survival status until death or the data cut-off for the primary analysis, whichever is the sooner. The analysis of all primary and secondary objectives will occur 6 months after the last patient has commenced study treatment (data cut-off).

Given the design of the study, there will not be an independent data monitoring committee.

Table 1 Study Schedule – Visit 1 – Screening

(See section 6.2.1 for further details)

Day	**-28 to -1**	**-7 to -1**
Informed consent	X	
Demographics	X	
Medical and surgical history	X	
Current signs and symptoms	X	X
Inclusion/exclusion criteria	X	
Physical examination	X	
Vital signs, body weight (Includes BP [supine position], pulse and temperature)	X	
ECOG performance status	X	
ECG		X
Haematology /clinical chemistry/urinalysis	X	
Pregnancy test[a]		X
Blood sample for disease-specific marker[b]		X
Tumour Assessment (CT or MRI according to RECIST 1.1)[c]	X	
Adverse Events (from time of consent)	X	X
Concomitant medications	X	X
Confirmation of pre-existing documented *BRCA* mutation status	X	

[a] Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7 days prior to starting treatment and a confirmatory test before treatment at visit 1. 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 Known tumour markers should be measured eg, CA-125 for ovarian cancer, CA15-3 for breast cancer, CEA for colorectal cancer.

c RECIST 1.1 assessments will be performed using CT or MRI scans of the appropriate anatomical area applicable to the tumour under investigation. 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.

Table 2 Study schedule – on treatment and follow up

(See section 6.2 for Further details)

Visit number	2[a]	3	4	5[a]	6[a]	7[a]	[a]Visit 8, 10, 12 etc onwards *(Note that all visits after visit 7 are monthly but assessments vary depending on visit number)*	Visit 9, 11, 13 etc onwards	Treatment Discontinu-ation	Follow-up 30 days after last dose of study medication	Survival Every 8 weeks following treatment discontinu-ation
Day	**1**	**8**	**15**	**29**	**57**	**85**	**(ie, days 113, 169, 225 etc)**	**(ie, days 141, 197, 253 etc)**			
Visit Window		±1d	±1d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d
Physical exam	X[b]			X	X	X	X	X	X		
Vital signs, body weight (Includes BP [supine position], pulse and temperature	X[b]			X	X	X	X	X	X	X	
ECOG performance status	X[b]			X	X	X	X	X	X	X	
ECG & urinalysis[c]					X					X	
Haematology & clinical chemistry	X[b]	X	X	X	X	X	X	X	X	X	
Pregnancy test before treatment	X										
Blood sample for disease-specific marker	X			X	X	X	X	X	X		
Tumour Assessment (CT or MRI according to RECIST)[d]					X		X		X		
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Olaparib dispensed/returned	X			X	X	X	X	X	X		

Table 2 Study schedule – on treatment and follow up

(See section 6.2 for Further details)

Visit number	2[a]	3	4	5[a]	6[a]	7[a]	[a]Visit 8, 10, 12 etc onwards *(Note that all visits after visit 7 are monthly but assessments vary depending on visit number)*	Visit 9, 11, 13 etc onwards	Treatment Discontinu-ation	Follow-up 30 days after last dose of study medication	Survival Every 8 weeks following treatment discontinu-ation
Day	**1**	**8**	**15**	**29**	**57**	**85**	**(ie, days 113, 169, 225 etc)**	**(ie, days 141, 197, 253 etc)**			
Visit Window		±1d	±1d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±7d
Survival and post-withdrawal treatment											X[e]

[a] Visit to take place on Day 1 of a 4 week (28 day) visit period.

[b] 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.

[c] ECG and urinalysis performed at baseline. ECG the performed at 8 weeks (day 57), at final follow-up and then if clinically indicated at any other time, see Section 6.4.7. ECG should be performed once the patient has been in the supine position for at least 5 minutes in each case. After baseline, urinalysis only required if clinically indicated.

[d] RECIST 1.1 assessments will be performed using CT or MRI scans of the appropriate anatomical area applicable to the tumour under investigation. After the initial baseline assessments, follow-up assessments will be performed every 8 weeks after start of treatment until 6 months has elapsed or objective disease progression as defined by RECIST 1.1. If the patient is still ongoing after 6 months, the scan frequency can be changed to up to a 12-week interval. Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

e Following confirmed disease progression patients will continue to be contacted to assess survival status until death or data cut-off for analysis, whichever is the sooner. Data on treatment post-withdrawal should also be collected if possible.

3.2 Rationale for study design, doses and control groups

Olaparib has demonstrated significant anti-tumour activity and an acceptable safety profile in both genetic *BRCA1* and *BRCA 2*-mutated breast cancer patients and ovarian cancer patients who have received previous platinum therapy (Tutt et al 2009; Abeliovich et al 1997;Audeh et al 2009). Hence these populations will likely form the majority of the subjects of this study. This non-comparative study is designed to provide additional supporting information to the two initial proof-of-concept studies in the breast and ovarian disease area and to explore the extension of olaparib monotherapy into other tumour types, such as pancreatic and prostate cancer, where some patients may have genetic *BRCA* mutations. Tumour response according to RECIST 1.1 criteria has been selected as the primary efficacy outcome variable, since tumour regression is the most robust measure of a drug effect in single-arm studies.

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 must 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 $\geq$ 18 years of age.

3. Confirmed documented BRCA mutation. (The presence of a loss-of-function germline mutation in the *BRCA1* and/or *BRCA2* gene must be confirmed prior to consent according to local practice).

4. Histologically or, where appropriate, cytologically confirmed malignant solid tumour refractory to standard therapy and for which no suitable effective standard therapy exists.

5. For the breast cancer setting, patients must have failed at least three previous lines of chemotherapy in the metastatic/advanced setting (not including hormonal treatment).

6. For the ovarian cancer setting patients must have:

- documented progressive or recurrent disease according to either RECIST or GCIG criteria either during or within 6 months of completion of their most recent platinum-based chemotherapy regimen OR greater than 6 months from completion of most recent platinum-based chemotherapy, but not suitable for further platinum therapy. Any patient in this latter category must be discussed with the Sponsor prior to consent.

AND

- received prior treatment with liposomal doxorubicin or anthracyclines, giving a lifetime cumulative dose in excess of 360 mg/m^2 for non-liposomal doxorubcin or 540 mg/m^2 for epirubicin.

Note that in the ovarian cancer setting, eligibility also includes patients who have developed recurrent ovarian cancer with macroscopic peritoneal metastases outside the pelvis or distant metastases. In addition, patients with primary peritoneal carcinoma or Fallopian tube carcinoma may be considered for the study.

7. For the pancreatic cancer setting, patients must have either failed or be unsuitable for gemcitabine treatment in the advanced setting.

8. For the prostate cancer setting, patients must have:

- hormone-refractory disease, defined as a testosterone value in the castration range
- at least 2 consecutive rising PSA values above their nadir and measured at least two weeks apart
- at least 6 weeks from discontinuation of anti-androgen therapy.

9. 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) > 3 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN).
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case it must be ≤ 5x ULN

- Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

10. ECOG performance status ≤ 2 (see Appendix E)

11. Patients must have a life expectancy ≥ 12 weeks

12. 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:

    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinising hormone and follicle-stimulating hormone 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).

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

14. At least one lesion (measurable and/or non-measurable) at baseline that can be accurately assessed by CT/MRI and is suitable for repeated assessment at follow-up visits.

4.2 Exclusion criteria

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

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

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

3. Patient with any other malignancy which has been active or treated within the previous 5 years, with the exception of adequately treated cone-biopsied in situ carcinoma of the cervix uteri, endometrial carcinoma stage 1A or 1, or non-melanoma skin lesions.

- Patients with a history of ovarian or breast cancer within the past 5 years are eligible in the case of adequately treated stage I or II disease without evidence of recurrence.

4. Patients receiving any systemic 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. Prostate cancer patients may also continue to receive LHRH.

5. 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

6. Persistent toxicities (>CTCAE grade 2), excluding alopecia, caused by previous cancer therapy.

7. 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.

8. Patients with spinal cord compression, unless they have received definitive treatment for this and have evidence of clinically stable disease for at least 28 days prior to study entry

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

10. 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.

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

12. Breast-feeding women.

13. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus.

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

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

16. Patients with uncontrolled seizures.

For 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 (e.g. hormone implants)
- Placement of an intra-uterine device (see Appendix D as consideration should be given to the type of device/system used)

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

Other Concomitant treatment

1. No other chemotherapy, hormonal therapy (hormone replacement therapy is acceptable) or other novel agent is to be permitted during the course of the study for any patient (the patient can receive a stable dose of corticosteroids during the study as long as these were started at least 4 weeks prior to treatment, as per exclusion criteria above). Palliative radiotherapy is allowed for pre-existing small areas of painful metastases that cannot be managed with local or systemic analgesics as long as no evidence of disease progression is present (see section 5.6.3).

2. Patients with hormone-refractory prostate cancer may continue to take LHRH agonist treatment during the study if, in the investigator's opinion, this is appropriate.

3. 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.

4. Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 enzyme activity and drugs that are known to be CYP3A4 substrates (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.

5.2 Patient enrolment 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. Assign potential patient a unique enrolment number, beginning with "E#".

3. Determine patient eligibility. See Sections 4.1 and 4.2

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 Case Report Forms (CRFs).

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

5.2.1 Procedures for randomisation (Not Applicable)

5.3 Procedures for handling patients incorrectly enrolled

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

Where patients that do not meet the selection criteria are enrolled 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

5.4.1 Methods for ensuring blinding (Not Applicable)

5.4.2 Methods for unblinding the study (Not Applicable)

5.5 Treatments

5.5.1 Identity of investigational product

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

Investigational product[a]	Dosage form and strength	Manufacturer
olaparib	50 mg capsule	Patheon on behalf of AstraZeneca

[a] Descriptive information for olaparib can be found in the IB.

5.5.2 Doses and treatment regimens

For all centres, olaparib will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. At each dosing visit the patient will be dispensed sufficient capsules for at least each cycle period plus overage. Olaparib will be dispensed to patients on Day 1 and every 28 days thereafter until the patient completes the study, withdraws from the study or closure of the study.

Patients will take olaparib orally twice daily at 400 mg bd continually. Eight 50 mg capsules should be taken at the same times each day, approximately 12 hours apart, morning and evening, with a glass of water.

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.

Patients will continue with olaparib until objective disease progression (determined by RECIST 1.1) as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

5.5.3 Additional study drug (Not Applicable)

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 labels will include blank lines for quantity of capsules to be taken, patient enrolment code (E-code) and date of dispensing.

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.

Olaparib must not be stored under refrigerated conditions.

5.5.6 Management of toxicity of olaparib (monotherapy treatment)

Any toxicity observed during the course of the study 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 2 dose reductions already, (to a minimum dose of 100 mg bd), 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 3. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose

reduction made. If, on restarting 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.

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 3 Dose reductions for olaparib

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

[a] olaparib must not be decreased below 100 mg bd

Olaparib should be stopped before surgery and restarted following recovery. No stoppage of olaparib is required for any biopsy procedures.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic radiation treatment. This is not required where palliative doses are used.

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.

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 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 the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions:

- Fluvoxamine, fluconazole, fluoxetine, amiodarone, paroxetine, quinidine ketoconazole, itraconazole, ritonavir, idnavir, saquinavir, telithromycin, clarithromycin

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

- Fluoxetine - 5 weeks; paroxetine - 2 weeks; any of the others - 1 week wash-out period

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers are excluded:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, 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 during the course of the study, 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 during the study, 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-emetics/Anti-diarrhoeals: Prophylactic anti-emetics and/or anti-diarrhoeals will not routinely be given. Should a patient develop nausea, vomiting and/or 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.

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. Patients with hormone-refractory prostate cancer may continue with LHRH agonist treatment if, in the investigator's opinion, it is appropriate.

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 CRF.

5.7 Treatment compliance

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

Patients should be given clear instructions on how and when to take their study treatment. 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 staff will make capsule counts at regular intervals during treatment, ideally at the patient's monthly visits. 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 study 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(s) 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.

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), olaparib, 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 with the study protocol
- Any CTC grade 3 or 4 events that have not reverted to CTC grade 1 or less within 4 weeks (28-days). At the investigator's discretion, following dose interruption, patients may be considered for dose reductions providing they have not already undergone the maximum number of dose reductions allowed for guidelines see section 5.5.6. However, if upon re-challenging with olaparib at the lowest reduced dose, 100 mg bd (for guidelines refer to Section 5.5.6), any CTC grade 3 or 4 adverse events recur, the patient must be discontinued.
- Objective progression according to RECIST 1.1 criteria:

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). Adverse events will be followed up (see sections 6.4.3 and 6.4.4), study drug should be returned by the patient.

Any patient discontinuing investigational product should be seen at 30 days post-discontinuation for the evaluations outlined in the study schedule. The patient's tumour status should be assessed clinically and, if appropriate, disease progression should be confirmed by radiological assessment. After discontinuation of study medication, the principal investigator/ sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, they will record on the 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 occurring during the 30 calendar days

after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 6.4.4) and followed to resolution as above. Patients should be contacted 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 has not yet shown objective disease progression at withdrawal and not commenced subsequent anti-cancer therapy should continue to be followed as per RECIST 1.1 as detailed in section 6.2.3.4.

All patients must be followed for survival, unless they withdraw consent, up to the point at which the study is closed ie, 6-months after the last patient was first dosed.

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 6.4.4), 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 with the 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 electronic CRFs 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

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent (ie, any invasive screening tests).

A schedule for the tests and evaluations to be conducted in this study is contained in this Section 6.2 and **Table 2**.

6.2.1 Screening

The following assessments and procedures should be performed within 28 days prior to first dose of study treatment unless otherwise stated.

- 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)
- Confirmation of pre-existing *BRCA1/2* mutation status
- Medical and surgical history
- 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. ECG (within 7 days prior to starting study treatment),.
- Haematology, clinical chemistry and urinalysis
- Tumour assessment (scans of the appropriate anatomical area applicable to the tumour under investigation and other sites as clinically indicated for assessment of disease by CT/MRI).

- Disease-specific blood biomarker (eg, CA-125 for ovarian, CA-15.3 for breast cancer PSA for prostate cancer etc) to be done within 7 days prior to starting study treatment.

- Adverse events (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 continuously. The visit schedule is based on 28 days periods. Patients will attend the clinic on days 1 (1st day of treatment), 8, 15, 29, 57 and every 28 days thereafter and the following assessments will be performed at time points specified in the study schedule (see **Table 2**)

- Physical examination, including ECOG performance status and vital signs every visit

- ECG on Day 57 only (ie, +8 weeks from starting study treatment)

- Haematology, clinical chemistry and urinalysis

- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day of first treatment)

- AEs/SAEs and concomitant medications

- Disease-specific tumour marker where appropriate (CA-125, CA15.3, PSA, CEA etc)

- Tumour assessments (scans of the appropriate anatomical area applicable to the tumour under investigation and other sites as clinically indicated for assessment of disease by CT/MRI) every 8 weeks after day 1. Note that, after 6 months on study treatment, the scanning frequency can be increased to every 12 weeks.

Patients will continue with olaparib until radiological objective disease progression by RECIST 1.1 or as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8. Once patients on olaparib have been discontinued from treatment, other treatment options will be at the discretion of the investigator.

Patients will be evaluated until objective disease progression by RECIST or commencement of subsequent anti-cancer therapy, as per the study schedule (see **Table 2**), and then followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent. A repeat scan is needed at the next scheduled tumour assessment (at least ≥ 4 weeks) for confirmation of a PR and CR by RECIST 1.1.

The imaging modalities used for RECIST assessment will be CT or MRI scans of the relevant sites clinically indicated for assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged. Clinical examination (eg, photography of skin lesions) is acceptable for assessment of non-target lesion response.

6.2.2.1 Disease-specific tumour marker plasma samples

All patients will supply plasma samples for tumour- specific marker assessment (if appropriate) at the beginning of each monthly visit prior to the patient receiving olaparib.

6.2.2.2 *BRCA* status

A patient's *BRCA* status must be known before enrolment into the study. Details of a patient's *BRCA1/2* mutation status will be collected on the eCRF.

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 the study schedule (**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 olaparib. 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, 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 CRF.

6.2.3.3 Survival visit

Assessments for survival should be made every 8 weeks following objective disease progression. 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 after discontinuation of treatment will be collected. Survival data and subsequent therapy information will be collected up to the time of the primary analysis. In addition, patients should be contacted in the week following the data cut-off for the primary analysis to provide current survival data.

6.2.3.4 CT or MRI scans (RECIST 1.1)

Baseline and follow-up contrast-enhanced CT of the specific sites appropriate to the patient's tumour should be performed with other regions where clinically indicated for the adequate assessment of tumour burden. All baseline radiological tumour assessments must be performed no earlier than 28 days before the start of study treatment. Scans that were

performed as part of standard of care prior to signature of the informed consent form can be analysed for the purposes of the study if they were performed within the correct time frame and of sufficient quality. Subsequent tumour assessments according to RECIST should be performed at the end of every 8 weeks (+/-1 week) up to 6 months after starting treatment and then every 12 weeks thereafter according to the planned study schedule (see **Table 2**) up to objective progression by RECIST 1.1 (Therasse et al 2000). Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST disease progression.

Tumour evaluations using CT/MRI according to RECIST will continue in the study until the data cut-off for the analysis. At this point investigators will be notified that CT/MRI for study purposes are no longer required.

6.3 Efficacy

6.3.1 Efficacy variable

Table 4 Efficacy and Variables

Objective	Variable
To assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of tumour response	Tumour Response Rate
To assess the efficacy of oral olaparib in patients with advanced cancer who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation, by assessment of objective response rate (ORR), progression-free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR)	Objective response rate (ORR) Progression-free survival Overall survival Duration of response Disease control rate

6.3.2 Tumour Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining tumour response, progression-free survival (PFS) times, objective response rates (ORR), duration of response (DOR) and disease control rate (DCR) The RECIST 1.1 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 C.

The methods of assessment of tumour burden used at baseline -CT or MRI scans of neck, chest, abdomen, pelvis as appropriate to the tumour type under investigation - must be used at each subsequent follow-up assessment.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks ±1 week up to 6 months after starting study treatment and then every 12 weeks thereafter until objective disease progression as defined by RECIST 1.1.

If a patient discontinues treatment (and does not receive subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

For patients with measurable disease at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 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.

For patients with non-measurable disease only at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non-CR/Non-PD.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTL (non-target lesion) 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.

Following progression, patients should continue to be followed up for survival every 8 weeks as outlined in the study plan.

The analysis for this study will be based on the tumour assessments recorded on the CRF.

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

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any AEs/SAEs that are unresolved at the patient's last AE assessment (ie, 30 day follow-up visit) 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 (30days). 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 collect 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) and study procedures/other medications
- action taken with regard to investigational product
- 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 National Cancer Institute CTCAE version 3.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation is the CTCAE criteria that convert mild, moderate and severe events into CTCAE grades should be used.

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

For each episode, 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 an SAE.

Causality collection

The investigator will assess causal relationship between the study medication 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 olaparib?"

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 (CSR). 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 olaparib.

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 (eg, 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 (DUS) 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 (patients with advanced cancers who have a confirmed genetic *BRCA1* and/or *BRCA2* mutation), 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 DUS, 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, or to the study procedure(s). 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 an SAE to the appropriate AstraZeneca representative by telephone.

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

The reference document for definition of expectedness/listedness is the IB for olaparib.

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**)

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 thromboplastin time {APTT} and international normalised ratio {INR)]) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin.

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 by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

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**).

A 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 E) 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, at 8 weeks after starting study treatment and at the follow up visit after patient has discontinued study medication 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. ECGs are required within 7 days prior to starting study treatment, at end of cycle 1, at the final follow up visit and when clinically indicated. A copy of the ECG indicating the study number, without patient identifiers will be collected by the study monitor.

6.4.8 Vital signs

6.4.8.1 Pulse and blood pressure

Supine BP and pulse rate will be measured using 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 2**).

The date and time of collection and measurement will be recorded on the appropriate eCRF.

6.4.8.2 Body temperature (Not Applicable)

6.4.9 Other Safety Assessments

6.4.9.1 Serum or urine pregnancy test

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

6.5 Patient-reported outcomes (PRO) (Not Applicable)

6.6 Pharmacokinetics (Not Applicable)

6.7 Pharmacogenetics (Not Applicable)

6.8 Health economics (Not Applicable)

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 5 Volume of blood to be drawn from each patient[a]

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	6	8	48
	Haematology	10	8	80
Tumour marker		4	8	32
Total		20	24	160

a Figures based on patient remaining on study for 6 months. However the number of samples is only an estimate and will vary depending on the length of time a patient stays on the study. Samples will be analysed at the local hospital laboratories and the volumes may vary slightly dependant on method

7.2 Handling, storage and destruction of biological samples (Not Applicable)

7.3 Labelling and shipment of biohazard samples (Not Applicable)

7.4 Chain of custody of biological samples (Not Applicable)

7.5 Withdrawal of informed consent for donated biological samples (Not Applicable)

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.

8.3 Ethics and regulatory review

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

The investigator will ensure the distribution of these documents to the applicable ethics committee and to the study site staff.

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

The Ethics Committee should approve all advertising used to recruit patients for the study.

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

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

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

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

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal investigators with safety updates/reports according to local requirements.

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.

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

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 is 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.

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, the principal investigator and AstraZeneca.

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

The amendment should be approved by each Ethics Committee 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 patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA 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 and the WBDC system 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 in 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 in 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).

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 CSA for location of source data.

9.4 Study agreements

The Principal investigator at each centre should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, 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 CSA 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 CSA.

9.5 Study timetable and end of study

The end of this study is defined as the date when all patients receiving olaparib have been followed for a minimum period of 6 months since start of treatment or the date of the final analysis of the data, whichever is the later. 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 defined end of study, 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 defined as the end of the study, 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 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, or if results from any other study change the risk/benefit profile of olaparib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data management will be performed by AstraZeneca Data Management Centre staff. The data collected through third party sources will be obtained and reconciled against study data.

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

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

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

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

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

11.1 Calculation or derivation of efficacy variable(s)

Patients will undergo regular tumour assessments until documented objective disease progression as defined by RECIST 1.1 (see Appendix C).

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 patient 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 (i.e. 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 ≥ 5 mm) 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

Tumour Response

Patients who have a confirmed CR or PR prior to progression or commencement of subsequent anti-cancer therapies will be classified as responders for the primary endpoint, tumour response. Tumour Response is defined as the percentage of patients who are responders.

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging at least 4 weeks later with no evidence of progression between confirmation visits.

Patients with measurable disease at baseline will be considered to have a visit response if they meet the visit response criteria for CR or PR. Patients with non-measurable disease at baseline will only be considered to have a visit response if they meet the visit response criteria for CR.

A visit response of CR is defined when all target and non-target lesions present at baseline have disappeared (with the exception of lymph nodes which must be <10 mm 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 with baseline (with no evidence of progression) and the NTLs are at least stable with no evidence of new lesions.

11.1.2 Secondary Endpoints

Objective Response Rate (ORR)

A ‘measurable disease’ population will be derived for the analysis of ORR, DOR and DCR and will exclude patients who do not have measurable disease at entry.

ORR is defined as the percentage of patients who have a confirmed CR or PR prior to any evidence of progression (as defined by RECIST 1.1).

Progression free survival (PFS)

PFS is defined as the time from start of treatment until objective disease progression as defined by RECIST 1.1 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. Similarly, patients who start subsequent anti-cancer therapy prior to documented objective progression 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.

Overall survival

Overall survival is defined as the time from start of treatment until death by any cause.

Patients who have not died at the time of the statistical analysis will be censored at the time they were last known to be alive.

Duration of response (DoR)

Duration of response is defined as the date of first documentation of response (CR/PR) until the date of disease progression as defined by RECIST 1.1 or death (by any cause in the absence of disease progression).

Disease Control Rate (DCR)

Disease Control Rate is defined as the percentage of patients who have at least one visit response of CR or PR or who have demonstrated SD for a minimum interval of 16 weeks following start of treatment.

11.2 Calculation or derivation of safety variable(s)

All adverse events will be listed for each patient and summarised according to the system organ class (SOC) and preferred term assigned to the event using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs. The CTC grade will be assigned by the investigator.

At the point of the data cut-off for the statistical analysis, any patients still on treatment and gaining benefit can continue to receive study treatment. However, no further data will be entered on to the clinical database. However, the sites must continue to report any SAEs for pharmacovigilance purposes.

Changes from baseline (ie, latest available value pre-first dose of study treatment) will be calculated for laboratory and vital signs outcome variables. Laboratory values outside laboratory reference ranges will be identified.

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 CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

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

11.3 Calculation or derivation of patient reported outcome variables (Not Applicable)

11.4 Calculation or derivation of health economic variables (Not Applicable)

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

The following table summarises the analysis population definitions

Table 6 Definition of Analysis Populations

Analysis Set	Definition
Full Analysis Set (FAS)	This will include all enrolled patients who take at least one dose of olaparib. This is the primary analysis set for the efficacy outcome variables
Safety Analysis Set (EFS)	This will include all patients who received at least one dose of olaparib. This is the primary analysis set for the safety outcome variables

12.1.1 Efficacy analysis set

The efficacy analysis (Full Analysis Set) will follow the intention to treat (ITT) principle and will include all enrolled patients who take at least one dose of olaparib. The efficacy outcome variables will be summarised using the Full Analysis Set.

12.1.2 Safety analysis set

All patients who received at least one dose of olaparib will be included in the safety analysis set. All safety outcome variables will be summarised using the safety analysis set.

12.2 Methods of statistical analyses

All efficacy analyses will be based on the investigator's assessment of RECIST data..

12.2.1 Primary outcome variable

Tumour response is defined in Section 11.1.1.

The tumour response rate will be summarised and 95% CI for the response rate will be calculated using a binomial distribution. The denominator for the tumour response rate summaries will be the FAS. The tumour response rate will also be summarised for each of the defined tumour types separately (breast, ovarian, prostate and pancreatic tumour types and any other tumour types where sufficient numbers are recruited).

The unconfirmed tumour response rate will also be summarised in the same way.

12.2.2 Secondary outcome variables

Secondary outcome variables are defined in Section 11.1.2

12.2.2.1 Objective Response Rate (ORR)

The confirmed ORR will be summarised for patients who have measurable disease at baseline.

The ORR will be summarised and will be further split according to the categories CR, PR, SD, PD and NE. Ninety-five percent CIs will be calculated for the ORR using a binomial distribution. The denominator for the ORR summaries will be the number of patients included in the 'measurable disease' population.

12.2.2.2 Progression-free survival (PFS)

A Kaplan-Meier plot of PFS will be presented. The median time to progression, estimated from the Kaplan-Meier curve, will be presented along with the corresponding 95% CIs. Progression rates at predefined timepoints may also be presented.

12.2.2.3 Overall survival (OS)

The same summaries detailed in Section 12.2.2 for PFS will be presented for OS.

12.2.2.4 Duration of response (DOR)

The DOR in responding patients will be summarised and a Kaplan-Meier curve will be presented. The denominator for the DOR summaries will be the number of patients included in the 'measurable disease' population.

12.2.2.5 Disease Control Rate (DCR)

The DCR will be summarised in patients included in the 'measurable disease' population.

12.2.2.6 Safety

Assessment of safety will be based on the SAS population. For listings and summaries of changes from baseline, the latest available value pre-first dose of study treatment will be used.

All adverse events will be listed for each patient and summarised according to the system organ class (SOC) and preferred term assigned to the event using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs. The CTCAE grade will be assigned by the investigator.

Any AEs occurring after the first dose of study treatment and within 30 days of the last dose of study treatment will be included in the AE summaries. AEs occurring before the first dose of study treatment or more than 30 days after the last dose of study treatment will not be included in AE summaries but will be included and identified in the patient listings.

Clinical chemistry, haematology and vital signs (pulse rate and blood pressure) data will be listed for each patient and summarised with descriptive statistics (mean, standard deviation, median, minimum, maximum, number of patients) by scheduled visit. Both absolute values and changes from baseline will be presented. ECG results (normal and abnormal) will be summarised by visit using frequency counts and percentage of patients for each treatment group.

12.2.3 Interim analyses (Not Applicable)

No interim analyses are planned for this study.

12.3 Determination of sample size

No formal sample size calculation has been performed since the study is considered exploratory in nature. Up to 150 patients will be recruited to the study. It is intended that there will be at least 20 patients in each of the breast, ovarian, prostate and pancreatic tumour type groups in order to provide descriptive information on the effect of olaparib treatment on tumour response in a variety of tumour types.

12.4 Data monitoring committee

As the study is open, non-randomised and non-comparative, it does not require an IDMC, as it would not add anything to the on-going safety evaluation.

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 Study Delivery Team Physician at the AstraZeneca Research and Development site.

Name	Role in the study	Address and telephone number
[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, 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 CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

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

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

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

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Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Developme
site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation

This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

[redacted]

ASTRAZENECA SIGNATURE(S)

A Phase II, Open-Label, Non-Randomised, Non-Comparative, Multicentre Study to Assess the Efficacy And Safety of Olaparib Given Orally Twice Daily in Patients With Advanced Cancers Who Have A Confirmed Genetic *BRCA1* And/Or *BRCA2* Mutation

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This Clinical Study Protocol has been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

[redacted]

Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00042

[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, KU-0059436)
Study Code	D0810C00042

[redacted]

Appendix C
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 the D0810C00042 study 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

Patients with at least one lesion (measurable and/or non-measurable) that can be accurately assessed by CT/MRI at baseline and follow up visits should be included in this study.

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 <15 mm 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 <10 mm 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 the D0810C00042 study it is recommended that CT examinations of the neck, chest, abdomen, pelvis 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 the D0810C00042 study, 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 the D0810C00042 study, chest x-ray assessment will not be used for assessment of TL as they will be assessed by CT examination or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

3.3.2 Plain X-ray

In the D0810C00042 study 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 the D0810C00042 study, ultrasound examination will not be used for assessment of TL and NTL as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

3.5 Endoscopy and laparoscopy

In the D0810C00042 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 D0810C00042 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

In this study appropriate tumour markers, including but not limited to, CA-125, CA15.3, PSA, are 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 D0810C00042 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 D0810C00042 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 D0810C00042 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. Follow-up assessments will be performed every 8 weeks +/- 1 week after the start of treatment up to 6 months and then every 12 weeks thereafter until objective disease progression as defined by RECIST 1.1. 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 5 mm 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 eg, 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 5 mm.
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.
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: ie, 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 (only relevant if there were no TL/NTLs at baseline).

5. CONFIRMATION OF RESPONSE

In the D0810C00042 study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST assessment ie, 8 weeks (certainly no less than 4 weeks) following the date the criteria for response were first met.

6. CENTRAL REVIEW – NOT APPLICABLE

Not applicable.

7. 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.

7.1 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.

7.2 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.

7.3 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 minutes 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 minutes 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.

7.3.1 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.

8. REFERENCES

Eisenhauer 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247

Clinical Study Protocol Appendix D

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00042
[redacted]	

Appendix D
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 (eg, EE and etonogestrel)
- Cerazette (desogestrel) + male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.

Clinical Study Protocol Appendix E

Drug Substance	Olaparib (AZD2281, KU-0059436)
Study Code	D0810C00042

[redacted]

Appendix E
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.