AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Olaparib (AZD2281)
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A randomized, double-blinded, placebo controlled, multicentre phase III study to assess the efficacy and safety of olaparib (AZD2281) in combination with paclitaxel, compared to placebo in combination with paclitaxel, in Asian patients with advanced gastric cancer (including the gastro-oesophageal junction) who have progressed following first line therapy

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

[redacted]

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

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1	[redacted]		
2			

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

PROTOCOL SYNOPSIS

A randomized, double-blinded, placebo controlled, multicentre phase III study to assess the efficacy and safety of olaparib (AZD2281) in combination with paclitaxel, compared to placebo in combination with paclitaxel, in Asian patients with advanced gastric cancer (including the gastro-oesophageal junction) who have progressed following first line therapy

International Co-ordinating Investigator

Professor Yung-Jue Bang, MD, PhD; Seoul National University, College of Medicine and Cancer Research Institute. 28, Yeongeon-dong, Jongno-gu. Seoul, 110-744, Republic of Korea

Study centre(s) and number of patients planned

Approximately 50 centres in Asia, including China, Japan, Korea and Taiwan will be initiated for this study. Approximately 550 patients will be enrolled in this study to achieve 500 patients randomized.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2013	PIII
Estimated date of last patient completed	Q4 2017	PIII

Objectives

Primary:

- To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by overall survival (OS) in all patients, and the subgroup of patients whose tumours test negative for ATM by immunohistochemistry (IHC), with advanced gastric cancer (including the gastro-oesophageal junction [GEJ]) who have progressed following first-line therapy

Secondary:

- To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by progression-free

survival (PFS), and objective response rate (ORR) including the time to response and the duration of the response, in all patients and the subgroup of patients whose tumours test negative for ATM with advanced gastric cancer (including GEJ) who have progressed following first-line therapy

- To investigate plasma exposure to olaparib in a subgroup of olaparib dosed patients in the presence of paclitaxel and assess the impact of previous gastric surgery on that exposure.

To assess the effects of olaparib when given in combination with paclitaxel compared to paclitaxel in combination with placebo on the time to deterioration of health related quality of life (HRQoL) as assessed by the EORTC QLQ-C30 global HRQoL scale in all patients and the subgroup of patients whose tumours test negative for ATM

Safety

- To investigate the safety and tolerability of olaparib when given in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy

Exploratory:

- To explore potential biomarkers (such as but not limited to mutational status) in archival tumour, and in optional plasma/serum samples, which may influence the development of cancer and/or response to study treatment

- To collect and store Deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (i.e. distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer

- To explore changes in health utility status in all patients and the subgroup of patients whose tumours test negative for ATM receiving olaparib plus paclitaxel or placebo in combination with paclitaxel

- To explore the impact of treatment and disease state on symptoms and HRQoL as measured by the EORTC QLQ-C30 + STO22 disease related multi-item symptom scales and multi-item functional scales in all patients and in the subgroup of patients whose tumours test negative for ATM

- To investigate the impact of olaparib plus paclitaxel and placebo in combination with paclitaxel on gastric cancer management resource use

- To explore the efficacy of olaparib by assessment of OS adjusting for the impact of spontaneous switching [outside of study design] to Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or other potentially active investigational agents

- To investigate further the impact of a complete absence of measured ATM protein in archival tumour on efficacy of study treatment

Study design

This study is a phase III, randomized, double-blinded, multi-centre study of olaparib in combination with paclitaxel, compared with placebo in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy (i.e. 2nd line gastric cancer patients).

Approximately 500 patients will be randomized onto this study from Asia, including China, Japan, Korea and Taiwan. Patients will be randomized 1:1 onto one of two arms:

- Olaparib 100mg tablets p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle

- Placebo p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle

This study has 2 primary populations: all patients (overall population) and all patients in the subgroup of patients whose tumours test negative for ATM. Data generated from resection samples, outside of the trial, have been used to define a threshold for ATM Status. Full details of the testing procedure will be prospectively defined in a standard operating procedure prior to analysis of the mandatory tumour samples. In case it is needed to prospectively enrol the patients whose tumours test negative for ATM by IHC, patients must be ATM negative based on the central test result using an ATM IHC assay. If required, recruitment into the ATM negative subgroup will be extended to ensure that a sufficient number of deaths are observed for a meaningful analysis. If there are less ATM negative patients than required then the ATM negative subgroup will be enriched by up to approximately 30 further patients. Tumour evaluation using RECIST 1.1 will be conducted at screening (within 28 days prior to randomization) and every 8 weeks relative to the date of randomization, up to week 40, then every 16 weeks until objective disease progression (within a window of +/- 7 days of the scheduled date).

Study treatment will be continued until objective disease progression (unless other criteria for treatment discontinuation are met). Patients may continue olaparib/placebo beyond progression (according to RECIST 1.1), at the discretion of the investigator if they are clinically benefiting from the treatment and they do not meet any other discontinuation criteria; this should be agreed with the AstraZeneca study physician.

If a patient discontinues study treatment prior to disease progression, they should continue to be assessed using RECIST 1.1 until disease progression and then followed up for survival. Assessments for survival should be made every 8 weeks following objective disease progression. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

The imaging modalities used for RECIST 1.1 assessment will be CT or MRI scans of chest, abdomen and pelvis. RECIST 1.1 scans will be analysed by the investigator on site; a central review will not be conducted.

To determine plasma exposure to olaparib in a subgroup of olaparib dosed patients and assess the impact of previous gastric surgery on that exposure, at least 40 patients in each of the following sub-groups: a) patients who have had a previous full gastrectomy; b) patients who have had a partial gastrectomy; and c) patients who have not had gastric surgery will have PK samples collected after the first dose of the study. Samples from placebo patients will not be analyzed.

Provision of tumour sample (from either a resection or biopsy) is mandatory for eligibility into this study. For biopsy based samples, 3 to 5 (minimum of 3) biopsy samples must be provided.

Patients will also be requested to provide optional tumour samples from the primary or metastatic tumours at baseline and on progression. Sample provision is optional, subject to a specific consent, and will aid understanding of resistance mechanisms.

Optional blood samples for exploratory biomarkers and pharmacogenetic analyses will also be obtained from consenting patients and stored for exploratory purposes.

Target patient population

Patients with advanced gastric adenocarcinoma (including GEJ adenocarcinoma) that have progressed following first-line therapy.

Patients must have imaging confirmed progression on 1st line chemotherapy for gastric cancer treatment, which must have contained doublet 5-fluoropyrimidine and platinum based regimen, with at least one lesion (measurable and/or non-measurable). Previous adjuvant/neoadjuvant chemotherapy is allowed, if completed more than 6 months prior to starting the 1st line treatment. HER2 positive patients are excluded from this study. Patients must not have received previous therapy with a taxane.

Investigational product, dosage and mode of administration

Olaparib or matching placebo will be supplied to the investigator as film coated tablets. This will be administered at a dose of 100mg orally twice daily, throughout each cycle (28 days) at the same times each day, with a glass of water. Once paclitaxel dosing is stopped, the planned monotherapy olaparib/placebo dose will be 300mg twice daily.

Comparator, dosage and mode of administration

Paclitaxel will be administered as an IV infusion over 1 hour at 80 mg/m^2 weekly on days 1, 8 and 15 of a 28 days schedule and should be given at least 1 hour after the patient has taken their olaparib or matching placebo morning dose.

Paclitaxel should be sourced locally or may be supplied through AstraZeneca if local sourcing is not feasible.

Duration of treatment

Patients will be administered paclitaxel based on normal clinical practice, and it is expected that patients will receive between 4-10 cycles of paclitaxel + olaparib or paclitaxel + matching placebo on a 28-day cycle schedule with no minimum or maximum number of combination cycles.

Patients will continue to receive study treatment as described above, until they demonstrate objective disease progression (determined by RECIST 1.1) or they meet any other discontinuation criteria.

Once patients have stopped receiving paclitaxel due to any other reasons rather than objective disease progression (such as toxicity), they will continue to receive olaparib/matching placebo as monotherapy until they demonstrate objective disease progression (determined by RECIST 1.1) or they meet any other discontinuation criteria. There is no maximum duration of treatment with olaparib/matching placebo.

Patients may continue with olaparib/placebo as monotherapy beyond objective disease progression (determined by RECIST 1.1) at the discretion of the investigator if they are clinically benefiting from the treatment and they do not meet any other discontinuation criteria; this should be agreed with the AstraZeneca study physician.

Outcome variable(s):

- Primary outcome variable
  - OS
- Secondary outcome variable
  - PFS and ORR including the time to response and the duration of the response assessed by RECIST 1.1
  - Pharmacokinetics (PK)
  - Time to deterioration of HRQoL as assessed by the EORTC QLQ-C30 global HRQoL scale
  - Adverse events (AEs), physical examination, vital signs (including blood pressure (BP) and pulse), electrocardiogram (ECG) (if clinically indicated) and laboratory findings including clinical chemistry, haematology and urinalysis (if clinically indicated)
- Exploratory outcome variable
  - Status of other biomarkers such as, but not limited to, BRCA-1, MDC-1, MSI, 11q deletion

- The impact of treatment and disease state on symptoms and health related quality of life (HRQoL) as measured by the EORTC QLQ-C30+STO22 disease related multi-item symptom scales and multi-item functional scales in all patients and in the sub-group of patients whose tumours test negative for ATM

- EuroQol five dimensions, five level (EQ-5D-5L) health state utility index

- Resource use, for health economic analyses, will be captured using the CONPRO (Concomitant Procedure) module that has been modified for gastric cancer indications focussing on gastric cancer palliative procedures and the reason for the intervention.

- Biomarkers to be measured include circulating free DNA; others to be defined. Samples may be analyzed retrospectively. Any biomarker data generated may be reported separately and may also form part of a pooled analysis with other olaparib studies.

- Determination of genotype or phenotype as potential genetic explanations for variability in observed efficacy, PK, safety and tolerability. Any pharmacogenetic data generated may be reported separately and may also form part of a pooled analysis with other olaparib studies.

Statistical methods

The treatment comparison is olaparib 100mg bd in combination with paclitaxel vs placebo in combination with paclitaxel. The primary endpoint is OS. There will be two primary analysis populations: the first will comprise all patients (overall population); the second will comprise all randomised ATM negative patients. The primary subgroup was defined based on data generated outside of this trial. The primary and all secondary endpoints will be analysed in the overall population and in the primary subgroup unless otherwise stated.

As there are two primary populations the test mass (alpha) will be split with 50% of the test mass (alpha) assigned to testing in the overall population (overall type I error rate of 2.5%) and 50% to testing in the ATM negative subgroup (overall type I error rate of 2.5%).

The study is sized on a hazard ratio (HR) of 0.7 in the overall population assuming a 90% power and a 2.5% alpha with 1:1 randomization, which requires 391 deaths. With 391 deaths, a hazard ratio of 0.8 or lower would achieve statistical significance ($p \leq 0.025$) in the overall population. Assuming non-linear recruitment and no enrichment of ATM negative patients are required, if 500 patients are recruited in 2 years and assuming an 8 month median in the comparator arm, 391 deaths are expected to occur approximately 37 months after FSI. The data maturity for OS would be approximately 70% at the final analysis.

A minimum of 70 ATM negative patients will be randomised in total. The ATM negative subgroup is sized on a hazard ratio of 0.35 assuming a$\geq$90% power and a 2.5% alpha, which

requires 49 deaths and a hazard ratio of 0.53 or lower would achieve statistical significance ($p \leq 0.025$) in the ATM negative subgroup.

The primary statistical analysis of the efficacy of olaparib in combination with paclitaxel will include all randomized patients and will compare the treatment groups on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and health-related QoL data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set in the overall population. This will include all patients who receive at least one dose of randomized treatment (olaparib or placebo). The safety data will be summarised descriptively and will not be formally analysed. Safety data will also be presented for patients in the primary subgroup.

The primary endpoint of OS and the secondary endpoints of PFS and time to deterioration in HRQoL will be analysed using a Cox proportional hazards model adjusted for ATM status, country and gastrectomy status at baseline in the overall population and country and gastrectomy status at baseline in the ATM negative primary subgroup. The HR (olaparib vs placebo) together with its corresponding confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib). In both the overall population and the ATM negative subgroup 97.5% Cis will be presented. Kaplan-Meier plots and summaries of the medians for time to event variables will be presented by treatment group. ORR will be analysed using a logistic regression model adjusted for the same covariates. Median time to and duration of response will be summarised by treatment arm.

Descriptive statistics summarizing the PK data by gastrectomy status will be reported in the overall population; there will be no formal statistical analysis of the data performed. PK data may also be presented for patients in the ATM negative primary subgroup.

Supportive exploratory analyses will be performed for the following EORTC symptom scores for time to worsening: nausea and vomiting score, STODYS (dysphagia) score, STOEAT (eating restriction) score, STOPAIN (stomach pain) score, STOFX (reflux) score and STOANX (anxiety) score. Descriptive statistics, graphs and listings will be reported for health state utility index values and visual analogue scale by visits as well as change in these scores from baseline. An exploratory health economic analysis will be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of olaparib.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated Partial Thromboblastin Time
AST	Aspartate aminotransferase
ATM	Ataxia-Telangiectasia Mutation
AUC_{0-12}	Area under the plasma concentrtaion time curve from zero to 12 hours after dosing
bd	Twice daily
BoR	Best objective Response
BP	Blood Pressure
BRCA-1	BReast CAncer gene
BUN	Blood Urea Nitrogen
CHO	Chinese Hamster Ovary
CI	Confidence Interval
Cmax	Maximum concentration
CR	Complete response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCO	Data Cut Off
DNA	Deoxyribonucleic acid
DOR	Duration Of Response

Abbreviation or special term	Explanation
DUS	Disease under Study
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	EuroQol 5 Dimension 5 Level health state utility instrument
EWB	Emotional Well Being
FAS	Full Analysis Set
FWB	Functional Well Being
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GEJ	Gastro-esophageal Junction
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRD	Homologous Recombination Deficiency
HRQoL	Health Related Quality of Life
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Management Committee
LDH	Lactic Dehydrogenase
IHC	Immunohistochemistry
INR	International Normalised Ratio
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IP	Investigational Product

Abbreviation or special term	Explanation
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MDC-1	Mediator of DNA damage checkpoint protein 1
MRI	Magnetic resonance imaging
MRE-11	Meiotic recombination 11 homolog
MSI	Microsatellite instability
NCI	National Cancer Institute
OAE	Other Significant Adverse Event (see definition in Section 11.2.1)
ORR	Objective Response Rate
OS	Overall Survival
PAR	Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)]
PARP	Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation
PD	Progression of Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PR	Partial Response
PK	Pharmacokinetic(s)
p.o	Per os
PRO	Patient Reported Outcome(s)
QLQ-C30	Quality of Questionnaire Core 30 item module
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event (see definition in Section 6.4.2).
STO22	Gastric Module
SAP	Statistical Analysis Plan
SD	Stable Disease
Tmax	Time to reach maximum plasma concentration
ULN	Upper Limit of Normal

Abbreviation or special term	Explanation
WBC	White Blood Cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

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

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

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

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

PARP 1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP 1 have been shown to have delayed DNA repair. Like PARP1, PARP

2 also respond to DNA damage and is similarly involved in single strand DNA repair. For both proteins, inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP 1 activity in cells or in knockout mice leads to both radio and chemo-sensitisation. Moreover, increased PARP 1 activity has been found in many tumour types. The use of PARP inhibitors has confirmed that in combination an enhancement of the anti-tumour activity of radiation and DNA damaging cytotoxic agents occurs (Virag et al 2002; Nguewa et al 2005).

1.1.2 Homologous recombination deficiency and PARP

Olaparib (AZD2281, KU-0059436) is an inhibitor of PARP 1 and shows monotherapy activity in tumour cells with defective components of homologous recombination (HRD) pathway, which includes cells with the BRCA1-/- and BRCA2-/- genotype, as well as those with low ataxia-telangiectasia mutation (ATM) expression. Due to the molecular targeting of olaparib to specific subgroups of tumours, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP 1 inhibitor compared with conventional treatments, such as chemotherapy. For further information please refer to the current version of the olaparib Investigator's Brochure (IB).

BRCA gene testing is widely available and has been used in to prospectively select and characterise patients in clinical studies of olaparib in breast and ovarian cancer. ATM is an important factor in the repair of double-strand breaks in DNA. It was hypothesised that gastric cancer patients whose tumours were considered to be deficient in DNA repair through loss of expression of ATM protein might receive greater benefit from PARP inhibition with olaparib. The phase II Study 39 (which evaluated the combination of olaparib and paclitaxel in 2nd line gastric patients in South Korea) was enriched (50%) for patients classified as ATM 'negative'. This classification was defined as low ATM expression as determined by IHC analysis of a single slide derived from an archival tumour biopsy or surgical resection. During the course of the phase II study, emerging data (Kim et al 2013) demonstrated a lack of concordance in determination of ATM status between different sampling sites within a tumour and between different tumour sites within a patient (primary tumour vs metastatic site). It is currently unknown how this heterogeneity of ATM expression between tumour samples impacts the ability of the testing methodology to adequately identify 'ATM negative' patients, However, recent publications have strengthened the rationale for expecting a potential differential clinical benefit based on ATM status. Firstly, associative and causative data links ATM deficiency to olaparib sensitivity in preclinical models (Hodgson et al, 2014). Secondly, low IHC based protein staining has been unequivocally associated with loss of function ATM mutations in gastric and pancreas cancer (Hodgson et al, 2014 and Kim et al, 2014). Thirdly, ATM mutations associated have been associated with responses to olaparib in prostate cancer (Mateo et al, 2014)

Refs:

Hodgson et al, 2014
Hodgson D, Mason H, Oplustilova L, Harbron C, Yin X, Im S-A, Jones H, Zhongwu L, Dougherty B, McLoughlin M, Bradford J, Dickinson A, Fielding A, Robertson J, Kim WH, Womack C, Gu Y, Bang Y-J, Lau A, Barrett JC, O'Connor MJ. Activity of the PARP

inhibitor olaparib in ATM-deficient gastric cancer: from preclinical models to the clinic. In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 2398.

Kim et al, 2014
Kim H1, Saka B, Knight S, Borges M, Childs E, Klein A, Wolfgang C, Herman J, Adsay VN, Hruban RH, Goggins M. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poorer prognosis. Clin Cancer Res. 2014 Apr 1; 20(7):1865-72. Doi: 10.1158/1078-0432.CCR-13-1239. Epub 2014 Jan 31.

Mateo et al, 2014
Mateo J, Hall E, Sandhu S, Omlin AG, Miranda S, Carreira S, Goodall J, Gillman A, Mossop H, Ralph C, Zafeiriou Z, Perez Lopez R, Tunariu N, Ferraldeschi R, Nava Rodrigues D, Kunju LP, Robinson D, Attard G, Chinnaiyan A, De Bono JS. Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial. Ann Oncol (2014) 25 (suppl4):doi:10.1093/annonc/mdu438.20

Therefore the ATM IHC assay is thought to represent a valid method for identifying patients with a potential greater benefit from olaparib treatment.

1.1.3 Gastric Cancer

Gastric cancer is the fourth-most common cancer and is the second-most common cause of cancer death worldwide(Garcia et al 2007; Kamangar et al 2006) with more than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia (mainly in China). Most patients present with inoperable treatment, although early detection is more common in Asia than in other regions. There is currently no single well established standard of care, but fluropyrimidine-based and platinum-based combinations with or without a third drug (usually docetaxel or epirubicin) are the most widely used combination worldwide. However, almost all patients with metastatic gastric cancer will develop progressive disease after first-line therapy (Takiuchi et al 2007), and 30-50% of patients with advanced gastric cancer will receive second-line therapy (Wesolowski et al 2009).

Most recently reported studies of second-line chemotherapy consist of small-scale phase II or retrospective trials. No randomized control trial to establish standard treatment for second line therapy has been conducted. In clinical practice, taxane, including paclitaxel is commonly selected for the second line treatment, however, the effect of treatment are limited (Im et al 2009; Hironaka et al 2006; Kodera et al 2007).

Recently, emerging data suggests that in addition to standard cytotoxic chemotherapy, including 5-fluorouracil, capecitabine, oxaliplatin, cisplatin, S-1, or irinotecan, targeted therapy may be of clinical benefit in a percentage of patients. Approximately 20% of patients with gastric cancer will express ErbB2 (Her-2) on the tumour surface (Im et al 2009; Ajani et al 2007; Bang et al 2009) suggesting a targeted therapeutic option that was studied in a

randomized trial recently completed, in which patients whose tumours expressed Her-2 were treated with trastuzumab (Herceptin; Roche-Genentec). In this study, survival was extended by less than three months in patients treated with trastuzumab (Herceptin; Roche-Genentec). Despite these results, 80% of patients remain trastuzumab-ineligible, and additional targeted therapies are warranted.

1.1.4 Pre-clinical experience

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

1.1.5 Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies to examine for potential effects on the cardiovascular, respiratory, central, peripheral and autonomic nervous systems. In a hERG-encoded potassium channel assay, olaparib had an IC_{50} of 226 μM which is >50-fold higher than the human mean free C_{max} (3.9 μM) at a 300 mg bd clinical dose. In addition, in anaesthetised dogs, olaparib showed no evidence for QT prolongation following intravenous administration. This suggests little potential for QT prolongation in humans at the proposed clinical dose of 100 mg bd. In addition, there were no significant findings in the studies assessing effects on the respiratory parameters, following intravenous dosing in anaesthetised dogs, or on central, peripheral and autonomic nervous systems following oral dosing in rats.

Olaparib was also tested in single oral and intravenous toxicity studies in rats and mice, in 1 and 6 month repeat oral dose toxicity studies in rats and dogs, in reproductive toxicology studies in rats assessing effects on embryofetal survival and development, and on male and female fertility, and in a battery of *in vitro* and *in vivo* genotoxicity studies. There were relatively few findings of concern in these studies, although exposures in the *in vivo* studies were generally below those achieved at the clinical dose of 300 mg bd olaparib. The key findings from these toxicity studies were as follows:

- In repeat dose oral toxicity studies of up to 6 months duration in rats and dogs, the principal target organ for toxicity was the bone marrow, with associated changes in peripheral haematology parameters, which may be related to the primary pharmacology of olaparib. All changes showed full or partial recovery following withdrawal of olaparib.

- In genotoxicity studies, olaparib showed no mutagenic potential in a bacterial mutation test, but was clastogenic in mammalian cells *in vitro* and induced micronuclei in the bone marrow of rats following oral dosing. These findings are consistent with genomic instability resulting from the primary pharmacology of olaparib.

- In reproductive toxicology studies in rats, oral dosing of olaparib prior to mating produced no adverse effects on male fertility. In female rats, although conception rates were unaffected by pre and peri-conception dosing, embryofetal survival was decreased. Administration of olaparib during organogenesis had an adverse effect

on embryofetal survival and also increased major fetal malformations at dose levels that were not maternally toxic. The effects on embryofetal development are considered to be related to the primary pharmacology of olaparib.

In conclusion, the nonclinical safety evaluation studies conducted with olaparib (including single and repeat dose toxicity studies of up to 6 months duration in rats and dogs, reproductive toxicology studies in rats, genotoxicity studies and a battery of safety pharmacology studies) support the use of olaparib for the treatment of patients with advanced gastric cancer.

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

1.1.6 Clinical experience

The clinical experience can be found in the current version of the olaparib IB.

1.2 Research hypothesis

The research hypothesis under test in this study is that olaparib, in combination with paclitaxel, improves overall survival in patients with advanced gastric cancer (including GEJ), who have progressed following first line therapy. The study will also aim to identify a subgroup of patients with an identified biomarker in the tumour where the benefit of olaparib may be greater.

1.3 Rationale for conducting this study

Based on the results of study 39, AstraZeneca is planning to conduct the current phase III trial to confirm the benefit of olaparib in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy (i.e. 2nd line gastric cancer patients).

Study 39 was a randomized, double-blinded study of olaparib+paclitaxel versus matching placebo+paclitaxel in Korean patients with advanced gastric cancer who had progressed following first-line chemotherapy conducted in South Korea. The primary endpoint was PFS. There were 2 populations of interest in the analyses in this study; overall population containing all randomized patients and ATM negative population containing only the randomized patients whose ATM status was negative. Analyses of PFS, OS, ORR, and change in tumour size at week 8 have been performed in both populations. In total, 124 patients were randomized in the study (62 in the OP arm and 62 in the PP arm). The effect on PFS was not statistically significant between the treatment arms for either the overall population or the ATM negative population. In the overall population, 3.55 months in the PP arm with HR 0.80 and the median PFS was 3.91 months in the OP arm; 80% CI 0.62, 1.03; 1-sided p-value=0.131. In the ATM negative population, 3.68 months in the PP arm with HR=0.74 and the median PFS was 5.29 months in the OP arm; 80% CI 0.51, 1.08; 1-sided p-value=0.157. There were 110/124 (88.7%) progression events in the overall population and 54/63 (85.7%) progression events in the ATM negative population. A statistically significant and clinically meaningful OS benefit was demonstrated for olaparib in combination with

paclitaxel in second-line gastric cancer patients in the overall population and the ATM negative population. In the overall population, 8.3 months in the PP arm with HR 0.56 and the median OS was 13.1 months in the OP arm; 80% CI 0.41, 0.75; 1-sided p-value=0.005. In the ATM negative population, the median OS was not calculable for the OP arm as there were too few events, while the median OS was 8.2 months in the PP arm (HR=0.35; 80% CI 0.22, 0.56; 1-sided p-value=0.002). There were 81/124 deaths in the overall population and 35/63 deaths in the ATM negative population.

Given the enrichment for ATM negative patients in study 39, an exploratory analysis of OS was performed that was weighted for ATM status to estimate the expected treatment effect of olaparib in a population where the ATM negative prevalence was ~14%, reflecting the actual screening prevalence rate, rather than the 50% enrichment. This weighted OS analysis showed OS HR 0.69; 95% CI 0.41, 1.16; 80% CI 0.49, 0.97. Based on this data the phase III study will explore the efficacy in the overall population and will also aim to identify a subgroup of patients where the clinical benefit of olaparib may be greater. Therefore this study has been designed and sized to assess efficacy in the overall gastric cancer population, but in addition to assess the efficacy in subgroup that will be defined prior to analysis.

ATM is an important factor in the repair of double strand breaks in DNA. It was hypothesised that gastric cancer patients whose tumours were considered to be homologousrecombination deficient through loss of expression of ATM protein might receive greater benefit from PARP inhibition with olaparib. The phase II Study 39 was enriched (50%) for patients classified as ATM 'negative'. This classification was defined as low ATM expression as determined by IHC analysis of a single slide derived from an archival tumour biopsy or surgical resection. During the course of the phase II study, emerging data (Kim et al 2013) demonstrated a lack of concordance in determination of ATM status between different sampling sites within a tumour and between different tumour sites within a patient (primary tumour vs metastatic site). It is currently unknown how this heterogeneity of ATM expression between tumour samples impacts the ability of the testing methodology to adequately identify 'ATM negative' patients, However, recent publications have strengthened the rationale for expecting a potential differential clinical benefit based on ATM status. Firstly, associative and causative data links ATM deficiency to olaparib sensitivity in preclinical models (Hodgson et al, 2014). Secondly, low IHC based protein staining has been unequivocally associated with loss of function ATM mutations in gastric and pancreas cancer (Hodgson et al, 2014 and Kim et al, 2014). Thirdly, ATM mutations associated have been associated with responses to olaparib in prostate cancer (Mateo et al, 2014)

Refs:

Hodgson et al, 2014
Hodgson D, Mason H, Oplustilova L, Harbron C, Yin X, Im S-A, Jones H, Zhongwu L, Dougherty B, McLoughlin M, Bradford J, Dickinson A, Fielding A, Robertson J, Kim WH, Womack C, Gu Y, Bang Y-J, Lau A, Barrett JC, O'Connor MJ. Activity of the PARP inhibitor olaparib in ATM-deficient gastric cancer: from preclinical models to the clinic. In:

Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; 2014. Abstract nr 2398.

Kim et al, 2014
Kim H1, Saka B, Knight S, Borges M, Childs E, Klein A, Wolfgang C, Herman J, Adsay VN, Hruban RH, Goggins M. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poorer prognosis. Clin Cancer Res. 2014 Apr 1;20(7):1865-72. Doi: 10.1158/1078-0432.CCR-13-1239. Epub 2014 Jan 31.

Mateo et al, 2014
Mateo J, Hall E, Sandhu S, Omlin AG, Miranda S, Carreira S, Goodall J, Gillman A, Mossop H, Ralph C, Zafeiriou Z, Perez Lopez R, Tunariu N, Ferraldeschi R, Nava Rodrigues D, Kunju LP, Robinson D, Attard G, Chinnaiyan A, De Bono JS. Antitumour activity of the PARP inhibitor olaparib in unselected sporadic castration-resistant prostate cancer (CRPC) in the TOPARP trial. Ann Oncol (2014) 25 (suppl4):doi:10.1093/annonc/mdu438.20

Therefore the ATM IHC assay is thought to represent a valid method for identifying patients with a potential greater benefit from olaparib treatment.

Therefore the patients whose tumours test negative for ATM by IHC is defined as subpopulation in this study.

1.4 Benefit/risk and ethical assessment

Gastric cancers frequently recur after primary treatment. At recurrence, these cancers are generally incurable. The goals of treatment for advanced gastric cancer are to improve survival, prolong PFS and promote good quality of life. In the current study, all patients will receive a weekly regimen of paclitaxel at a dose and schedule with proven efficacy. Weekly paclitaxel has become a widely-used second-line treatment of patients with advanced gastric cancer. The prolongation of survival demonstrated in the phase II study support the further investigation of olaparib in the advanced gastric cancer population offering the possibility of improving upon the efficacy of paclitaxel administered alone. In addition, in study 39, overall Olaparib 100mg bd in combination with weekly paclitaxel 80mg/m^2 was well tolerated, with no new unexpected safety findings. The current study aims to provide a clearer understanding of the role of olaparib in the treatment of advanced gastric cancer and which patients may benefit most.

If in the opinion of the investigator and after discussion with AstraZeneca a patient with objective disease progression according to RECIST is considered to still be receiving clinical benefit from treatment, then olaparib/placebo treatment may be continued (in the absence of other criteria for discontinuation) for as long as the patient is considered to be receiving clinical benefit.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is:

- To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by OS in all patients, and the subgroup of patients whose tumours test negative for ATM with advanced gastric adenocarcinoma (including GEJ adenocarcinoma) who have progressed following first-line therapy

2.2 Secondary objectives

The secondary objectives of this study are:

- To investigate the efficacy of olaparib when given in combination with paclitaxel compared to placebo in combination with paclitaxel as defined by progression-free survival (PFS), and objective response rate (ORR) including the time to response and the duration of the response, in all patients and a subgroup of patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy

- To investigate plasma exposure to olaparib in a subgroup of olaparib dosed patients in the presence of paclitaxel and assess the impact of previous gastric surgery on that exposure

- To assess the effects of olaparib when given in combination with paclitaxel compared to paclitaxel in combination with placebo on the time to deterioration of health related quality of life (HRQoL) as assessed by the EORTC QLQ-C30 global HRQoL scale in all patients and the subgroup of patients whose tumours test negative for ATM

2.3 Safety objective

- To investigate the safety and tolerability of olaparib when given in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy

2.4 Exploratory objectives

The exploratory objectives of this study are:

- To explore potential biomarkers (such as but not limited to mutational status) in archival tumour, and in optional plasma/serum samples, which may influence the development of cancer and/or response to study treatment

- To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer.

- To explore changes in health utility status in all patients and the subgroup of patients whose tumours test negative for ATM receiving olaparib plus paclitaxel or placebo in combination with paclitaxel.

- To explore the impact of treatment and disease state on symptoms and health related quality of life (HRQoL) as measured by the EORTC QLQ-C30 + STO22 disease related multi-item symptom scales and multi-item functional scales in all patients and in the subgroup of patients whose tumours test negative for ATM

- To investigate the impact of olaparib plus paclitaxel and placebo in combination with paclitaxel on gastric cancer management resource use

- To explore the efficacy of olaparib by assessment of OS adjusting for the impact of spontaneous switching [outside of study design] to Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitors or other potentially active investigational agents

- To investigate further the impact of a complete absence of measured ATM protein in archival tumour on efficacy of study treatment

3. STUDY PLAN AND PROCEDURES

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

3.1 Overall study design and flow chart

This study is a phase III randomized, double-blinded study of olaparib in combination with paclitaxel compared with placebo in combination with paclitaxel in patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy (i.e. 2nd line gastric cancer patients).

Approximately 500 patients will be randomized onto this study in Asia, including China, Japan, Korea and Taiwan. Patients will be randomized 1:1 onto one of two arms:

- Olaparib 100mg tablets p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle

- Placebo p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle

This study has 2 primary populations: all randomized patients and the subgroup of patients whose tumours test negative for ATM. If required, recruitment into the ATM negative subgroup will be extended to ensure that a sufficient number of deaths are observed for a meaningful analysis. If there are less than 70 ATM negative patients then the ATM negative subgroup will be enriched by up to approximately 30 further patients to provide a maximum of 70 ATM negative patients. These additional ATM negative patients will be identified prospectively in Screening (all other ATM negative patients will have been identified retrospectively as the assay was not previously available).

Patients must have imaging confirmed progression on 1st line chemotherapy for gastric cancer treatment, which must have contained 5-fluoropyrimidine and platinum based regimen, with at least one lesion (measurable and/or non-measurable)

Tumour evaluation using RECIST 1.1 will be conducted at screening (within 28 days prior to randomization) and every 8 weeks relative to the date of randomization, up to week 40, then every 16 weeks until objective disease progression.

The imaging modalities used for RECIST 1.1 assessment will be CT or MRI scans of chest, abdomen and pelvis. RECIST 1.1 scans will be analysed by the investigator on site; a central review will not be conducted.

If a patient discontinues study treatment prior to disease progression, they should continue to be assessed using RECIST 1.1 until disease progression and then followed up for survival.

If in the opinion of the investigator and after discussion with AstraZeneca a patient with objective disease progression according to RECIST is considered to still be receiving clinical benefit from treatment, then olaparib/placebo treatment may be continued (in the absence of other criteria for discontinuation) for as long as the patient is considered to be receiving clinical benefit.

Assessments for survival should be made every 8 weeks following objective disease progression. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

Provision of tumour sample (from either a resection or biopsy) is mandatory for eligibility into this study. For biopsy based samples, 3 to 5 (minimum of 3) biopsy samples must be provided.

To determine plasma exposure to olaparib in a subgroup of olaparib dosed patients and assess the impact of previous gastric surgery on that exposure, at least 40 patients in each of the following sub-groups; a) patients who have had a previous full gastrectomy; b) patients who have had a partial gastrectomy; and c) patients who have not had gastric surgery will have PK samples collected after the first dose of the study. Samples from placebo patients will not be analysed.

Patients will also be requested to provide optional tumour samples from the primary or metastatic tumours at baseline and on progression. Sample provision is optional, subject to a specific consent, and will aid understanding of resistance mechanisms.

Optional blood samples for exploratory biomarkers and pharmacogenetic analyses will also be obtained from consenting patients and stored for exploratory purposes.

Figure 1 Study Flow Chart

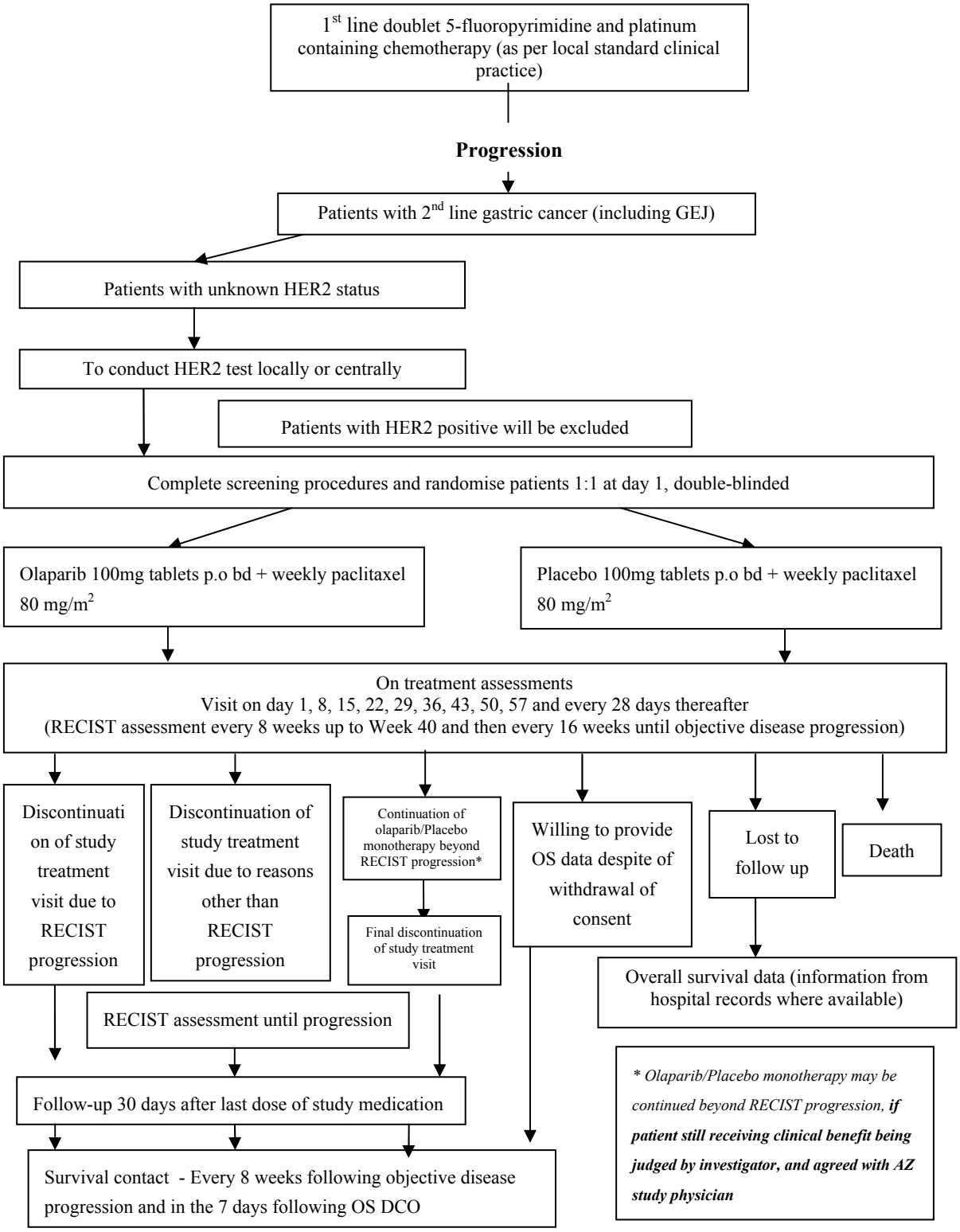

Table 1 Study Schedule – Screening

Visit	**1**		**Details, please refer to Section**
Day	**-28 to -1**	**-7 to -1**	
Informed consent	X		
Informed consent –genetic sample	X		
Demographics	X		
Medical and surgical history	X		
Previous cancer therapy	X		
Inclusion/exclusion criteria	X		4
Collection of archival or newly collected (FFPE) tumour samples (mandatory)	X		**6.2.2.1**
Physical examination	X		**6.4.6**
Vital signs, body weight, height (Includes BP [supine position], pulse and body temperature)	X		**6.4.8**
ECOG performance status	X		**6.4.6**
ECG		X	**6.4.7.1**
Haematology/clinical chemistry/urinalysis	X		**6.4.5**
Pregnancy test	X		**6.4.9.1**
Tumour assessment (CT or MRI according to RECIST 1.1)	X		**6.3.1**
HER2 test (if not already conducted)	X		
Adverse events (from time of consent)	X		**6.4.3**
Concomitant medications	X		**5.6**
Centralized ATM testing if required	X		**6.2.1**

Table 2 Study Schedule – On treatment and follow up (see section 6.2 for further details)

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Subsequent visits – every 28 days. Visit No.10 onwards**	**Treatment discontinuation**	**Follow-up 30 days after last dose of study medication**	**Survival contact Every 8 weeks following objective disease progression and in the 7 days following OS DCO**	**Details please refer to Section**
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 1 – next visit period (e.g. day 57, 85)**				
Visit Window		**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±2d**	**±3d**	**±3d**	**±3d**	
Randomization	X												5.2.1
Physical examination	X				X				X	X			6.4.6
Vital signs (Includes BP [supine position], pulse)	X				X				X				6.4.8
ECOG performance status	X				X				X	X	X	X	6.4.6
ECG									X		X		6.4.7.1
Haematology/clinical chemistry/urinalysis	X	X	X	X	X	X	X	X	X	X	X		6.4.5
Pregnancy test before treatment	X												6.4.9.1
Blood for PK (optional)	X												6.6

Table 2 Study Schedule – On treatment and follow up (see section 6.2 for further details)

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Subsequent visits – every 28 days. Visit No.10 onwards**	**Treatment discontinuation**	**Follow-up 30 days after last dose of study medication**	**Survival contact Every 8 weeks following objective disease progression and in the 7 days following OS DCO**	**Details please refer to Section**
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 1 – next visit period (e.g. day 57, 85)**				
Visit Window		**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±2d**	**±3d**	**±3d**	**±3d**	
Blood for circulating biomarker (optional)	X									X			6.2.2.4
Blood for pharmacogenetics (optional)	X												6.2.2.5
Serial tumour biopsies (optional)	X									X			6.2.2.2
Tumour assessment (CT/MRI)									X				6.3.1
EQ5D and Patient Reported Outcome– EORTC QLQ-C30 + STO22 and EQ-5D-5L	X				X				X	X	X		6.5
Olaparib or matching placebo dispensed/ returned	X				X				X	X			5.5.2
Paclitaxel infusion	X	X	X		X	X	X		X				5.5.2

Table 2 Study Schedule – On treatment and follow up (see section 6.2 for further details)

Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**Subsequent visits – every 28 days. Visit No.10 onwards**	**Treatment discontinuation**	**Follow-up 30 days after last dose of study medication**	**Survival contact Every 8 weeks following objective disease progression and in the 7 days following OS DCO**	**Details please refer to Section**
Day	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**Day 1 – next visit period (e.g. day 57, 85)**				
Visit Window		**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±1d**	**±2d**	**±3d**	**±3d**	**±3d**	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X		**5.6**
Concomitant Procedures	X	X	X	X	X	X	X	X	X	X	X		**5.6**
Adverse Events	X	X	X	X	X	X	X	X	X	X	X		**6.4.3**
Post discontinuation cancer therapy											X	X	**5.6**
Survival												X	**6.2.3.3**

3.2 Rationale for study design, doses and control groups

3.2.1 Rationale for study design

The proposed Phase III study is designed to confirm the efficacy and clinical benefit of olaparib in combination with paclitaxel for the treatment of patients with advanced gastric cancer (including GEJ) who have progressed following first-line therapy (i.e. 2nd line gastric cancer patients) as previously demonstrated in the phase II study D0810C00039 (Section 1.3).

The study design will be randomized and double-blinded in order to minimise bias when assessing whether olaparib in combination with paclitaxel shows better efficacy than placebo in combination with paclitaxel.

The primary endpoint of OS is chosen as it is considered the gold standard for the assessment of efficacy of cancer treatment, and it is supported by a number of secondary endpoints which will provide further support for the clinical benefit of olaparib in this patient population; these will include PFS and ORR by RECIST 1.1, safety and tolerability, plasma exposure and patient reported outcome measures.

There is no accepted standard therapy for patients with advanced gastric cancer who have progressed following first-line therapy, and no curative therapy. In clinical practice, taxane including paclitaxel is commonly selected in the treatment of advanced gastric cancer.

Study D0810C00039 suggested that the overall gastric cancer population may derive survival benefit from the addition of olaparib to chemotherapy and that there may be an even greater benefit in certain sub-groups of patients. This study has therefore been designed and sized to assess efficacy in the overall gastric cancer population, and assess the benefit in those sub-groups.

In preclinical models from cells with low BRCA and ATM expression, these abnormalities lead to an increased sensitivity to olaparib. In a phase II study evaluating the combination of olaparib and paclitaxel in 2nd line gastric patients in South Korea (study D0810C00039), patients whose tumour tested negative for ATM expression by IHC appeared to gain more benefit from the combination of olaparib and paclitaxel. Therefore the patients whose tumours test negative for ATM by IHC is defined as subpopulation in this study. If in the opinion of the investigator and after discussion with AstraZeneca a patient with objective disease progression according to RECIST is considered to still be receiving clinical benefit from treatment, then olaparib/placebo treatment may be continued (in the absence of other criteria for discontinuation) for as long as the patient is considered to be receiving clinical benefit.

The OS analysis will be conducted when the later of approximately 391 deaths in the overall population or 49 deaths in the ATM negative subgroup have occurred.

3.2.2 Rationale for dosing

The doses selected for olaparib and weekly paclitaxel are based upon current efficacy and safety data from study 39, in which, olaparib (continuous doses of olaparib 100 mg bd) in

combination with weekly paclitaxel 80mg/m^2 demonstrated a statistically significant and clinically meaningful improvement in OS compared to weekly paclitaxel alone in a 2nd line gastric cancer population in South Korea. Weekly paclitaxel 80 mg/m^2 IV on days 1, 8 and 15 of a four-week cycle is an widely used dose of paclitaxel given on this schedule in this patient population and study 39 demonstrated the combination of continuous doses of olaparib 100 mg bd with weekly paclitaxel 80 mg/m^2 on days 1, 8 and 15 of a four-week cycle is well tolerated with no new unexpected safety findings.

The tablet dose of olaparib as monotherapy to be used in this study is 300mg bd. This tablet dose has been chosen based on data from an ongoing study, D0810C00024. The most common AEs were consistent with the known safety profile of olaparib, namely low grade nausea, vomiting, fatigue; and anaemia. Further information is provided in the IB.

3.2.3 Rationale for PK

Olaparib is given as an oral medication and achievement of exposure to the drug will be dependent upon dissolution of the dosage form in the stomach followed by absorption of the dissolved drug in the small intestine. Since the olaparib tablet is an erodable tablet prior gastric surgery could have a profound impact on dosage form dissolution and thus on the drug exposures achieved. The PK sampling in a subgroup of olaparib dosed patients in the study (20 patients who have had no prior gastric surgery, 20 who have had a partial gastrectomy and 20 who have had a full gastrectomy) will allow assessment of the magnitude of any such effect.

3.2.4 Rationale for exploratory biomarkers

As part of the clinical drug development program of olaparib, AstraZeneca plans to include investigations into exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, RNA and/or proteins. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from olaparib treatment. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future analysis of data derived from studies with olaparib.

3.2.5 Rationale for pharmacogenetics

See Appendix G for details.

3.2.6 Rationale for Patient reported outcomes

In addition to assessing OS and other clinical endpoints in oncology clinical trials it is important to assess the impact on the HRQoL of the patient, to aid understanding of how clinical benefit relates to patient wellbeing, and for taking into account in making risk-benefit evaluations. Moreover, patient reported outcomes assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes.

Time to deterioration of HRQoL will be assessed by the EORTC QLQ-C30 + STO22 global HRQoL scale. The rationale for selecting the EORTC QLQ-C30 + STO22 is primarily because it has good coverage of the conceptual model of Gastric cancer symptom and impact concepts. The primary HRQoL analysis is time to deterioration in global HRQoL.

4. PATIENT SELECTION CRITERIA

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

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

4.1 Inclusion criteria

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

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

2. Patients must be ≥18 years of age. Age ≥20 if Japanese.

3. Advanced gastric adenocarcinoma * (including GEJ adenocarcinoma) that has progressed following first-line therapy, confirmed by imaging modalities.

   - The 1st line regimen must have contained doublet 5-fluoropyrimidine and platinum based regimen. (triplet chemo-regimen is not allowed)

   - Relapse within 6 months of completion of adjuvant/neoadjuvant chemotherapy containing doublet 5-fluoropyrimidine and platinum based regimen is considered as 1st line therapy.

4. Previous adjuvant/neoadjuvant chemotherapy is allowed, if completed more than 6 months prior to starting the 1st line therapy.

5. Provision of tumour sample (from either a resection or biopsy). For biopsy based samples, 3 to 5 (minimum of 3) biopsy samples must be provided.

6. Patients are willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

7. ECOG performance status ≤ 1.

8. Patients must have a life expectancy ≥ 16 weeks from proposed first dose date.

9. Patients must have acceptable bone marrow, liver and renal 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 ULN

10. At least one lesion (measurable and/or non-measurable) that can be accurately assessed by imaging (CT/MRI) at baseline and following up visits.

    - Local disease confined to the stomach or GEJ mass is classified as "non-measurable"

11. 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
    - LH and FSH levels in the post menopausal range for women under 50
    - Radiation-induced oophorectomy with last menses >1 year ago
    - Chemotherapy-induced menopause with >1 year interval since last menses
    - Or surgical sterilisation (bilateral oophorectomy or hysterectomy)

12. See Appendix G for additional inclusion criteria for the Optional pharmacogenetics research.

    *The ATM status of each patient in the overall co-primary population will be assessed. To ensure the required number of ATM negative patients for the other co-primary population are available for analysis, prospective ATM status testing may occur once the co-primary overall population of approximately 500 patients has been randomised. A study notification letter will be released to investigators to confirm information regarding prospective screening for ATM negative patients.

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. Previous randomization in the present study.

3. More than one prior chemotherapy regimen (except for adjuvant/neoadjuvant chemotherapy with more than 6 month wash out period) for the treatment of gastric cancer in the advanced setting.

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

5. Any previous treatment with a taxane, including paclitaxel and docetaxel.

6. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥5 years.

7. HER2 positive patients.

8. Patients unable to swallow orally administered medication.

9. Treatment with any investigational product during the last 14 days before the randomization (or a longer period depending on the defined characteristics of the agents used).

10. Patients receiving any systemic chemotherapy, radiotherapy (except for palliative reasons), within 3 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 or denusomab for bone metastases, before and during the study as long as these were started at least 4 weeks prior to treatment.

11. Concomitant use of known potent CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir.

12. With the exception of alopecia, any ongoing toxicities (>CTCAE grade 1) caused by previous cancer therapy.

13. Intestinal obstruction or CTCAE grade 3 or grade 4 upper GI bleeding within 4 weeks before the randomization.

14. Resting ECG with measurable QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.

15. Patients with myelodysplastic syndrome/acute myeloid leukaemia.

16. 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. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

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

18. 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, extensive bilateral interstitial lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent.

19. Immunocompromised patients, e.g., patients who are known to be serologically positive for human immunodeficiency virus (HIV).

20. Patients with known active hepatic disease (i.e. Hepatitis B or C)

21. Patients with a known hypersensitivity to olaparib, paclitaxel or any of the excipients of the product.

22. Pregnant and breastfeeding women.

23. See Appendix G for additional exclusion criteria for the Optional pharmacogenetics research.

Procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5. STUDY CONDUCT

5.1 Restrictions during the study

5.1.1 Olaparib and CYP3A4

Patients should avoid concomitant use of drugs and herbal supplements known to modulate CYP3A4/5 enzyme activity (section 5.6.2) from the time they enter the screening period until 30 days after the last dose of study medication.

5.1.2 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 three months after last dose of study drug(s).

For details refer to Appendix E Acceptable Birth Control Methods.

5.2 Patient enrolment and randomization and initiation of investigational product

The principal investigator (PI) 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#" using Interactive Web Response System (IWRS) or Interactive Voice Response System (IVRS).

3. Determine patient eligibility. See Sections 4.1 and 4.2.

4. Allocate a unique randomization code to an eligible patient.

5. Allocate kit ID using IWRS/IVRS and dispense study drug.

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 (e.g., 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 electronic Case Report Forms (eCRFs).

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

5.2.1 Procedures for randomization

Patient eligibility will be established before treatment randomization. Once the eligibility of a patient has been confirmed, the Investigator (or delegated study site staff) should contact the IVRS/IWRS Centralised Randomization Centre for allocation of randomized therapy.

The actual treatment given to individual patients will be determined by a randomization scheme that has been loaded into the (IVRS/IWRS) database. The randomization scheme will be produced by a computer software program called GRand (AstraZeneca Global Randomization system) that incorporates a standard procedure for generating random numbers.

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

The randomization scheme will not be stratified.

Patients will be identified to the Centralised Randomization Centre using patient initials, E-code and date of birth.

Randomization codes will be assigned strictly sequentially as patients become eligible for randomization.

Eligible patients will be randomized in a 1:1 ratio as specified below:

- Olaparib 100mg tablets p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle
- Placebo p.o bd continuous + paclitaxel 80mg/m^2 given days 1, 8 and 15 of a 28 day cycle

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

The IVRS/IWRS Centralised Randomization Centre will inform the investigator of the Kit ID number to be allocated to the patient at the randomization visit. The investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number.

The Kit ID number dispensed at each visit will correspond to the treatment to which the patient was originally randomized.

If a patient discontinues participation in the study, then their enrolment/randomization code cannot be reused.

5.3 Procedures for handling patients incorrectly randomized

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

Where patients that do not meet the selection criteria are randomized in error or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post randomization, a discussion should occur between the AstraZeneca Study 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 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

Olaparib and matching placebo treatment will be blinded.

The study medication will be labeled using a unique Kit ID number, which is linked to the randomization scheme. The active and placebo tablets will be identical and presented in the same packaging to ensure blinding of the study medication.

The treatment codes and results should be kept strictly confidential to safeguard the integrity of the blind of Investigator and patient, and hence to minimize any possible bias in data handling.

Patient safety only has access in the cases of emergency whereas IPS and the PK vendor have access to enable product supply and PK testing.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacist(s) at the study centre from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca retains the right to break the code for serious adverse events (SAE) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

Except for safety reasons, patients, investigators and study monitors in the field will have no access to the individual treatment code until after the OS analysis.

5.5 Treatments

5.5.1 Identity of investigational product(s)

AstraZeneca's Pharmaceutical Development, R&D Supply Chain will supply olaparib and matching placebo to the Investigator as film-coated tablets.

Table 3 Investigational product(s)

Investigational product	Dosage form and strength
Olaparib[α]	Tablets - 100 mg and 150 mg
Placebo to match olaparib[α]	Tablets to match each strength of olaparib

[α] The manufacturer information can be found in the relevant R& D CMC package for this study

Paclitaxel should be sourced locally or may be supplied through AstraZeneca if local sourcing isn't feasible.

Descriptive information for paclitaxel can be found in the local package insert supplied with the drug.

5.5.2 Doses and treatment regimens

For all centres, olaparib and matching placebo will be packed in bottles with child-resistant closures. The randomized study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. Multiple bottles of olaparib or matching placebo may be required for dispensing in order to make up the desired dose.

Olaparib or matching placebo is available as a film-coated tablet containing 150 mg or 100 mg. Patients will be administered olaparib or matching placebo orally twice daily (bd) at 100mg continually. Doses of study treatment should be taken at the same times each day approximately 12 hours apart. All doses should be taken with approximately 240ml of water. Study treatment tablets can be taken with a light meal/snack (e.g, two pieces of toast or a couple of biscuits).

The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided.

If vomiting occurs shortly after the olaparib or matching placebo tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient randomized in the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of two hours after that scheduled dose time. If greater than two 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.

Paclitaxel should be given at least 1 hour after the patient has taken their olaparib or matching placebo morning dose. Paclitaxel will be administered as an IV infusion over 1 hour at 80 mg/m^2 weekly on days 1, 8 and 15 of a 28 days schedule.

Patients will be administered paclitaxel based on normal clinical practice, and it is expected that patients will receive between 4-10 cycles of paclitaxel + olaparib or paclitaxel + matching placebo on a 28-day cycle schedule with no minimum or maximum number of combination cycles.

Patients will continue to receive study treatment as described above, until they demonstrate objective disease progression (determined by RECIST 1.1) or they meet any other discontinuation criteria.

Once patients have stopped receiving paclitaxel due to any other reasons (such as toxicity) rather than objective disease progression, they will continue to receive olaparib/matching placebo as monotherapy until they demonstrate objective disease progression (determined by RECIST 1.1) or they meet any other discontinuation criteria. The olaparib/matching placebo dose will be increased to 300 mg bd as monotherapy. There is no maximum duration of treatment with olaparib/matching placebo.

Patients may continue with olaparib/placebo as monotherapy beyond objective disease progression (determined by RECIST 1.1) at the discretion of the investigator if they are clinically benefiting from the treatment and they do not meet any other discontinuation criteria; this should be agreed with the AstraZeneca study physician.

All patients should be premedicated (as per local standard practice) prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg p.o administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

Patients will be unblinded after the OS analysis. Within this study, placebo patients cannot cross over treatment arms to receive olaparib.

5.5.3 Labelling

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

Specific dosing instructions will not be included on the label, the site must complete the "Patient Dispensing Card" with the details of the dosing instructions at the time of dispensing.

The patient emergency contact details will not be on the label, but can be found in the informed consent and the "Patient Dispensing Card". For emergency purposes the patient must be in possession of the emergency contact details at all times.

5.5.4 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 IB specifies the appropriate storage and shipment.

5.5.5 Management of toxicity

Any toxicity observed during the course of the study will be managed by interruption of olaparib and/or paclitaxel, as deemed appropriate by the Investigator. Each patient should receive three paclitaxel doses in a four-week period as toxicity permits however interruption or dose modification of paclitaxel must follow labelled recommendations where appropriate (for example, myelosuppression). Interruption of olaparib for paclitaxel-specific toxicities (for example, peripheral neuropathy) should be avoided.

Treatment with paclitaxel may continue at the full dose of 80 mg/m^2 (unless previously dose reduced) on Days 1, 8 and 15 of each cycle as long as the following criteria are met, else paclitaxel should be held until restoration of ANC and platelet count:

- ANC $\geq$ 1.5 x 10^9/L
- Platelets $\geq$ 100 x10^9/L

In the event that a patient has not recovered sufficiently to enable the next chemotherapy cycle to start, then the cycle should be delayed until the toxicity has recovered sufficiently to allow further dosage. The maximum cycle delay is permitted in 28 days. In the event that only the paclitaxel needs to be held and the patient is still receiving continuous dosing of olaparib, then the start of the chemotherapy cycle should be delayed, however the patient should continue the olaparib doses during the delay period, unless any other criteria requires doses to be omitted.

Further dose modifications are described in Table 4, Table 5, Table 6 and Table 7.

Management of prolonged haematological toxicities while on study treatment:

If patient develops prolonged haematological toxicity such as:

- $\geqslant$2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence
- $\geqslant$2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- $\geqslant$2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index, RI = Ret count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be considered. If any blood parameters remain clinically abnormal after 28 days of dose interruption, the patient should be considered to be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. All sudy treatment should be discontinued if a diagnosis of myelodysplastic syndrome is confirmed.

Management of new or worsening pulmonary symptoms:

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

5.5.5.1 Management of haematological toxicity (paclitaxel and olaparib)

At the first occurrence of CTCAE grade 3 and 4 haematological toxicity, both olaparib and paclitaxel should be held until resolution of toxicity or CTCAE grade 1 or baseline. At the resolution of the first occurrence of any of these toxicities, no change should be made to dose. At the second occurrence, upon resolution of toxicity, olaparib should be reduced by the 1st dose reduction to 100 mg bd days 1-14 of a 28-day cycle (Table 4). If despite this change, at the third occurrence, upon resolution of toxicity, paclitaxel should be reduced by the first dose reduction to 65 mg/m^2/dose (Table 4). At the fourth occurrence, upon resolution of toxicity, olaparib should be reduced by the 2nd dose reduction to 100 mg bd days 1-7 of a 28-day cycle (Table 4). If despite these changes, toxicity recurs, the patient should be withdrawn from the treatment.

Refer to Table 6 for specific dose modification guidance regarding haematological toxicity.

Please note that for simultaneous toxicities (for example, neutropenia and thrombocytopenia), if either olaparib or paclitaxel has been recently held or dose-reduced, and a second toxicity develops, the event should be considered singular and no further dose modification should be made, providing that both toxicities resolve within 28 days. However, sequential toxicities (for example, neutropenia followed by thrombocytopenia) should follow Table 6; if a recent dose reduction has been made, a second modification may be required before beginning the next cycle.

Table 4 Dose reductions for olaparib or matching placebo when combined with paclitaxel

Reduction	Dose Level
Initial dose level	100 mg bd days 1-28 of a 28-day cycle
1st dose reduction [a]	100 mg bd days 1-14 of a 28-day cycle
2nd dose reduction [a]	100 mg bd days 1-7 of a 28-day cycle
3rd dose reduction	No reduction allowed; withdraw patient

[a] Dose must not be re-escalated even if toxicities have resolved.

Table 5 Dose reductions for paclitaxel

Reductions	Dose Level
Initial dose level	80 mg/m^2 on days 1, 8 and 15 of a 28 day cycle
1st dose reduction [a]	65 mg/m^2 on days 1, 8 and 15 of a 28 day cycle
2nd dose reduction	No additional reduction allowed; stop paclitaxel

[a] Dose may be re-escalated to full dose once toxicities have resolved, depending on toxicity (see below for exceptions).

Filgrastim or PEG-filgrastim may be used at the investigator's discretion.

In addition, paclitaxel should be permanently reduced to 65 mg/m^2/dose in case of the following haematological toxicities:

- Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 x 10^9/L), requiring hospitalisation and IV antibiotics.
- Bleeding associated with platelet count of ≤ 40 x 10^9/L or any platelet count of ≤ 20 x 10^9/L.

5.5.5.2 Management of non-haematological treatment-related adverse events attributable to olaparib

Non-hematological CTCAE grade 3 and 4 toxicities observed during the course of the study and attributable to olaparib will first be managed by interruption of the dose. Repeat dose interruptions are to be allowed as required. The maximum duration of any dose interruption is 28 days. If an interruption of longer than 28 days is required, the patient should be withdrawn. When olaparib is interrupted, the patient must either recover completely or the toxicity must revert to NCI CTCAE ≤ grade 1 or to the baseline CTCAE grade before restarting treatment. Patients whose NCI CTCAE grade 3 or 4 event does not resolve to ≤ grade 1 or to the baseline CTCAE grade after a full 28 day dose interruption should be withdrawn from the study.

Where toxicity recurs following re-challenge with olaparib, and where further dose interruptions are considered inadequate for management of toxicity, then dose reduction or withdrawal is indicated.

Upon appropriate resolution of the toxicity (i.e. to CTCAE grade 1 or to baseline CTCAE grade), the patient should restart treatment with olaparib but with a dose level reduction (as per Table 4).

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

5.5.5.3 Management of non-haematologic treatment related adverse events attributable to paclitaxel

Treatment with paclitaxel may be continued on Day 1, 8, 15 of each cycle as long as each of the following criteria are met:

- AST ≤ 5 x ULN
- Bilirubin < 27 μmol/L (1.6 mg/dL)

If any of the following criteria are met:

- AST > 5 x ULN and ≤ 10 x ULN
- Bilirubin 27-43 μmol/L (1.6-2.5 mg/dL)

Then hold paclitaxel until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If paclitaxel is withheld for >1 cycle (28 days) the patient should not restart paclitaxel.

In the case of CTCAE grade 3 neuropathy, paclitaxel should be withheld and then resumed at 65 mg/m^2 on resolution to CTCAE grade 1 or less.

Paclitaxel should be permanently discontinued for the following non-haematological toxicities:

- Severe (CTCAE grade 3 or 4) hypersensitivity reactions.
- CTCAE grade 3 or 4 neuropathy lasting more than 4 weeks.
- CTCAE grade 3 or 4 neuropathy recurring after dose reduction.
- AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days.
- Bilirubin CTCAE grade 3 or above.

Dose delays of paclitaxel as a consequence of non-haematological toxicities:

The treatment of a patient can be postponed for up to 28 days (one cycle) if the patient has not recovered to CTCAE grade 1 or less non-haematological toxicity at the beginning of cycle (day 1).

Dose reductions of paclitaxel as a consequence of non-haematological toxicities:

For non-haematological toxicities other than those mentioned above and excluding nausea, vomiting and asthenia:

- If CTCAE grade 3, patients should have a permanent dose reduction to 65 mg/m^2
- Patients who experience CTCAE grade 4 non-haematological toxicity may have their dose held for up to 28 days (one cycle) to permit recovery to CTCAE grade 3 or below followed by a permanent dose reduction to 65 mg/m^2

Hypersensitivity reactions:

Discontinue paclitaxel infusion for significant hypersensitivity reactions defined as:

- Hypotension requiring pressor therapy.
- Angioedema.
- Respiratory distress requiring bronchodilator therapy.
- Generalised urticaria.

For other hypersensitivity reactions, paclitaxel may be discontinued at the discretion of the investigator.

Any significant hypersensitivity reaction and any hypersensitivity reaction requiring treatment discontinuation should be reported as an AE or SAE.

The following management of hypersensitivity reactions is recommended or local standard practice:

- Administer chlorpheniramine 10 mg IV, or equivalent.
- Administer adrenaline (or its equivalent) sub-cutaneous every 15-20 minutes until the reaction subsides or a total of 6 doses given.
- If hypotension is present that does not respond to adrenaline, administer IV fluids.
- If wheezing is present that is not responsive to adrenaline, administration of nebulized salbutamol solution (or equivalent) is recommended.

Although corticosteroids have no effect on the initial reaction, they have been shown to block "late" allergic reactions to a variety of substances. Thus, methylprednisolone 125 mg IV (or its equivalent) may be administered to prevent recurrent or ongoing allergy manifestations.

Patients should not be re-challenged with paclitaxel in case of a severe hypersensitivity reaction. These patients should be discontinued from treatment with paclitaxel.

Table 6 Summary of guidance on the management of toxicity for olaparib or matching placebo and paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
Haematological toxicities		
Neutropenia ANC > 1 x 10^9/L and < 1.5 x 10^9/L (CTCAE grade 2)	No action required.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
Neutropenia ANC ≤ 1 x 10^9/L (CTCAE grade ⩾ 3)	1st occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.
	2nd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at original dose. If withheld for > 28 days patient should not restart paclitaxel.

Table 6 Summary of guidance on the management of toxicity for olaparib or matching placebo and paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
	3rd occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 1st reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at reduced dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.
	4th occurrence Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at 2nd reduced dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Withhold dose for up to 28 days until toxicity has resolved to CTCAE grade 1 or baseline, then resume at a dose of 65 mg/m^2. If withheld for >28 days patient should not restart paclitaxel.
Febrile neutropenia (temperature ≥ 38.5°C, ANC < 1.0 x 10^9/L), requiring hospitalisation and IV antibiotics	Withhold dose for up to 28 days until recovery to ≤ CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤ CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Bleeding associated with platelet count of ≤ 40 x 10^9/L or any platelet count of ≤ 20 x 10^9/L (CTCAE grade ⩾3)	Withhold dose for up to 28 days until recovery to ≤CTCAE grade 1 then resume at original dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib.	Permanent dose reduction to 65 mg/m^2.
Platelets > 20 x 10^9/L and < 100 x10^9/L	No action required.	Reduce dose to 65 mg/m^2, may be re-escalated at next cycle.
Peripheral neuropathy		

Table 6 Summary of guidance on the management of toxicity for olaparib or matching placebo and paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
CTCAE grade 2	No change	Start next course with dose reduced by 1 dose level (65 mg/m^2)
CTCAE grade 3	Withhold dose for up to 1 cycle (28 days) until recovery to ≤CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover, discontinue olaparib	Withhold paclitaxel for up to 1 cycle (28 days) until recovery to ≤CTCAE grade 1 then dose reduce subsequent cycles to 65 mg/m^2. If symptoms recur after dose reduction discontinue paclitaxel
Hepatotoxicity (CTCAE grade ⩾3)	Withhold dose for up to 1 cycle (28 days) until recovery to ≤CTCAE grade 1 then dose reduce by 1 dose level. If symptoms do not recover to ≤CTCAE grade 1, discontinue olaparib	Withhold dose until toxicity has resolved to CTCAE grade 1 or baseline, then reduce dose to 65 mg/m^2. Dose may return to full dose (80 mg/m^2) in subsequent cycles. If withheld for > 1 cycle (28 days) patient should not restart paclitaxel – AST > 5 x ULN and ≤ 10 x ULN – Bilirubin 27-43 μmol/L (1.6 – 2.5 mg/dL Stop paclitaxel – AST and/or ALT CTCAE grade 3 or above (CTCAE grade 4 or above in case of liver metastases) lasting more than 7 days – Bilirubin CTCAE grade 3 or above
Other non-haematological toxicities (excludes nausea, vomiting, asthenia) that are not listed above		
CTCAE grade 3	Withhold dose for up to 1 cycle (28 days) until recovery to ≤ CTCAE grade 1, reduce by 1 dose level	Permanent dose reduction to 65 mg/m^2

Table 6 Summary of guidance on the management of toxicity for olaparib or matching placebo and paclitaxel

Toxicity	Olaparib or matching placebo	Paclitaxel
CTCAE grade 4	Withhold dose for up to 1 cycle (28 days) until recovery to ≤CTCAE grade 1, reduce by 1 dose level	Withhold dose for up to 1 cycle (28 days) until recovery to CTCAE grade 3 or below, permanent dose reduction to 65 mg/m^2
CTCAE grade 3 or 4 allergic reaction/hypersensitivity that is clearly attributable to paclitaxel	No change	Stop paclitaxel

5.5.5.4 Management of Toxicity (Monotherapy Only)

When olaparib or matching placebo is given as monotherapy (upon completion or discontinuation of paclitaxel), the dose will be increased to 300 mg orally bd.

Any toxicity observed during the course of the monotherapy treatment of olaparib/placebo could be managed by interruption of the dose of olaparib/placebo if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion (with the exception for management of anaemia, thrombocytopenia and prolonged haematological toxicity where maximum interruption could be up to 28 days). If the interruption is any longer than this the AstraZeneca study team must be informed. Olaparib/placebo must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge with olaparib/placebo, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue olaparib/placebo. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the Investigator considers to be related to administration of olaparib/placebo.

Management of anaemia:

AEs of anaemia CTCAE grade 1 or 2 (Hb > 8 g/dl) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anaemia. Common treatable causes of anaemia (e.g. iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. However, if patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, olaparib/placebo should be interrupted for up to maximum of 28 days to allow for bone marrow recovery and patient should be managed appropriately. Olaparib/placebo can be restarted at the same dose if Hb has recovered to > 9 g/dl. Any subsequently required anaemia related interruptions,

considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require olaparib/placebo dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without olaparib/placebo interruptions and becomes blood transfusion dependant as judged by investigator, olaparib/placebo should be interrupted for up to a maximum of 28 days to allow for bone marrow recovery. Olaparib/placebo should be restarted at a reduced dose.

Management of neutropenia and leukopenia:

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if patient develops febrile neutropenia, olaparib/placebo should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h of the last dose of olaparib/placebo.

Olaparib/placebo can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade >1 (ANC > 1.5 x 10^9/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require olaparib/placebo dose reductions to 250 mg bd as a first step and to 200 mg bd as a second step.

Management of thrombocytopenia

An AE of thrombocytopenia should be managed as deemed appropriate by the investigator. If patient develops thrombocytopenia CTCAE grade 3 or worse olaparib/placebo should be interrupted for a max of 28 days. In some cases management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

Management of prolonged haematological toxicities while on olaparib/placebo:

If patient develops prolonged haematological toxicity such as:

- ≥2 week interruption/delay in olaparib/placebo due to CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in olaparib/placebo due to CTCAE grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in olaparib/placebo due to CTCAE grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index, RI = Ret count x haematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 28 days of dose interruption, the patient should be referred to haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of a confirmed myelodysplastic syndrome or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety. Olaparib treatment should be discontinued if diagnosis of myelodysplastic syndrome is confirmed.

Management of new or worsening pulmonary symptoms:

Please see the detailed guidance provided in section 5.5.5.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. The events of nausea and vomiting are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

No routine prophylactic antiemetic treatment is required at the start of olaparib/placebo, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter in accordance with local treatment practice guidelines.

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

Table 7 Dose reductions for olaparib/placebo

Initial Dose	Dose reduction 1	Dose reduction 2
300mg	250mg[α]	200mg[α]

[a] Dose must not be re-escalated even if toxicities have resolved.

5.6 Concomitant and post-study treatment(s)

Any medications (with the detailed exceptions) which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the investigator, providing the medications, the doses, dates and reasons for administration are recorded.

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 addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded. This includes any blood transfusions.

The reasons for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate sections of the eCRF.

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

5.6.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (HRT is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication.

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.

5.6.2 CYP3A4/5

Olaparib produced little/no direct inhibition in vitro of CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 or 2E1 but inhibition of CYP3A4 was seen when olaparib was tested at high concentrations, suggesting that olaparib has the potential to cause clinically relevant interactions with other CYP3A4 substrates in the liver or gastrointestinal tract. Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro, with CYP3A4 being most likely to be induced to a clinically relevant extent. Since olaparib may reduce exposure to substrates of CYP3A through enzyme induction, the efficacy of hormonal contraceptives may be reduced if co-administered with olaparib. In vitro data have also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and in vivo data have shown that co-administration with itraconazole (a known CYP3A4/5 inhibitor) increases olaparib AUC by an average of 2.7-fold. Consequently, to ensure patient safety, the following potent inhibitors of CYP3A4/5 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:

- ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir

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

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

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

For patients taking any of the above, the required wash-out periods prior to starting study treatment are 5 weeks for phenobarbitone, 3 weeks for any of the others.

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

5.6.3 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that prothrombin time (international normalised ratio (INR) and activated partial thromboplastin time (APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin is permitted.

5.6.4 Anti-emetics/Anti-diarrhoeals

Should a patient develop nausea, vomiting and or diarrhoea, then these symptoms should be reported as AEs (see section 6.4.3) and appropriate treatment of the event given.

5.6.5 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. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 28 days as long as any bone marrow toxicity has recovered.

5.6.6 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 or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 28 days prior to beginning study treatment.

5.6.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer and/or details of surgery for the treatment of the cancer, after discontinuation of treatment, will be collected. Reasons for starting subsequent anti-cancer therapies including access to other PARP inhibitors or investigational drugs will be collected and included in the exploratory assessments of OS.

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 or matching placebo. Compliance of the first dose and dose taken on the day of any study visit of olaparib or matching placebo will be assured by supervised administration by the investigator or delegate. Study site（pharmacy）staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the eCRF. After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib or matching placebo at the appropriate scheduled visit, when a new bottle will be dispensed. Patients will be instructed to notify study site personnel of missed doses. Dates of missed or held doses will be recorded on the eCRF.

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

5.7.1 Accountability

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

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

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

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

5.8 Discontinuation of investigational product

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

- Objective progression according to RECIST criteria(unless in the investigator's opinion they are clinically benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 5.8)
- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- AE
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)
- Severe non-compliance to study protocol

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 AEs. 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), and remaining study drug or placebo 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 (olaparib or placebo).

After discontinuation of the study medication at any point in the study, all ongoing AEs and 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. For guidance on reporting adverse events after the 30 day follow up period see Section 6.4.3.

Any patient, who has not yet shown objective disease progression should continue to be followed as per RECIST 1.1 as detailed in Section 6.2.3.5.

All patients must be followed for survival, unless they withdraw consent.

If a patient is withdrawn from study, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. 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); questionnaires (e.g., for patient reported outcomes) and all study drugs should be returned by the patient.

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

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

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

*If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

  - further participation in the study including any further follow up (e.g., survival calls)
  - withdrawal of consent to the use of their study generated data

– withdrawal to the use of any samples (see section 7.5).

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 eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.2 Data collection and enrolment

6.2.1 Screening

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

- Signed informed consent for the study; include main inform consent and an optional consent form for circulating biomarker research and a separate consent for pharmacogenetics research
- Date of birth, race and ethnicity
- Medical and surgical history
- Current and concomitant medications including previous cancer therapies (if applicable)
- Physical examination
- ECOG performance status
- Vital signs (blood pressure, pulse and body temperature), body weight and height.
- Haematology, clinical chemistry and urinalysis
- Menopausal status; serum or urine pregnancy test for women of childbearing potential (within 28 days prior to study treatment start and a confirmatory test before treatment at visit 2)
- HER2 test (if not already conducted)

- Tumour assessment (scans of the abdomen/pelvis/other sites as clinically indicated for assessment of disease [CT/MRI]), performed within 28 days prior to randomization, ideally should be performed as close as possible to the start of the 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 consistent with RECIST guidelines for CT or MRI

- Concomitant medications

- Collection of archival or newly collected (FFPE) tumour samples. Either archival samples obtained, or newly collected (FFPE) samples taken from the patient prior to enrolment on the study (mandatory)

- Adverse events must be captured from time of consent

- Centralized ATM testing if required.

The assessment and procedures of ECG should be performed within 7 days prior to first dose of study treatment.

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

6.2.2 Treatment period

Olaparib or matching placebo is self-administered by the patient twice daily as instructed continuously. The visit schedule is based on 28 day periods. Patients will attend the clinic on day 1 (1st day of treatment), 8, 15, 22, 29, 36,43, 50 and every 28 days thereafter and the following assessments will be performed at time points specified in the study schedule (see Table 1 and Table 2)

- Vital signs

- Physical examination including ECOG performance status (day 1 of each 4 week period)

- ECG on Day 57 only (i.e. +8 weeks from stating study treatment), when clinically indicated

- Haematology, clinical chemistry and urinalysis (every visit and if clinically indicated)

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

- AE (every visit)

- Concomitant medications (every visit)
- Tumour assessments via CT or MRI (every 8 weeks until Week 40, then every 16 weeks, relative to date of randomization until objective disease progression)
- PRO instruments (EORTC QLQ-C30 + STO22 and EQ-5D-5L) (day 1 of each 4 week period)
- Concomitant procedures (resource use) (each visit)
- Blood samples for circulating biomarker analysis (optional).
- Biopsy sample prior to dosing and at documented disease progression (optional)
- A pharmacogenetic sample will be obtained from consenting patients and stored for long-term experimental pharmacogenetic analysis (optional).
- PK samples to be collected on Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after the first dose of the studyonly from subgroup of olaparib dosed patients.

If in the opinion of the investigator and after discussion with AstraZeneca a patient with objective disease progression according to RECIST is considered to still be receiving clinical benefit from treatment, then olaparib/placebo treatment may be continued (in the absence of other criteria for discontinuation) for as long as the patient is considered to be receiving clinical benefit.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of the scheduled visit ± 1 week window interval and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective disease progression by RECIST, as per the study schedule (see Table 1 and Table 2), and then followed for survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

The imaging modalities used for RECIST assessment will be CT or MRI scans of chest, abdomen and pelvis. Any other sites at which new disease is suspected should also be appropriately imaged. The radiological examinations performed in the conduct of this study should be retained at site as source data and be available for collection by the sponsor for centralised review.

In the event of suspected pregnancy during the study, the test should be repeated and, if positive, the patient discontinued from study treatment immediately.

6.2.2.1 Archival tumour tissue for ATM and biomarker analysis

Provision of tumour sample (from either a resection or biopsy) is mandatory for eligibility into this study. For biopsy based samples, 3 to 5 (minimum of 3) biopsy samples must be provided.

Tumour samples will preferably be in the form of a formalin fixed paraffin embedded block, alternatively 12-20 (minimum 12) slides of freshly prepared unstained 4µm sections from each block may be provided. All the samples submitted after the patient has been randomized will be stored for retrospective testing at clinical central testing labs located in Asia. If there are less ATM negative patients than required then the ATM negative subgroup will be enriched by up to approximately 30 further patients. Testing for these additional patients will be performed prospectively and patient samples will be required to be provided and a test result obtained prior to randomisation. ATM status will be determined upon the mandatory archival tumour samples using an immunohistochemical method. Patients will be classified as having a tumour that is negative, positive or unknown ATM status prior to treatment unblinding. This classification will be determined by individuals who are blinded to treatment assignment and data collected on the clinical database.

6.2.2.2 Collection of serial tumour biopsies (optional)

Patient participation in this part of the study is optional but desirable. For consenting patients additional samples may be provided as follows:

- If the mandatory archival tumour sample is derived from the primary tumour, it is highly recommended that FFPE tumour biopsies (blocks or slides) from any metastatic lesion are also provided where possible.

A recent study showing low concordance between the ATM status of metastases and primary tumours has been reported (Kim et al 2013). These samples are requested to further understand the variability of ATM status in the primary tumour versus metastatic tumour.

- A newly collected (FFPE) tumour biopsy taken prior to the start of dosing and an additional biopsy (block or slides) collected at the time of documented progression

Samples will be collected to understand the variability and potential evolution of biomarkers such as ATM in the progression of the disease and response to therapy.

6.2.2.3 Exploratory analysis on tumour samples

Any residual material remaining after the main analysis on tumour samples maybe used to investigate expression of other biomarkers, such as but not limited to BRCA-1, MDC-1, MSI, 11q deletion.

6.2.2.4 Blood sample for circulating biomarker (optional)

Patients will be required to provide 2 x 12 ml blood samples for preparation of plasma and serum. The first sample will be taken prior to first dose and the second on treatment discontinuation.

The samples may be analysed for a range of biomarkers which may correlate with drug response. Samples may be analysed retrospectively. Any biomarker data generated may be reported separately to the clinical study report, and may also form part of a pooled analysis with other olaparib studies.

6.2.2.5 Pharmacogenetic research sample (optional)

See Appendix G.

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 (see Table 2).

Patients who have objective radiological disease progression but continue on study treatment

Patients should be discontinued from study treatment if they have objective radiological disease progression according to RECIST1.1 (see Appendix D), unless in the Investigator's opinion they are clinically benefiting from treatment, after getting the agreement with AstraZeneca study physician and they do not meet any other discontinuation criteria as outlined in (Section 5.8). These patients will continue on treatment following procedures, including PRO assessments, as per Table 2 and will be followed for OS. Safety assessment can occur with the same frequency as the visits unless more frequent testing is clinically indicated.

At RECIST progression visits for patients who discontinue study treatment prior to progression

Patients should be continuously followed based on the RECIST1.1 schedule, till objective radiological disease progression.

PRO assessments (EORTC QLQ-C30 + STO22 and EQ-5D-5L) and Concomitant Procedures should continue to be assessed at the RECIST progression visits for patients who discontinue study treatment prior to progression.

6.2.3.2 Follow-up 30 day after last dose of study medication (follow-up visit)

Follow-up 30 day after last dose of study medication (follow-up visit) should be conducted 30 days after the last dose of olaparib or matching placebo. 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 eCRF. Detailed in the study schedule (see Table 2).

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. If possible, any information to get on patients ECOG status will be collected. Survival data will be collected up to the time of the OS analysis.

In addition, patients should be contacted in the week following the data cut-off for the survival analyses to provide complete survival data.

In the event that the patient has actively withdrawn consent to the processing of their personal data the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

6.2.3.4 Patient management post OS analysis

The data cutoff date for the statistical analysis of the study will be established when the later of 391 deaths in the overall population or 49 deaths in the ATM negative subgroup have occurred.At this time point, the clinical study database will close to new data and all patients will be unblinded. Patients who are receiving active treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit; patients may continue to receive study treatment. All patients will receive follow up care in accordance with standard local clinical practice.

Patients that are on placebo will not be offered olaparib as a study treatment.

AstraZeneca will continue to supply olaparib after completion of this study until either olaparib is licenced in that country, or it is determined that the benefit to risk profile does not support continued development of olaparib, or the national health authority has deemed the drug not approvable. In all these scenarios, AstraZeneca will work with investigators on the proper transition of patients to alternative therapies if possible.

SAEs will continue to be reported to AstraZeneca Patient Safety Department, for any patients who continue on olaparib until 30 days after study treatment is discontinued, in accordance with Section 6.4.4. Additionally any SAE or non-SAE, that is ongoing at the end of the study, must be followed up to resolution unless the event is considered by the investigator to be unlikely to be resolved, or the patient is lost to follow-up. 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.

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

6.2.3.5 CT or MRI scans (RECIST)

Aassessments to be performed using CT or MRI scans of chest, abdomen, and pelvis. To be measured according to RECIST 1.1 guidelines by the site investigator. 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. Any other sites at which new disease is suspected should be appropriately imaged. Baseline assessments should be performed no more than 28 days prior to date of randomization, and ideally should be performed as close as possible to the start of study treatment. Follow-up assessments will be performed every 8 weeks relative to date of randomization, up to Week 40, then every 16 weeks until objective disease progression (within a window of +/- 7 days of the scheduled date). 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. Radiological examinations performed in the conduct of this study should be retained at site as source data and be available for collection by the sponsor for centralised review (if required).

Scan should ideally 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 consistent with RECIST guidelines for CT or MRI.

6.3 Efficacy

This study will assess the efficacy of olaparib when given in combination with paclitaxel, compared with matching placebo + paclitaxel, in patients with advanced gastric cancer who have progressed following first-line therapy.

6.3.1 Tumour Evaluation

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS and ORR. 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 D.

The methods of assessment of tumour burden used at baseline, CT or MRI scans of chest, abdomen and pelvis 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 relative to date of randomization, until week 40, at which time assessments will be carried out every 16 weeks until objective disease progression as defined by RECIST 1.1. See Study Schedule (Table 1 and Table 2) for further details.

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

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 (i.e. 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.

Local disease confined to the stomach or GEJ mass is classified as “non-measurable”.

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.

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.

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 weeks as outlined in the Study Schedule (see Table 1 and Table 2).

It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in section 3.1 and CT/MRI scans in section 6.2.3.5.

6.4 Safety

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

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, 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.

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 (i.e. run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

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

6.4.3 Recording of adverse events

Time period for collection of adverse events

AEs will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-day follow-up period. All ongoing and any new AEs/SAEs identified during the 30 calendar days follow up period after last dose of study medication must be followed to resolution.

SAEs will be recorded from the time of informed consent.

Follow-up of unresolved adverse events

Any SAE or non-serious AE that is ongoing at the time of the 30 day follow-up, 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.

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

For Pharmacovigilance purposes and characterisation of events of special interest, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported as a SAE (or AE if at least one of the criteria for SAE is not met, such as for nonmelanoma skin cancers, see Section 6.2) to AstraZeneca Patient Safety regardless of investigator's assessment of causality or knowledge of the treatment arm. A Questionnaire

will be sent to any investigator reporting MDS/AML or new primary malignancy as an aid to provide detailed information on the case.

At any time after a patient has completed the study, if an Investigator learns of any SAE including death, 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 all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe.

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

Variables

The following variables will be collect for each AE;

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason that AE is serious (“due to”)
- Date of hospitalisation
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE

Severity of AE

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 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 an 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.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades the recommendation is that 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.

Causality collection

The investigator will assess causal relationship between Investigational Product and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

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

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

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

NB. Cases where a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix H 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

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

New cancers

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

Deaths

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

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

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within **24 hours** (see Section 6.4.4 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the 'death eCRF'.

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

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, 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 immediately, or **no later than 24 hours** 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 AEs 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 immediately, or **no later than 24 hours** of when he or she becomes aware of it.

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

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

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the times indicated in the Study Schedule (see Table 1 and Table 2).

Hematology/clinical chemistry should be performed on Day 1, 8 and 15 of a 28-day cycle prior to paclitaxel infusion.

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.

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

The following laboratory variables will be measured:

6.4.5.1 Full haematology assessments for safety

- Haemoglobin
- Red blood cells (RBC)
- Platelets
- Mean cell volume (MCV)

- Mean cell haemoglobin concentration (MCHC)
- Mean cell haemoglobin (MCH)
- WBC
- Absolute differential white cell count
  - (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and Band forms should be performed at each visit and when clinically indicated. If absolute differentials not available please provide % differentials

6.4.5.2 Coagulation

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

6.4.5.3 Biochemistry assessments for safety

- Sodium
- Potassium
- Calcium
- Magnesium
- Creatinine
- Total bilirubin
- Gamma glutamyltransferase (GGT)
- ALP
- AST
- ALT
- Urea or blood urea nitrogen (BUN)

- Total protein
- Albumin
- Lactic dehydrogenase (LDH)

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

For blood volumes see Section 7.1.

6.4.5.4 Urinalysis

Urinalysis should be performed at screening and if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.

If being assessed within 7 days before randomization 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.

6.4.5.5 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged haematological toxicities as defined in Section 5.5.5.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. Full reports must be provided by the investigator for documentation on the Patient Safety database.

6.4.6 Physical examination

For timing of individual measurements refer to the Study Schedule (see Table 1 and Table 2).

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

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

If being assessed within 7 days before randomization 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.

6.4.7 ECG

6.4.7.1 Resting 12-lead ECG

ECGs are required within 7 days prior to starting study treatment, at Week 9 (day 57) after starting study treatment, when clinically indicated and at the follow up visit after patient has discontinued study medication.

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. A copy of the ECG indicating the study number and E-code will be included in the study file.

6.4.8 Vital signs

Height will be assessed at screening only.

Weight will be assessed at screening and as clinically indicated at any other time.

Any changes in vital signs should be recorded as an AE, if applicable.

6.4.8.1 Pulse and blood pressure

Supine BP and pulse rate will be measured using a semi-automatic BP recording device with an appropriate cuff size, after patient has rested for at least 10 minutes and will be assessed on Day 1 of Cycle 1, D29 and then will be performed every 8 weeks relative to date of randomization, up to Week 40, then every 16 weeks until objective disease progression (within a window of +/- 7 days of the scheduled date).

If being assessed within 7 days before randomization 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.

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

6.4.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at screening and as clinically indicated at any other time.

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

6.4.9 Other Safety Assessments

6.4.9.1 Serum or urine pregnancy test

Two pregnancy tests on 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)

6.5.1 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 + -STO22 Questionnaires

HRQoL is important in gastric cancer because most patients are symptomatic when diagnosed and the disease is usually incurable. Patients who survived gastric cancer surgery may continue to suffer from symptomatic, nutritional or functional problems. Even when treatment improves overall or progression-free survival this benefit can be counterbalanced by the burden of treatment and or its potential effect on patients' HRQoL. (Ajani et al 2007).

In this study patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 + STO22 questionnaires. The EORTC QLQ-C30 questionnaire was developed to assess HRQoL (Aaronson et al 1993). It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al 1993) and has been used in gastric cancer trials (Ajani et al 2007).

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive and social); 3 multi-item symptom scales (fatigue, pain, nausea and vomiting); a 2-item global HRQoL scale; 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease.

The STO22 is a well-validated module developed specifically for patients with gastric cancer (Vickery et al 2001; Blazeby et al 2004) and has also been validated for use in Asian patients (Huang et al 2007; Morita et al 2008). It consists of 22 questions which can be grouped into 5 disease related multi-item symptom scales (dysphagia, eating restriction, stomach pain, reflux, anxiety) and 4 single items (dry mouth, body image, hair loss, taste problem).

All the EORTC scales range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, while a high score for a symptom scale / item represents a high level of symptomatology / problems.

QLQ-C30 + STO22 data will be self-reported through patient questionnaires according to the study plan. Patients will be asked to report their HRQoL over the course of the previous 7

days. All patients will be asked to complete the QLQ-C30 + -STO22. The QLQ-C30 + STO22 questionnaire will be administered at day 1 (visit 2), day 29 (visit 6) and then, from visit 10 onwards, on the 1st day of each 4 week treatment period. Patients will also complete it upon treatment discontinuation and at follow up 30 days after last dose. If the patient discontinues therapy for reasons other than RECIST progression, QLQ-C30 + -STO22 completion should continue until RECIST progression is confirmed.

6.5.2 EQ-5D-5L

Patient reported health state utility will be assessed using the EQ-5D-5L. The EQ-5D-5L is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care.

The instrument asks patients to respond to five different dimensions covering mobility, self-care, usual activities, pain/discomfort, anxiety/ depression, as well as rate how they feel on the day of assessment via a visual analogue scale.

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility. This exploratory analysis will be primarily used to support future economic evaluations of olaparib.

6.5.3 Administration of PRO questionnaires

Paper questionnaires will be given to the patient at baseline, Day 1 of each 4 week treatment period, then on treatment discontinuation and at follow up. If the patient discontinues therapy for reasons other than RECIST progression, the questionnaire should continue to be administered until progression has been confirmed (see Table 2). Patients are to complete the questionnaire during their clinic visit. The site staff can either enter the information directly into the WBDC (RAVE) electronic database system or arrange to have the paper questionnaires sent to the Data Management centre for entry into the WBDC (RAVE) database.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (e.g. a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AstraZeneca Study Team (or delegate) will provide relevant training in administration of the questionnaires. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- If possible, patients should be reminded to bring reading glasses to the clinic prior to the visit

- The PRO questionnaires should be completed in the following order, EORTC QLQ-C30, EORTC QLQ-STO22, EQ-5D-5L
- They must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions
- If the patient cannot complete the questionnaire, the reason for this should be provided on the title page of the questionnaire.
- They must be completed in private by the patient
- Patient should be provided with a clipboard and pen
- The patient should be given sufficient time to complete at their own speed
- The patient should not receive help from relatives, friends or clinic staff to answer the questionnaire. However, if the patient is unable to read the questionnaire (e.g.is blind or illiterate) the questionnaires may be read out by trained clinic staff and responses recorded
- On completion of the questionnaires they should be handed back to the person responsible for questionnaires who should check for completeness
- Only one answer should be recorded for each question

6.6 Pharmacokinetics

Pharmacokinetic sampling will be performed on day 1 in a subgroup of patients in order to deliver evaluable PK data from 20 olaparib treated patients who have had no previous gastric surgery, 20 olaparib treated patients who have had previous partial gastrectomy and 20 olaparib treated patients who have had previous full gastrectomy. In order to maintain the blind, samples will need to be collected from a total of at least 40 patients in each category. Samples from placebo dosed patients will not be analysed.

6.6.1 Collection of samples

Blood samples (2 mL) for determination of olaparib in plasma will be taken at the times on pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after first dose of study.

Results will be only reported for samples shipped within a timeframe for which the stability of olaparib in the samples has been validated and shown to be acceptable. Placebo samples will not be analyzed unless specified.

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

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

Samples for determination of olaparib concentrations in plasma will be analyzed by [redacted] AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

For each placebo patient, samples will only be analysed on a 'for cause' basis, eg, if no quantifiable concentrations were observed in a patient's samples when the drug was expected to be present.

6.7 Pharmacogenetics

6.7.1 Collection of pharmacogenetic samples

See Appendix G.

For blood volume see Section 7.1.

6.8 Health economics

The assessment of gastric cancer palliative interventions (resource use) will increase the understanding regarding the relationship between treatment impact on tumour and related cancer symptoms on resource use, such as the need for palliative procedures to address obstruction and bleeding.

As per the study plan (Table 2), procedures undertaken and the reason for the procedure should be captured as part of the “Concomitant Procedure” form that should be completed at each clinic visit whilst on study treatment. Where a patient discontinues study treatment prior to progression, procedures should continue to be collected at each clinic visit when they return for their RECIST assessment. This form will provide guidance on procedures of particular interest including gastrectomy, gastrostomy, jejunostomy, stenting, endoscopic ablation, and arterial embolization.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

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

Table 8 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples[a]	Total volume (mL)
Safety	Clinical chemistry	6[b]	10[c]	60
	Haematology	10[b]	10[c]	100
Biomarker blood sample		12	2	24
PK sample [d]		2	10	20
Pharmacogenetics		9	1	9
Total		39	33	213

(a) Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.
(b) These are approximate volumes that are patient to site-specific change.
(c) Number of samples is based on patients on average completing 4 cycles of combination therapy.
(d) Only 20 olaparib dosed patients in 3 sub-groups need be taken the PK sample. Detail in section 6.6.

7.2 Handling, storage and destruction of biological samples

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

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

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be anonymised by pooling or destroyed/disposed of. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report (CSR). Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

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

7.2.2 Pharmacogenetic samples

For information relating to the Pharmacogenetics sample see Appendix G.

7.3 Labelling and shipment of biohazard samples

The Principal investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual, see Appendix C 'IATA 6.2 Guidance Document'.

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

7.4 Chain of custody of biological samples

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

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

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

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

7.5 Withdrawal of informed consent for donated biological samples

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

As collection of the archival tumour samples is an integral part of the study, then the patient is withdrawn from further study participation.

As collection of serial tumour biopsies, biomarker and pharmacogenetic blood samples is an optional part of the study, then the patient may continue in the study.

The PI:

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

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

- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

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 International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

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

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

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

8.3 Ethics and regulatory review

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

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

The opinion of the EC should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

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

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

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

AstraZeneca will provide Regulatory Authorities, EC and PIs with safety updates/reports according to local requirements, including SUSARs (Suspected Unexpected Serious Adverse Reactions), where relevant.

Each Principal Investigator is responsible for providing the EC/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

This study consists of two ICFs, the main ICF that allows patient to participate in the mandatory part of the study and the optional ICF for the genetic testing ICF. The patient may participate in the main study without participating in the optional component. To participate in the optional component of the study, the patient must sign and date both the consent forms for the main study and the optional component of the study. The enrolment code must be obtained from IVRS/IWRS. Signed and dated original of both consent forms must be given to the patient and the second signed and dated original should be filed at the study centre. The PI(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue the optional biomarker aspect of the study at any time.

The PI(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, including information on any optional biomarker or pharmacogenetic sampling.

- 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 patient "E-code" has been entered on the ICF after enrolling the patient into the study by IWRS/IVRS.
- Ensure the original, signed ICF(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed ICF 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 ICF that is approved by an EC.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator and AstraZeneca.

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

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

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each PI(s). For distribution to EC see Section 8.3.

If a protocol amendment requires a change to a centre's ICF, AstraZeneca and the centre's EC are to approve the revised ICF before the revised form is used.

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

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an EC 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, GCP, guidelines of the (ICH, and

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

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 Clinical Study Agreement (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 (i.e. IVRS) and the WBDC system utilised.

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

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

9.3 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 (e.g., clinic charts).

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

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

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this CSP and the CSA, the terms of CSP shall prevail with respect to the conduct of the study and the treatment of 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 of the last visit of the last patient undergoing the study.

There will be a data cut-off (DCO) defined as the date of the last patient last visit relating to overall survival analysis of the data. 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 clinical benefit from treatment with olaparib. For patients who do continue to receive treatment beyond the time of this data cut-off, investigators will continue to report all SAEs to AstraZeneca Patient Safety until 30 days after study treatment is discontinued, in accordance with Section 6.4.3 (Reporting of Adverse Events). 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. Additionally as stated in Section 6.4.3 (Recording of adverse events), any SAE or non-serious adverse event that is ongoing at the

time of this data cut-off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. The study is expected to start in 3Q 2013 and to end by 4Q 2017.

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 with olaparib adversely affect the risk/benefit profile of the investigational product.

9.6 Post Study Access to Study Treatment

No plans to provide olaparib after completion of the study treatment.

10. DATA MANAGEMENT BY ASTRAZENECA

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.

AEs 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.

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.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca. Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database. In the case of biomarker (tumour tissue or blood for exploratory analyses) data, only the original date of biopsy (historical tumour tissue sample and the actual date the sample(s) were collected) will be recorded in the eCRF and database.

See Appendix G for data generated from the Pharmacogenetics sample.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA

A comprehensive statistical analysis plan (SAP) will be prepared before the first patient is entered.

11.1 Calculation or derivation of efficacy variable(s)

11.1.1 Overall Survival

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

Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO.

11.1.2 Secondary endpoints

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

11.1.2.1 Progression Free Survival (PFS)

PFS is defined as the time from randomization until the date of objective radiological disease progression according to RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. Given the scheduled visit assessment scheme, for the first 40 weeks from randomisation two missing visits will equate to more than 18 weeks since the previous RECIST assessment, allowing for early and late visits. After 40 weeks, two missing visits will equate to more than 34 weeks. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at day 1 unless they die within two visits of baseline (17 weeks allowing for visit window).

The PFS time will always be derived based on scan/assessment dates not visit dates.

RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

(a) Date of progression will be determined based on the **earliest** of the RECIST assessment/scan dates of the component that triggered the progression

(b) When censoring a patient for PFS the patient will be censored at the **latest** of the RECIST assessment/scan dates contributing to a particular overall visit assessment

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective progression is defined as at least a 20% increase in the sum of the diameters of the target lesions (compared to previous minimum sum) or an overall non-target lesion assessment of progression or a new lesion. For patients with no evidence of disease at baseline, following a complete radiological response to chemotherapy, progression is defined by the detection of new lesions on follow-up radiological assessments.

11.1.2.2 Objective response rate (ORR)

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix D. It is the best response a patient has had during their time in the study up until RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorisation of best overall response will be based on the RECIST criteria (Appendix D) using the following response categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

Best objective response will be determined programmatically based on the RECIST criteria.

For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment will be used. SD should be recorded at least 8 weeks +/- 1 week, i.e. at least 49 days (to allow for the assessment window), after randomisation. For CR/PR, the initial overall visit assessment which showed a response will use the latest of the dates contributing towards a particular overall visit assessment.

For patients whose progression event is death, BoR will be calculated based on data up until the last evaluable RECIST assessment prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurred ≤119 days (i.e. 16 weeks ± 7 days) after randomization then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred > 119 days (i.e. 16 weeks ± 7 days) after randomization then BoR will be assigned to the non-evaluable (NE) category.

Progression events that have been censored due to them being >126 days (i.e. 16 weeks ± 7 days) after the last evaluable assessment will not contribute to the BoR derivation.

A patient will be classified as a responder if the RECIST criteria for a CR or PR are satisfied at any time up to and including the defined analysis cut-off point. For each treatment group, the objective response rate (ORR) is the number of CR and PR divided by the number of patients in the group in the FAS with measurable disease at baseline. Only patients with PR

and measurable disease at enrolment can achieve an objective response of CR or PR, other permissible categories of BoR are NE, PD, SD.

Duration of response (DOR) will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a patient does not progress following a response, then their duration of response will use the PFS censoring date as the date at which that patient is censored for DOR.

The time to response is the time from randomization to the first onset of a confirmed objective tumour response.

11.2 Calculation or derivation of safety variable(s)

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECG. These will be collected for all patients. Appropriate summaries of these data will be presented as described in Section 12.2.3.5.

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

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

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 EORTC

The EORTC QLQ-C30 + STO22 will be scored according to the EORTC scoring manual (Fayers et al 2001). Each scale will be transformed to a 100 point scale as per the manual. Higher scores on the functional scales indicate a higher level of functioning and on the global HRQoL score indicate a better quality of life. Higher scores on the symptom scales/items indicate a higher symptom burden.

Time to deterioration of HRQoL will be derived using the 2-item global HRQoL scale. The time to deterioration will also be calculated for the following additional EORTC QLQ-C30 + STO22 symptom scores but these will be exploratory endpoints: nausea and vomiting score, STODYS (dysphagia) score, STOEAT (eating restriction) score, STOPAIN (stomach pain)

score, STOFX (reflux) score, STOANX (anxiety) score. In addition, the time to deterioration in the following multi-item functional scales of the EORTC QLQ-C30 will also be calculated as exploratory endpoints: physical, role, emotional, cognitive and social. The remaining symptom scores of the EORTC QLQ-C30 and STO-22will be reported descriptively. For each subscale, if less than 50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimised.

The population for analyses of time to deterioration of HRQoL (global HRQoL score) will include a subgroup of the FAS population who have baseline global HRQoL score ≥ 10.

A change of at least 10 points in the global HRQoL score will be considered as a clinically relevant or a minimally important difference (Table 9).

Table 9 Time to deterioration of Health Related QoL

Score	Change from baseline	Visit response
Global HRQoL score	Increase of 10 points or more	Improved
	Decrease of 10 points or more	Deterioration
	Otherwise	No change
Symptom scores: nausea and vomiting score,STODYS (dysphagia) score, STOEAT (eating restriction) score, STOPAIN (stomach pain) score, STOFX (reflux) score, STOANX (anxiety) score	Decrease of 10 points or more	Improved
	Increase of 10 points or more	Deterioration
	Otherwise	No change
Functional scales: physical, role, emotional, cognitive and social	Increase of 10 points or more	Improved
	Decrease of 10 points or more	Deterioration
	Otherwise	No change

The deterioration must be sustained for at least 21 days (i.e. there must be no response of "improved" or "no change" within 21 days of the visit response of "deterioration").

The criteria in Table 9 will be used to assign a best QoL response for HRQoL based on the 2-item global HRQoL score.

Table 10 Best QoL response

Overall score response	Criteria
Improved	Two visit responses of "improved" a minimum of 21 days apart without an intervening visit response of "deterioration"
No change	Does not qualify for overall score response of "improved". Two visit responses of either "no change" or "improved" and "no change" a minimum of 21 days apart without an intervening visit response of "deterioration"
Deterioration	Does not quality for overall score response of "improved". A visit response of "deterioration" without a response of "improved" or "no change" within 21 days
Other	Does not quality for one of the above

Time to deterioration of HRQoL will be defined as the time from date of randomization to the date of a clinically important deterioration in the global HRQoL score or death (by any cause) in the absence of a clinically meaningful symptom deterioration, provided death occurs within 2 EORTC assessment visits of the last EORTC assessment where the global HRQoL score could be evaluated, and regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to deterioration in HRQoL. Patients whose global HRQoL score has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last EORTC assessment where the global HRQoL score could be evaluated. Also, if the global HRQoL score deteriorates after 2 or more missed EORTC assessment visits or the patient dies after 2 or more missed EORTC assessment visits, the patient will be censored at the time of the last EORTC assessment where the global HRQoL score could be evaluated.

Overall compliance will be defined as the number of patients who provided both a baseline and at least one post baseline assessment for which there were sufficient data recorded for the visit to be evaluable for the global HRQoL score, divided by the number of patients randomized. Compliance over time is calculated separately for each visit, including baseline, as the number of patients providing an evaluable assessment for the global HRQoL score at that visit divided by the number of patients expected to have provided an assessment.

11.3.2 EQ-5D-5L (exploratory analysis)

The EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care.

The EQ-5D-5L index comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). For each dimension, respondents select

which statement best describes their health on that day from a possible five options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems and unable to/ extreme problems). A unique EQ-5D health state is referred to by a five digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the five dimensions. This data will be converted into a weighted health state index by applying scores from EQ5D value sets elicited from general population samples (the base case will be the UK valuation set, with other country value sets applied in scenario analyses). Where values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied. In addition to the descriptive system, respondents also assess their health today on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

Analysis will be conducted on the FAS population.

11.4 Analysis will be conducted on the FAS population. Calculation or derivation of pharmacokinetic variables

The pharmacokinetic (PK) analyses will be performed at AstraZeneca R&D. The actual sampling times will be used in the PK calculations. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined:

Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}) and area under the plasma concentration-time curve from zero to 12 hours (AUC_{0-12}) after the first dose of olaparib.

11.5 Calculation or derivation of pharmacodynamic variable(s)

Not applicable.

11.5.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Not applicable.

11.5.2 Population analysis of pharmacokinetic/pharmacodynamic variables

Not applicable.

11.6 Calculation or derivation of pharmacogenetic variables

Details refer to Appendix G.

11.7 Calculation or derivation of health economic variables

Resource use will be analysed from procedures captured on the concomitant procedure module and, where required, supplemented, with data on hospitalisation length of stay logged as part of SAE recording. Frequency of palliative interventions and the reasons for the intervention will be estimated from the Concomitant Procedure form. Analysis will be conducted on the FAS population.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA

12.1 Description of analysis sets

A comprehensive statistical analysis plan (SAP) will be prepared and finalised before first subject in (FSI).

Table 11 gives a summary of outcome variables and analysis populations.

12.1.1 Full analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib will include all randomized patients and will compare the treatment groups on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy and HRQoL data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.

ATM negative primary subgroup: The primary subgroup will include all randomized patients whose tumour was assessed as ATM negative by an immnohistochemistry test on the mandatory tumour samples.

12.1.2 Safety analysis set

All patients who received at least one dose of randomized investigational product, olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated patients (e.g. those randomized to treatment A but actually given treatment B) will be accounted for in the treatment group of the treatment they actually received.

12.1.3 PK Analysis set

PK data will be analysed according to treatment received. This population will comprise all patients who receive study treatment as per protocol and do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. The population will be defined by the Study Team Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

Table 11 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- OS	FAS (ITT), ATM negative subgroup
- PFS, ORR, symptom/HRQoL endpoints	FAS (ITT), ATM negative subgroup
Demography	FAS (ITT), ATM negative subgroup
Pharmacokinetic data	PK

Table 11 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Safety Data	
- Exposure	Safety, ATM negative subgroup
- AEs	Safety, ATM negative subgroup
- Lab measurements	Safety , ATM negative subgroup
- Vital Signs	Safety , ATM negative subgroup

12.2 Methods of statistical analyses

The treatment comparison is olaparib 100mg bd in combination with paclitaxel vs placebo in combination with paclitaxel. The primary endpoint is OS. There will be two primary analysis populations: the first will comprise all patients (overall population); the second will comprise all randomised ATM negative tumours patients. All endpoints will be analysed in the overall population and in the ATM negative primary subgroup unless otherwise stated.

All descriptive statistics will be presented by treatment group. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.

Baseline will be the last assessment of the variable under consideration prior to first dose intake, except for efficacy variables, for which baseline will be defined as the last pre-randomization assessment.

All data collected will be listed.

Efficacy data will be summarised and analyzed as randomised for the FAS (ITT) analysis set and the ATM negative subgroup on an ITT basis.

Safety data will be summarised and analysed by treatment received for the safety analysis set and the ATM negative subgroup of the safety analysis set.

Results of all statistical analysis will be presented using a 95% confidence interval and 2-sided p-value. The following table details which endpoints are to be formally analysed.

Table 12 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
OS	Primary analysis will be performed by Cox PH model adjusted for ATM status (ATM negative, ATM positive, ATM status unknown), country (Korea, Japan, China, Taiwan) and gastrectomy status at baseline (Full, partial, none) in FAS and ATM negative subgroup
	Sensitivity Analyses (in FAS):
	If enrichment is required, weighted estimate of the overall HR
PFS	Cox PH model adjusted for ATM status (ATM negative, ATM positive, ATM status unknown), country (Korea, Japan, China, Taiwan) and gastrectomy status at baseline (Full, partial, none) in FAS and ATM negative subgroup
	Sensitivity Analyses (in FAS and ATM negative subgroup):
	1) Evaluation time bias analysis; Cox PH model adjusted for potential prognostic factors
	2) Attrition bias analysis (using alternative censoring rules); Cox PH model adjusted for potential prognostic factors
ORR	Logistic regression model adjusted for ATM status (ATM negative, ATM positive, ATM status unknown), country (Korea, Japan, China, Taiwan) and gastrectomy status at baseline (Full, partial, none) in FAS and ATM negative subgroup
Time to deterioration in HRQoL	Cox PH model adjusted for ATM status (ATM negative, ATM positive, ATM status unknown), country (Korea, Japan, China, Taiwan) and gastrectomy status at baseline (Full, partial, none) in FAS and ATM negative subgroup

12.2.1 Multiplicity strategy for primary populations and interim analyses

As there are two primary populations the Hochberg approach will be used to adjust for multiple statistical testing of overall survival across the two populations to maintain the overall type I error rate of 5% (Hochberg 1988). Correlation between the two populations is not accounted for in this approach and consequently the adjustment for multiple testing will be conservative. In this Hochberg approach 50% of the test mass (alpha) will be assigned to

testing in the overall population (overall type I error rate of 2.5%) and 50% to testing in the ATM negative subgroup (overall type I error rate of 2.5%). The Hochberg procedure will be implemented as follows:

Calculate the p-values for the OS treatment comparison for both the overall population and the ATM negative subgroup.

Order the p-values (p1, p2) from smallest to largest.

If the largest p-value (p2) ≤ 0.05 the null hypotheses associated with both p2 and p1 are rejected.

If the largest p-value (p2) > 0.05 then do not reject the corresponding hypothesis (one of the populations does not reject the associated null hypothesis), and then test the other population at the 2.5% level (half of the original 5% starting level).

Under point 4, if p1 ≤ 0.025 then the null hypothesis is rejected in the corresponding population. If p1 >0.025 the null hypothesis is not rejected in the corresponding population.

The multiplicity strategy for the three key secondary endpoints of PFS, ORR and time to deterioration in HRQoL will be implemented as follows:

1. The key secondary endpoints will be tested independently (assuming at least one OS hypotheses is rejected).

2. If both hypotheses for the ITT population and ATM negative subgroup for OS are rejected, then PFS will be tested for both the ITT population and ATM negative subgroup (as above for OS and starting at the 5% level using the Hochberg procedure). This will be repeated separately for ORR and time to deterioration in HRQoL.

3. If only the ATM negative subgroup hypothesis is rejected for OS, then PFS will be tested for the ATM negative subgroup only (at the 2.5% level). This will be repeated separately for ORR and time to deterioration in HRQoL.

4. If only the overall population hypothesis is rejected for OS, then PFS will be tested for overall population only (at 2.5% level). This will be repeated separately for ORR and time to deterioration in HRQoL.

12.2.2 .Analysis of primary endpoint

OS will be analysed when the later of approximately 391 deaths in the overall population or 49 deaths in the ATM negative subgroup have occurred. The final analysis in the ITT population will include all randomised patients enrolled into the study (regardless of ATM negative patient enrichment should it be required). No further analyses of OS are planned beyond this point unless requested by Health Authorities.

OS will be analysed using a Cox proportional hazards model adjusted for ATM status (as a 3 level factor: negative, positive and unknown), country and gastrectomy status at baseline (as a 3 level factor: full, partial and no gastrectomy) in the overall population and country and gastrectomy status at baseline in the ATM negative primary subgroup. The Cox proportional hazards model will be fitted using PROC PHREG in SAS using the Efron approach for handling ties. The confidence interval will be estimated using a profile likelihood approach. The p-value will be based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model including the pre-specified covariates.

The HR (olaparib vs placebo) together with its corresponding confidence interval (CI) and p-value will be presented (a HR less than 1 will favour olaparib). In both the overall population and the ATM negative subgroup 97.5% CIs will be presented. The statistical significance will be determined based on the p-values observed and not whether or not the CI excludes 1.

A Kaplan-Meier plot of OS will be presented by treatment group. Summaries of the median OS for each treatment will be produced.

The assumption of proportionality will be assessed. Note that in the presence of non-proportionality, the HR will be interpreted as an average HR over the observed extent of follow-up. Proportionality will be tested firstly by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, a time dependent covariate would be fitted to assess the extent to which this represents random variation.

The proportion of patients alive at 6 months and 12 months will be summarised (using the KM curve) and presented by treatment group.

The number of patients prematurely censored will be summarised by treatment arm together with baseline prognostic factors of the prematurely censored patients. A patient is defined as prematurely censored if their survival status was not known on or after the data-cut off date.

Subsequent therapies received after discontinuation of study treatment will be summarised.

Exploratory subgroup analyses will be conducted comparing OS between treatments in the following subgroups of the overall population:

- ATM status (Negative/Positive/Unknown)
- Country (Korea/Japan/China/Taiwan)
- Gastrectomy status at baseline (full/partial/none)
- Extent disease (locally advanced/metastasis)
- Measurability (measurable disease /non-measurable disease)
- Performance Status (0/1)

- Type (intestinal/diffuse/mixed or unknown)
- Number of metastatic sites at baseline (1-2/>2)
- Primary disease site (stomach/GEJ mass)
- Sex (male/female)
- Age (<60/≥60)
- Previous platinum treatment response (CRIPR vs SD vs PD)
- ATM null (complete absence of measured ATM protein in archival tumour)

Other baseline variables may also be assessed if there is clinical justification. For each subgroup, the HRs (olaparib + paclitaxel: placebo + paclitaxel) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term and the pre-specified covariates. The treatment effect HRs for each treatment comparison along with their confidence intervals will be obtained for each level of the subgroup from this single model. The HRs and 95% CIs will be presented on a forest plot including the HR and 95% CI from the overall population (using the primary analysis).

The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analysed. In this case, only descriptive summaries will be provided.

No adjustment to the significance level for testing will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of OS.

The presence of quantitative interactions will be assessed by means of an overall global interaction test. This will be performed in the overall population by comparing the fit of a Cox proportional hazards model including treatment, all covariates, and all covariate-by-treatment interaction terms, with one that excludes the interaction terms and will be assessed at the 2-sided 10% significance level. If the fit of the model is not significantly improved then it will be concluded that overall the treatment effect is consistent across the subgroups.

If the global interaction test is found to be statistically significant, an attempt to determine the cause and type of interaction will be made. Stepwise backwards selection will be performed on the saturated model, whereby (using a 10% level throughout) the least significant interaction terms are removed one-by-one and any newly significant interactions re-included until a final model is reached where all included interactions are significant and all excluded

interactions are non-significant. Throughout this process all main effects will be included in the model regardless of whether the corresponding interaction term is still present. This approach will identify the factors that independently alter the treatment effect and prevent identification of multiple correlated interactions.

Any quantitative interactions identified using this procedure will then be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail and Simon 1985).

12.2.2.1 Sensitivity Analyses for Primary Endpoint

A Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS analysis is reversed will be produced to assess attrition bias (i.e. whether there is an imbalance in censoring for OS).

If enrichment for ATM negative patients is required then a sensitivity analysis of OS will be conducted in which a weighted estimate of the overall HR (*HRoverall*) will be calculated using the estimated HR in the ATM negative subgroup

(*HRATM negative*), the estimated HR in the ATM positive subgroup (*HRATM positive*) and the estimated HR in the ATM unknown subgroup (*HRATM unknown*):

ln(HRoverall) = w1ln(HRATM negative) + w2ln(HRATM positive) + w3ln(HRATM unknown) where weights w1 , w2 and w3 (proportion of ATM negative patients, ATM positive patients and ATM unknown patients, respectively) will be estimated from the patients enrolled prior to enrichment occurring (i.e. in the non-enriched portion of the trial).

For calculation of confidence intervals, the overall variance (log scale) will take into account the variance of all groups (that are independent), and thus be calculated as:

$$var(ln(HRoverall)) = w1^2 var(ln(HRATM\ negative)) + w2^2 var(ln(HRATM\ positive)) + w3^2 var(ln(HRATM\ unknown))$$

The 100(1-α) % confidence interval will be calculated as:

$$exp[\ ln(HRoverall) \pm Z1\text{-}\alpha/2 \sqrt{}\ var(ln(HRoverall))]$$

The weighted hazard ratio (HR; olaparib + paclitaxel: placebo + paclitaxel) for treatment will be estimated together with two-sided 95% and 97.5% confidence intervals. If there are less than 20 events in the ATM unknown subgroup then the ATM positive subgroup and ATM unknown subgroup will be combined.

12.2.2.2 Exploratory Analyses for Primary Endpoint

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of the patients have crossed over. Methods such as Rank Preserving Structural Failure Time (RPSFT) (Robins et al 1991), inverse probability of censoring weighting (IPCW) (Robins 1993) and other methods in development will be explored. The decision to adjust and final choice of methods will be

based on a blinded review of the data and the plausibility of the underlying assumptions. Baseline and time-dependent characteristics will be explored, and summaries of baseline characteristics will be summarised for placebo patients, splitting between those that have and haven't switched at the time of the analyses. Further detail will be provided in the SAP and payer analysis plan.

12.2.3 Analysis of secondary endpoints

12.2.3.1 Progression-free survival (PFS)

PFS data will be analysed at the time of the analysis of OS and will use the same methodology and model.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (i.e. differential assessment times between treatment groups).

Summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment group.

(a) Evaluation-Time bias

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analysed using a Cox proportional hazards model, as described for the primary analysis of PFS. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010).

(b) Attrition bias

Attrition bias will be assessed by repeating the primary PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

Additionally a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be produced.

12.2.3.2 Objective response rate (ORR)

Objective response rate based on the investigator's assessment of RECIST will be analysed using logistic regression adjusted for the following covariates: ATM status, country and gastrectomy status at baseline (as a 3 level factor: full, partial and no gastrectomy) in the overall population and country and gastrectomy status at baseline in the ATM negative primary subgroup. The results will be expressed in terms of an odds ratio and its associated confidence interval and p-value. The p-value will be based on twice the change in log-

likelihood resulting from the addition of the treatment factor to the model that contains the specified covariates. Confidence intervals will be profile likelihood intervals.

The median duration of response and median time to response based on the investigator's assessment of RECIST will be summarised. Only patients who had a response will be included in these summary tables.

For each treatment arm, best objective response (BoR) will be summarised by n (%) for each category (CR, PR, SD, PD, NE). No formal statistical analyses are planned.

12.2.3.3 Analysis of PRO endpoints

The analysis population for HRQoL data will be the subgroup of the FAS (ITT) who have evaluable HRQoL data at the timepoints under study and who have baseline HRQoL scores ≥ 10.

Time to deterioration of HRQoL will be analysed using the same methodology and model as described for the primary analysis of OS. A sensitivity analyses will be performed to assess the impact of attrition bias.

Summary tables of the global HRQoL score best change rates (improvement, worsening, and no change) will be provided. Absolute values and change from baseline for the global HRQoL score will be summarised and plotted over time. Compliance overall and over time will be summarised by randomized treatment.

Supportive exploratory analyses will be performed for the following EORTC symptom scores for time to worsening: nausea and vomiting score, STODYS (dysphagia) score, STOEAT (eating restriction) score, STOPAIN (stomach pain) score, STOFX (reflux) score and STOANX (anxiety) score. In addition, the time to deterioration in the following multi-item functional scales of the EORTC QLQ-C30 will also be analysed as exploratory endpoints: physical, role, emotional, cognitive and social. Treatment estimates and 95% CI for each subgroup will be presented on forest plots. P-values will not be calculated for these supportive analyses.

The remaining symptom scores of the EORTC QLQ-C30 and STO-22 will be reported descriptively.

12.2.3.4 Pharmacokinetic analysis

The PK analysis set is defined in Section 12.1.3. The Cmax, Tmax and AUC_{0-12} data will be summarised by gastrectomy status and presented graphically. No formal statistical analysis will be performed.

12.2.3.5 Safety data

Safety and tolerability data will be presented by treatment received in the overall population. Summaries may be repeated in the primary subgroup if required. Appropriate summaries of these data will be presented. Safety and tolerability will be assessed in terms of AEs,

laboratory data and vital signs, which will be collected for all patients. AEs (both in terms of MedDRA preferred terms and CTCAE grade), laboratory data and vital signs data will be listed individually by patient and summarised by treatment received. For patients who have a dose modification, all AE data (due to toxicity or otherwise) will be assigned to the initial treatment received group. Vital signs data will be listed for each patient and changes in vital signs will be summarized for each treatment group.

12.2.4 The remaining symptom scores of the EORTC QLQ-C30 and STO22 will be reported descriptively.Exploratory endpoints analyses

Full statistical methods for exploratory endpoints will be defined in a separate analysis plan.

12.2.4.1 EQ-5D-5L

Descriptive statistics, graphs and listings will be reported for health state utility index values and visual analogue scale by visits as well as change in these scores from baseline. To support future economic evaluations of olaparib, additional appropriate analyses may be undertaken, for example, mean health state utility pre and post treatment, and pre and post progression.

12.2.4.2 Health economics

An exploratory health economic analysis of the frequency of gastric cancer related palliative interventions, time to interventions and reason for the intervention will be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of olaparib.

12.2.5 Interim analyses

No interim efficacy analyses will be performed.

Futility analyses will be based on the overall population and the ATM negative subgroup of patients.

12.3 Determination of sample size

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

The primary endpoint of the study is OS.

This study has two primary populations: all randomized patients and all randomized ATM negative patients. The study is sized on a hazard ratio of 0.7 (as observed in study 39 for the weighted analysis of OS) in the overall population assuming a 90% power and a 2.5% alpha with 1:1 randomization, which requires 391 deaths and a hazard ratio of 0.8 or lower would achieve statistical significance ($p \leq 0.025$) in the overall population. Assuming non-linear recruitment and no enrichment of ATM negative patients is required, if 500 patients are recruited in 2 years and assuming an 8 month median in the comparator arm, the study is expected to take approximately 37 months to complete.

A minimum of 70 ATM negative patients will be randomised in total. The ATM negative subgroup is sized on a hazard ratio of 0.35 assuming a ≥90% power and a 2.5% alpha, which requires 49 deaths and a hazard ratio of 0.53 or lower would achieve statistical significance ($p \leq 0.025$) in the ATM negative subgroup.

The overall sample size will depend on the amount of enrichment that is required (enrichment of up to approximately 30 ATM negative patients will be permissible).

12.4 Data monitoring committee

This study will use an external IDMC to perform periodic assessments of accumulating safety data. This committee will be composed of therapeutic area experts and statisticians, who are not employed by AZ, and do not have any major conflict of interest.

Following the review the IDMC will recommend whether the study should continue unchanged, be terminated, or be modified in any way. Once the IDMC has reached a recommendation, a report will be provided to AstraZeneca. The report will only include the recommendation and any potential protocol amendments and will not contain any unblinding information.

A separate IDMC charter will be developed which will contain details of the IDMC members and clearly define the responsibilities of the IDMC.

The safety of all AstraZeneca clinical studies is closely monitored on an-ongoing basis by AstraZeneca representatives in consultation with the Patient Safety Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to Investigators.

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 Team Leader. If the Study Leader is not available, contact the Study Physician at AstraZeneca Research and Development site shown below.

Name	Role in the study	Address & 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** 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 or matching placebo should be discontinued immediately.

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the 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** i.e. immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies

The same timelines apply when outcome information is available.

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

13.3.2 Paternal exposure

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

Pregnancy of the patient's partners is not considered to be an AE. 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 three months after the last dose should be followed up and documented.

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Clinical Study Protocol Appendix B

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00004
Edition Number	2
Date	[redacted]

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

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

Hospitalisation

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

Important medical event or medical intervention

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

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

Examples of such events are:

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

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

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

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

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

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

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

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

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

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

- Is there a known mechanism?

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

Clinical Study Protocol Appendix C

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00004
Edition Number	2
Date	[redacted]

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

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

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

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

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

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

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/Documents/Guidance-Document-Infectious-Substances.pdf)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

AstraZeneca

Clinical Study Protocol Appendix D	
Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00004
Edition Number	2
Date	[redacted]

Appendix D
Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

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LIST OF TABLES

1. INTRODUCTION

This appendix details the implementation of RECIST 1.1 Guidelines (Eisenhauer et al 2009) for the D081BC00004 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 imaging (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 <15mm short axis at baseline*).

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

Previously irradiated lesions**

Skin lesions assessed by clinical examination

Brain metastasis

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

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

Special Cases:

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

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

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

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

3. METHODS OF ASSESSMENT

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

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

Table 1 Summary of Methods of Assessment

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

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 D081BC00004 study it is recommended that CT examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (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 D081BC00004 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 D081BC00004 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 D081BC00004 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 D081BC00004 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 D081BC00004 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 D081BC00004 study tumour markers will not be used for tumour response assessments as per RECIST 1.1.

3.7 Cytology and histology

In the D081BC00004 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 D081BC00004 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 D081BC00004 study FDG-PET scans will not be used for assessment of tumour response as FDG-PET evaluations do not form part of the RECIST framework.

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 (see Study Schedule from Study Protocol) before the date of randomization. Follow-up assessments will be performed every 8 weeks (+/- 1 week) after randomisation, up to week 40, then every 16 weeks (+/- 1 week) (see Study Schedule from Study Protocol) until objective disease progression as defined by RECIST v1.1. 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 5mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention e.g. radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

4.2.2 Evaluation of target lesions

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

Table 2 Evaluation of target lesions

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

4.3 Non-Target lesions (NTL)

4.3.1 Evaluation of non-target lesions

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

Table 3 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL
Progression (PD)	Unequivocal progression of existing non-target lesions. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.

Table 3 Evaluation of Non-Target Lesions

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

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

4.4 New Lesions

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

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

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

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

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of Overall Visit Response

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

Table 4 Overall Visit Response

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

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if three are no TL/NTLs at baseline).

5. SPECIFICATIONS FOR RADIOLOGICAL IMAGING

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

5.1 CT Scan

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

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

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

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

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

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

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not “selected” images of the apparent lesion.

5.2 MRI Scan

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

possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

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

6. REFERENCES

Eisenhauer et al 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 E

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00004
Edition Number	2
Date	[redacted]

Appendix E
Acceptable Birth Control Methods

ACCEPTABLE BIRTH CONTROL METHODS

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

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

Acceptable Non-hormonal birth control methods include

- Total sexual abstinence. Abstinence must be for the total duration of the trial and the drug washout period.
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion plus male condom with spermicide.
- IUD plus male condom + spermicide. Provided coils are copper-banded.

Acceptable hormonal methods

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

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

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Table 1 ECOG/Karnofsky Scale

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

Clinical Study Protocol Appendix G

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC00004
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Appendix G
Pharmacogenetics Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical Study Report
DNA	Deoxyribonucleic acid
LIMS	Laboratory Information Management System
PGx	Pharmacogenetics

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic research in the olaparib clinical development programme to explore how genetic variations may affect the clinical parameters associated with olaparib and/or agents used in combination or as comparators. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Examples of genes that may be looked at are those encoding metabolising enzymes and transporter proteins. Genotyping participants in this study may provide an understanding of any observed variation in pharmacokinetics or clinical response.

Further research may suggest other genes as candidates for influencing not only response to olaparib but also susceptibility to cancer. Thus, this genetic research may involve study of additional un-named genes, but only related to disease susceptibility and drug reaction.

It is emphasised that AstraZeneca will only look for markers within genes relevant to the mode of action of, and response to olaparib and/or agents used in combination or as comparators, and gastric cancer under study within the current Clinical Study Protocol. No other research will be performed on the samples.

2. GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to olaparib and/or agents used in combination and/or as comparators and/or susceptibility to or prognosis of cancer.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

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

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

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

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample for genetic research will be obtained from the subjects at Visit 2 after randomisation. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at visit 2, it may be taken at any visit until the last study visit.

Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.3 Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

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

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

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

4.2 Subject data protection

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

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

5. DATA MANAGEMENT

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

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

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

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

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

7. LIST OF REFERENCES

None.

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Clinical Study Protocol Appendix H

Drug Substance	Olaparib (AZD2281)
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Appendix H
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

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1. INTRODUCTION

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

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

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

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **and** Total Bilirubin (TBL) ≥ 2xULN at any point during the study irrespective of an increase in Alkaline Phosphatase (ALP). The elevations do not have to occur at the same time or within a specified time frame.

Hy's Law (HL)

AST or ALT ≥ 3x ULN **and** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug. The elevations do not have to occur at the same time or within a specified time frame.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment in the presence of liver metastases (See Section 6)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there **is** an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT

This section is applicable to patients who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  - If there is no significant change no action is required

  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

At the first on study treatment occurrence of PHL criteria being, even if there has been no significant change the patient's condition[#] compared with pre-study treatment visits, the Investigator will:

- Notify the AstraZeneca representative who will inform the central Study Team.
- Follow the subsequent process described is Section 4.2 of this Appendix.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease << or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Section 6 >>?

If No: follow the process described in Section 4.2 of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

8. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Clinical Study Protocol Appendix I

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Appendix I
EORTC QLQ-30 + -STO22 Health Related Quality of Life Questionnaire Samples

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

Clinical Study Protocol Appendix J

Drug Substance	Olaparib (AZD2281)
Study Code	D081BC0004
Edition Number	2
Date	[redacted]

Appendix J
EQ-5D-5L Questionnaire

Health Questionnaire

English version for the UK

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
- 0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐