Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317-27. DOI: 10.1056/NEJMoa1903387

Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer

Supplement to: Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, including summary of changes.

Clinical Study Protocol

Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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

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

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

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Study centre(s) and number of patients planned: Approximately 80 centres worldwide will be initiated to randomise approximately 145 patients with germline *BRCA1/2* mutations and metastatic adenocarcinoma of the pancreas (hereafter referred to as pancreas cancer). Additional countries and centres may be added dependent on recruitment rates.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2014	III
Estimated date of last patient completed	Q2 2017	

Besides the main study, an exploratory study looking at the feasibility of assaying for and determining the prevalence of tumour tissue biomarkers (including but not limited to somatic *BRCA1/2* mutations, methylation and/or other HRD biomarkers) will be done on tissue samples submitted by patients screened for *gBRCA*. The information from this exploratory analysis may potentially guide future pancreas cancer Olaparib studies.

Objectives

Primary Objective:	**Outcome Measure:**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS)	• Progression Free Survival (PFS) by BICR using modified RECIST 1.1

Secondary Objective:	**Outcome Measure:**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo	• Overall Survival (observed and predicted using observed PFS and OS data) • Time from randomisation to second progression (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST). • Time from randomisation to study treatment discontinuation or death (TDT) • Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients • Disease Control Rate at 16 weeks by BICR using modified RECIST 1.1 criteria
• To assess the effect of Olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.	• Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire

Safety Objective:	**Outcome Measure:**
• To assess the safety and tolerability of Olaparib maintenance monotherapy	• Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

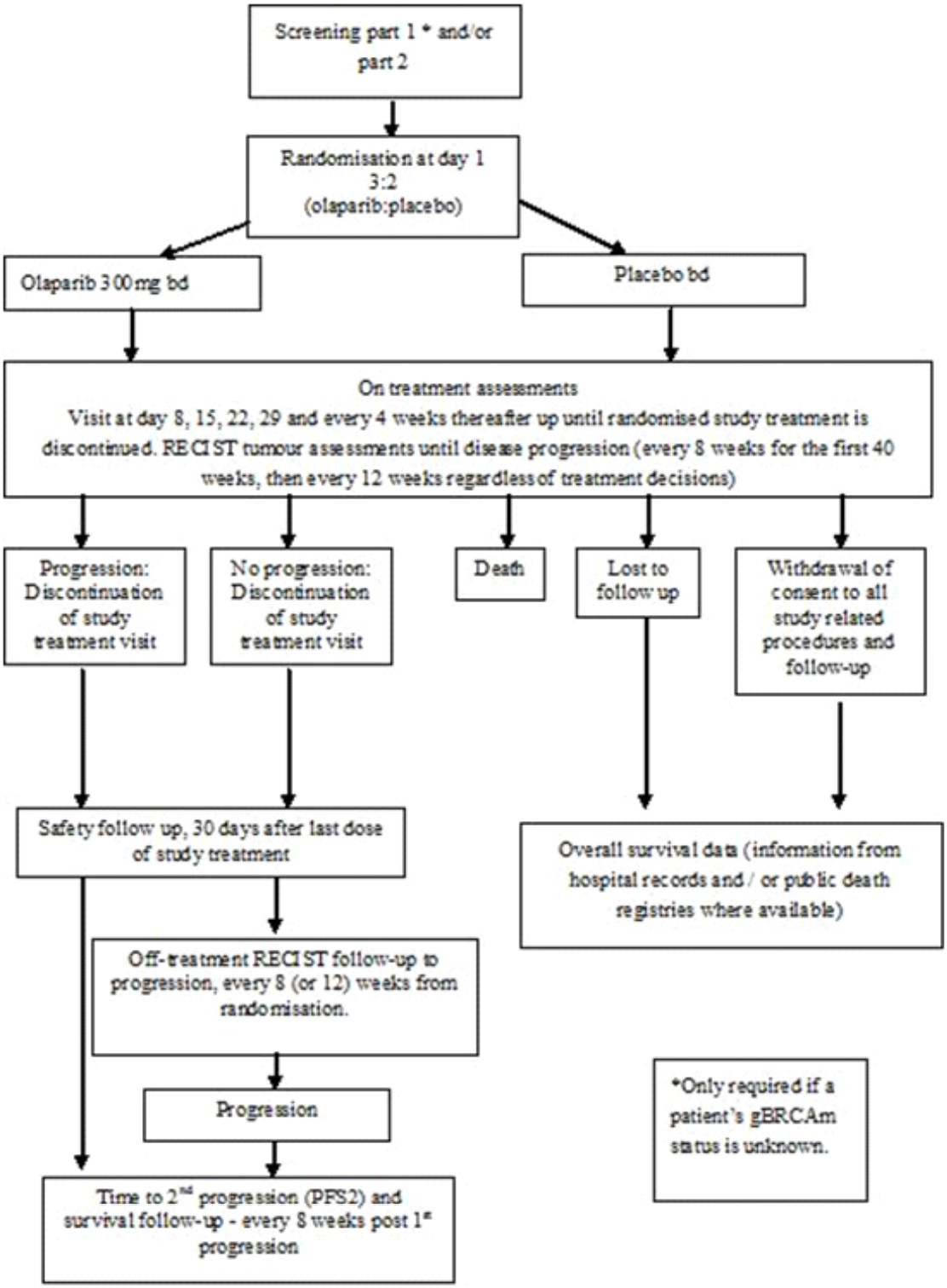
Exploratory Objective:	**Outcome Measure:**
• To assess the effect of Olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical,	• Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 + PAN26

role, cognitive, emotional and social). • To assess the effect of Olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales. • To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice • To assess change in performance status as measured by the ECOG Performance Status scale	symptom scales and items (pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice and on performance status measured by the ECOG Performance Status scale
• To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D
• To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals)
• To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.	• BRCA1 and/or BRCA2 mutation status in tumour
• To identify tumour tissue based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRCA methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches	• Potential tissue biomarkers identified

for development • Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.	

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

Study Flow Chart



Target Patient population

All patients randomised in the study will be selected based on the following 2 principles:

- **Genetic selection**: Documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients with g*BRCA1* and/or g*BRCA2* mutations that are considered to be non detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism," etc) will not be eligible for the study.

- **Treatment setting:** All eligible patients must have metastatic *gBRCAm* pancreas cancer, must have received a minimum of 16 weeks of platinum based treatment and must have no evidence of progression based on investigator's opinion. Study treatment will be started after randomisation as soon as possible but no less than 4 and no more than 8 weeks after last dose of first line chemotherapy. Tumour response during study treatment will be assessed using modified RECIST 1.1. Baseline assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis and should be performed no more than 28 days prior to start of study treatment, and as close as possible to randomisation. Follow-up assessments should be performed every 8 weeks (±1 week) for 40 weeks and then every 12 weeks ± 1 week relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1.

An exploratory study looking at the feasibility of assaying for and determining the prevalence of tumour tissue biomarkers (including but not limited to somatic *BRCA1/2* mutations, methylation and/or other HRD biomarkers) will be done on tissue samples submitted by patients screened for *gBRCA*. The information from this exploratory analysis may potentially guide future pancreas cancer Olaparib studies.

After confirmation of eligibility, patients will be randomised (using an IVRS) in a 3:2 ratio (Olaparib:placebo) to the treatments as specified below:

- Olaparib tablets po. 300 mg twice daily

- Placebo tablets twice daily

Investigational product, dosage and mode of administration

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of Olaparib. Patients will be administered study treatment orally at a dose of 300 mg twice daily (bid). The planned dose of 300 mg bid will be made up of two x 150 mg tablets bid with 100 mg tablets used to manage dose reductions.

Comparator, dosage and mode of administration

Placebo will be available as green film-coated tablets matching the Olaparib tablets. These should be taken as per instructions for Olaparib tablets.

Duration of treatment

Patients should continue to receive study treatment until objective radiological disease progression per modified RECIST 1.1 as assessed by the investigator or unacceptable toxicity and they do not meet any other discontinuation criteria. Patients who are determined to have progressed according to modified RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review one additional RECIST assessment will be requested preferably at the next scheduled RECIST visit. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. It is expected that many if not most patients will be restarted on a platinum based regimen at progression on study therapy. Whatever the regimen, they will be assessed for PFS2 and followed for survival.

Statistical methods

Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately 89 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for superiority and futility will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events). The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and 2.26% alpha (1-sided) (accounting for a single interim PFS analysis), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo. At the interim analyses, 0.5% of alpha (1-sided) will be spent, and controlling the type I error across the two time points, 89 PFS events will be required at the final analyses.

Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. Assuming 45 PFS events at the interim, a HR ≤ 0.46 would equate to a 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26% (Stone 2010). Assuming 89 PFS events, a HR ≤ 0.65 would equate to a 1-sided p-value <0.0226.

Assuming that the study accrual period will be approximately 15 months, 89 progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that 45 PFS events will occur approximately 13 to 14 months after the first patient enters the trial.

Patients are to be followed for the final analysis of OS (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 2.5% level (1-sided) if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6 month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

The primary statistical analysis of the efficacy of Olaparib will include all randomised patients (Full Analysis Set; FAS) and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. In addition, key sensitivity analyses of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a g*BRCA* mutation confirmed by the Myriad test. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (Olaparib or placebo). The safety data will be summarised descriptively and will not be formally analysed.

PFS will be analysed using a log rank test. The HR together with its 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib). The primary analysis will be based on a blinded independent central review (BICR) of disease progression by modified RECIST 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

Subgroup analyses will be conducted to assess consistency of treatment effect across potential prognostic factors (see Section 8.8.2 for all predefined subgroups). An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (ie, if there are less than 20 events in a subgroup).

OS analyses will be performed at the same time as the interim (if PFS null hypothesis rejected) and final analysis of PFS and will use the same methodology and model as PFS. A final analysis of OS will be performed when approximately 106 death events have occurred and a multiplicity adjustment will be made to account for the different analyses. At the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data.

Exploratory analyses of OS which attempt to adjust for any potential confounding impact of subsequent use of PARP inhibitors on the control arm may be performed if an appropriate proportion of patient's on the control arm receive such treatments and sufficient information is collected on subsequent therapy use.

PFS2 analyses will be performed at the same time as the interim and final analyses of PFS, and at the time of the final analysis of OS. PFS2 will be analysed using the same methodology and model as PFS.

In order to describe the nature of the benefits of Olaparib maintenance treatment, PFS, PFS2 and OS will be tested at a 1-sided significance level of 2.5%. However, in order to strongly control the type I error, a multiple testing procedure will also be employed where PFS is tested first using the full test mass and OS will be tested if the null hypothesis for PFS is rejected.

Secondary analyses of time to treatment discontinuation, time to first subsequent therapy or death, and time to second subsequent therapy or death will be provided, using the same methodology as specified for the primary analyses of PFS; however no multiplicity adjustment will be applied as these are viewed as supportive endpoints.

Objective tumour response rates and disease control rates (based on central review) will be summarised for the two treatment arms. In addition, the investigator reported response rates will also be summarised.

Patient Reported Outcomes

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales. Time to global QoL and pancreatic pain scale deterioration will be analysed using the same methodology and model as described for the primary analysis of PFS. Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model.

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

As supportive analyses, change from baseline in global QoL and pancreatic pain scale scores will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit.

Health Economics

An exploratory health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance. For utility, descriptive statistics, graphs and listings will be reported for health state utility by visit 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.

Biomarkers

The most important biomarker research will be done on non-randomised and randomised patients. Screened patients will submit tumour samples for t*BRCA/BRCA* methylation/ HRD analyses. A combination of evaluability, prevalence and sensitivity for

known g*BRCA* will be used to determine the feasibility of investigating Olaparib in future studies.

Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

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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 6.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboblastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BICR	Blinded Independent Central Review
bid	Bis in die (twice daily)
BoR	Best Overall RECIST Response
BP	Blood pressure
gBRCA	germline Breast Cancer susceptibility gene
BRCA mutation or *BRCAm*	Breast Cancer susceptibility gene mutation (see *gBRCA* mutation or *gBRCAm*)
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	ductal carcinoma in situ

DCO	Data Cut Off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DSB	Double strand break
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic Case Report form
EORTC QLQ-C30	The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients
EORTC QLQ-PAN26	The EORTC QLQ-PAN26 module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes)
EQ-5D-5L/ EQ-5D	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle stimulating hormone
gBRCA mutation or *gBRCAm*	The term "*gBRCA* mutation" is used to refer to a germline *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
gBRCA wt	gBRCA wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GRand	AZ Global Randomisation system
Hb	Haemoglobin
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus

HR	Hazard Ratio
HRD	Homologous recombination repair deficiencies
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IPCW	Inverse Probability of Censoring Weighting
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan Meier
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
m	Metre
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
mg	Milli-gram
MRI	Magnetic resonance imaging
nab	nanoparticle albumen bound
NCI	National Cancer Institute
NE	Not evaluable
NTL	Non-target lesions
OAE	Other Significant Adverse Event (see definition in Section 8.4.1)
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation

PD	Progressive disease
PFS	Progression Free Survival
p.o.	Per os (by mouth, orally)
PR	Partial response
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious adverse event (see definition in Section 6.2).
SAP	Statistical Analysis Plan
SD	Stable disease
SSB	Single strand break
SUSARs	Suspected Unexpected Serious Adverse Reactions
Study treatment	Olaparib or control arm chemotherapy
tBRCA mutation or *tBRCAm*	The term "*tBRCA* mutation" is used to refer to a somatic tumour *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
TL	Target lesions
US	United States
WBC	White blood cells
WBDC	Web Based Data Capture
wt	Wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Pancreas cancer and its treatment

Pancreas cancer is a life-threatening disease and is the fourth leading cause of cancer death in the West. In 2013, it is estimated that there were 45,220 newly diagnosed pancreas cancer cases in the US, and approximately 38,460 people deaths from pancreas cancer (American Cancer Society 2013). Worldwide, it was estimated that 266,000 people died of pancreas cancer in 2008 (Jemal A et al 2011).

The poor prognosis of pancreas cancer (~90% of patients who are diagnosed will die of the disease) is a function of late presentation of the disease when inoperable/ locally advanced or metastatic. Furthermore treatment of metastatic pancreas cancer even with the most "active" regimens such as FOLFIRINOX (Conroy et al 2011) or gemcitabine + nab paclitaxel (Von Hoff et al 2013) is associated with median survivals of less than one year, and for single agent treatments at best only 6 months. Unfortunately the toxicity of the most active combination chemotherapy regimens limits the duration of exposure to patients even if benefiting from the treatment. The neurotoxicity of both FOLFIRINOX and gemcitabine + nab paclitaxel in the former case generally leads to discontinuation of some or all of the drugs at or before 6 months of treatment and in the later case dose attenuation. The FOLFIRINOX study recommended no more than a total of 6 months of chemotherapy for patients who had a response (Conroy et al 2011).Furthermore there are few if any established second line regimens available (American Cancer Society 2013) and benefit if any, is at most a few months of survival (Rahma et al 2013). Despite the development of more "active" regimens for first treatment of metastatic pancreatic cancer in the last decade, their limited absolute benefit and significant toxicity strongly suggest that improving the results of initial therapy of metastatic pancreas cancer constitutes an unmet medical need. Furthermore to date there has been no marker, clinical or molecular that would predict for increased likelihood of benefit from systemic therapies for pancreas cancer.

Although carriers of deleterious germline mutations of the *BRCA1* and particularly *BRCA2* gene are known to have an increased risk of developing pancreas cancer (The Breast Cancer Linkage Consortium 1999, Goggins M. et al 1996), the prevalence of g*BRCA*m in the unselected cases of pancreas cancer is unclear but likely less than 5 % In a tissue based study, 7% of patients with resected pancreas cancer or human xenografts had "germline" mutations in their tumour (Goggins M. et al 1996) but this cohort may not represent the typical unselected cases and the prevalence is likely somewhat lower. There are specific populations, however, where the association is much stronger. In Ashkenazi Jewish patients with pancreas cancer, the prevalence of g*BRCA*m is 6-10% in unselected patients (Ferrone CR et al 2009, Ozcelik et al 1997,) and 15% in patients with a family history of the disease (Sadler ZK. 2012). In pancreas cancer patients with a family history of the disease, reported prevalence of carrying a germline *BRCA2* mutation may be as high as 17-19% (Murphy KM et al 2002, Hahn et al 2003).Given the small size of the g*BRCA*m subpopulation in pancreas cancer,

information comparing the natural history of this group with the overall pancreas cancer population is minimal. One study of the natural history of Ashkenazi Jews with pancreas cancer treated with surgery (most of whom eventually died of the disease) could find no difference in survival between those who had germline *BRCA*m (n=8) vs. those who did not (n=137). The study however did not extend beyond 2004 and did not include patients treated with more modern chemotherapies (Ferrone CR et al 2009). In a large study of the natural history of *BRCAm* associated pancreas cancer, the median all–stage overall survival (OS) for 58 patients was 14 months (95% CI 10-23 months). Median OS for patients with stage 1-2 disease has not been reached at 60 months. Median OS for stage 3-4 was 12 months (95% CI 6-15). Superior OS was observed for patients with stage III and IV disease treated with platinum versus those treated with non-platinum chemotherapies (22 vs 9 months; p=0.039 (Golan *et al* unpublished data). There are no approved treatments for patients with germline *BRCA1/2* mutations and these patients are treated with regimens used for standard advanced pancreas (Lowery M et al 2011).

Recent data suggest there may also be a number of pancreas cancer patients' tumours with ATM defects or a g*BRCA*-like or HRD phenotype (Cowley et al 2013). The development of a test to identify such tumours may broaden the patient population which could benefit from PARP inhibitors. Obtaining tumour tissue to look for the prevalence these other potential markers of drug sensitivity is another unmet need in advancing therapy of this serious illness.

1.1.2 Chemotherapy use in advanced pancreas cancer

Chemotherapy for metastatic pancreas cancer has modest, at best, impact on PFS and OS. The "best" regimens for use as initial treatment of metastatic disease, FOLFIRINOX or gemcitabine + nab paclitaxel have respectively PFS's of 6.4 and 5.5 mos. and OS's of 11.1 and 8.5 mos. (Conroy et al 2011, Von Hoff et al 2013). Toxicity particularly on the platinum based regimen was substantial (80% had hematologic toxicity, 45% ≥grade 3; 70% had peripheral neurotoxicity, 9% ≥grade 3) and led to dose reductions and treatment discontinuations. It is of note that median number of FOLFIRINOX cycles given was 10 (ie. ~5 months of treatment) but the median PFS was 6.4 months suggesting some discontinuation prior to the planned 12 cycles and evidence of progression. Nevertheless platinum based regimens are widely used as first line therapy of metastatic pancreas cancer.

1.1.3 PARP inhibition as a target for *BRCA* mutation positive cancer

Investigators should be familiar with the current Olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs).

Inhibiting PARPs leads to the persistence of SSBs, which are then converted to DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with homologous recombination deficiencies (HRD), such as ovarian cancers in patients with g*BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, Olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

gBRCA1 and g*BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fitzsimmons D et al 1999, Fong et al 2009, Fowble et al 2001). The mechanism of action for Olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knockout models, either as a stand-alone treatment or in combination with established chemotherapies.

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 eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of Olaparib. *Ex vivo* studies have confirmed that Olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test *in vitro*. When dosed orally, Olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that Olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

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

1.1.6 Clinical experience with Olaparib

Below is an outline of the monotherapy Olaparib studies conducted in pancreas cancer patients.

1.1.6.1 Olaparib monotherapy studies in pancreas cancer patients

Study D0810C00042

Study 42 was a single arm phase II study of Olaparib (capsules) 400mg po bid in patients with germline *BRCA*m malignancies across multiple tumour types. Twenty three patients with germline *BRCA*m-associated advanced pancreas cancer after therapy with gemcitabine were treated with Olaparib capsules 400mg po bid. All patients had seen a prior gemcitabine regimen and over half a prior platinum containing regimen. The ORR was 22%, DCR 57%, PFS 4.6 mos. and OS 9.8 mos. (Kaufman B et al 2013) This level of activity compares favourably with that reported for other therapies reported in advanced previously treated pancreas cancer (Rahma et al 2013). A retrospective analysis of the patient data from study 42 suggested greatest benefit from Olaparib in those (15) patients whose tumours had not progressed on a prior platinum treatment (ORR 33%, DCR 66%, PFS 6.4 mos., OS 13.1 mos.).

1.2 Research hypothesis

Single agent Olaparib tablet 300 mg bid has superior efficacy and acceptable tolerability profile as compared with placebo in patients with deleterious or suspected deleterious germline mutation in *BRCA1* and/or *BRCA2* and metastatic pancreas cancer who have achieved disease control(absence of objective progression) after receiving a minimum of 16 weeks of first line platinum based chemotherapy. The efficacy in this study will be assessed by the primary analysis of PFS defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST1.1 criteria, or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to disease progression. To reduce bias, primary analysis of PFS will be based on blinded, independent central review of RECIST scans. Secondary endpoints include overall survival, DCR at 16 weeks, ORR (in patients with baseline evaluable disease), PFS2, safety assessments and patient-reported symptoms, functioning and health related quality of life.

1.3 Rationale for study design, doses and control group

Mutations in g*BRCA1* and g*BRCA2* are a very rare but definable molecular subgroup of pancreas cancer which may be found in some identifiable populations with a prevalence as high as 15%. Cells that lack g*BRCA1/2* function, such as cancer cells from patients with germline mutations in these genes, are deficient in their ability to repair double-strand DNA breaks through homologous recombination (Roy et al 2012). This deficiency is presumed to underlie the observation that g*BRCA1/2*-deficient cells are sensitive to interventions that promote double strand DNA breaks or cross-links, such as ionizing radiation and platinum-based chemotherapeutic agents. Platinum based regimens are increasingly being used early in the treatment of advanced g*BRCA*-mutated breast and pancreas cancer, in addition to their established use in ovarian cancer. It is also presumed to underlie the observation that *gBRCA1/2*-deficient cells are sensitive to treatment with inhibitors of poly-(ADP-ribose)-polymerases (PARP inhibitors) (Bryant et al 2005) which are presumed to force repair of single-strand breaks towards the homologous repair pathway rather than the pathways that

usually address single-strand breaks. Phase I and proof-of-concept phase II studies have shown that PARP inhibitors have significant activity with limited toxicity when used as single agents in the treatment of g*BRCA1/2* mutation-associated breast and ovarian cancer (Tutt A et al 2010; Audeh et al 2010) and pancreas cancer (Kaufman B et al 2013). The present trial is an important step in defining the role of Olaparib as a PARP inhibitor in patients with deleterious germline *BRCA1/2* mutations and metastatic pancreas cancer and the strategy of switch maintenance to prolong disease control after beneficial effect of a platinum regimen as has been suggested for *gBRCA*-mutated ovarian cancer (Kim et al 2014, Ledermann et al 2013). The study will assess the efficacy of Olaparib relative to placebo as maintenance therapy after documentation of disease control(absence of progression) on an initial platinum based regimen for metastatic g*BRCA* pancreas cancer. The preliminary analysis of study 42 suggests selecting patients with tumours which are not known to be platinum resistant would increase the likelihood of benefit. Because of data to suggest that "sporadic" pancreas cancers may have tumour tissue *BRCA* mutations (Goggins M. et al 1996), an exploratory analysis of tumour tissue will be done to assess the prevalence and feasibility of assaying tumour tissue for *BRCA* mutations and/or other markers of HRD. In the future it may be possible to extend the use of PARPi to patients with tumours having non-*BRCA* deficiencies in dsDNA repair. Olaparib has shown activity in ATM negative gastric cancer (Bang et al 2013) and there is suggestion of a similar sub-population in pancreas cancer (Kim et al 2014). Furthermore, independent groups have also identifed genomic signatures in pancreas cancer predicted to be associated with sensitivity to PARP inhibitors (Alexandrov et al 2013; Cowley et al 2013). In order to further understand candidate methods for identifying these patients in future clinical trials we are asking all patients to donate a tumour sample at screening. In order to understand the prevalence and relationship of these markers to *BRCA* status it is important that we are able to test samples from patients with and without *gBRCA* mutations.

If the trial is successful it will give patients a relatively non-toxic oral therapeutic which will delay progression after stopping first line platinum based chemotherapy.

1.3.1 Rationale for using Myriad Genetics

The FDA has indicated that the g*BRCA1* and g*BRCA2* mutation assay will need to be approved as a companion diagnostic in the US.

Myriad Genetics has been chosen as a partner in developing a companion diagnostic for g*BRCA1* and g*BRCA2* testing because it has extensive experience of g*BRCA1* and *gBRCA2* mutation detection. Myriad keeps a comprehensive database on g*BRCA1* and g*BRCA2* gene mutations and their clinical relevance. Furthermore, Myriad has an established laboratory infrastructure, which supports high volume testing with turnaround times that can meet the needs of a clinical trial.

1.4 Benefit/risk and ethical assessment

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumours are estimated to have received treatment with Olaparib across

the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of Olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the Olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given Olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to Olaparib capsule for ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term Olaparib (capsule) monotherapy exposure.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

1.4.1 Important potential risks

1.4.1.1 Myelodysplastic syndrome/acute myeloid leukaemia

There have been 16 reports of myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) in patients treated with Olaparib as of 02 Oct 2013; 11 cases in Olaparib monotherapy trials and 5 cases in Olaparib combination studies with carboplatin and paclitaxel (n=4) or cediranib (n=1). A total of 2103 patients are estimated to have received Olaparib, giving a cumulative incidence of 0.76% for MDS/AML, similar to the cumulative incidence reported from control arms of Olaparib randomised studies 0.7% (2/304 patients). All 16 patients had primary ovarian or peritoneal cancer and 12 of them were g*BRCA1/2* positive (3 cases g*BRCA* status unknown; 1 case negative). It has been hypothesised that a deficiency in the expression of *BRCA* genes may leave patients more vulnerable to the adverse effects of chemotherapy, and therefore, at an increased risk of MDS/AML as a result of cancer treatment (Cole and Strair 2010). Most patients had been treated with extensive previous chemotherapy ranging from 6 to 95 cycles over periods of 3.5 months to 15 years, including platinum agents, topoisomerase II inhibitors, alkylating agents and taxanes. The median time from diagnosis of cancer to onset of MDS was 5.3 yrs (range 2.9 -12.7). The median time from start of Olaparib treatment to onset of MDS was 0.9 years (0.1 to 4.8 years). The reported events of MDS/AML occurred post discontinuation of Olaparib treatment in 8 of the 16 patients following a median of 0.1 years post treatment discontinuation (range: 0.1 to 1 years). Half of the patients (n=8) had received Olaparib for ≤ 12 months (5 patients had ≤ 6 months exposure) and the other 8 cases occurred following longer than 12 month Olaparib exposure (3 patients following 12-18 months exposure and 5 patients following >2 years exposure to Olaparib).

Since bone marrow is known to be a target organ for Olaparib toxicity, a risk of MDS/AML with long-term exposure to Olaparib cannot be excluded, but there is insufficient data at present to evaluate the strength, if any, of this relationship. Moreover, while non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following Olaparib treatment, there is no evidence to date linking Olaparib treatment to the generation of abnormal bone marrow precursors. Furthermore, all patients who developed MDS/AML had extensive prior chemotherapy and while it is not possible to exclude the contribution of Olaparib, it is also considered that there were other potential contributing factors in all cases. Preclinical data also suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect (Gaymes et al 2008).

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every 3 weeks during the rest of the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

1.4.1.2 Pneumonitis

As of 2nd of Oct 2013, 10 patients out of a total of 2103 patients estimated to have received Olaparib have reported pneumonitis, giving a cumulative incidence of 0.5% for pneumonitis. Pneumonitis was also reported for 2 patients (0.7%) of 304 patients that received placebo or comparator in the Olaparib trial programme (1 patient on placebo in Study 19 and 1 patient on paclitaxel in Study 39). The patients were treated with Olaparib for breast cancer (n=2), ovarian cancer (n=2), non-small cell lung cancer (n=2), small cell lung cancer (n=1), pancreas cancer (n=1), gastric cancer (n=1) and thymic cancer (n=1). Five of the 10 patients had a history of tobacco smoking. The majority of patients had received prior radiotherapy and/or chemotherapy. The majority of patients had relevant medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, haemoptysis, chest infection, allergic asthma, pleural effusion, and pleural metastases.

Investigation of any new or worsening pulmonary symptoms has been implemented as a safety management plan (section 6.7.2).

1.4.1.3 New Primary Malignancies

Overall, the number of reports of new primary malignancies is low, with 21 events (in 19 patients) being reported in 02 Oct 2103 Olaparib treated patients (0.9%) and one event (bladder cancer) reported in the placebo arm of the double-blind Study 19. In randomised controlled studies, 5 events of new primary malignancies have been reported in four Olaparib treated patients and one event in a placebo treated patient:

In the double blind maintenance Study 19, two events of new primary malignancies have been reported in Olaparib treated patients and one event in a placebo treated patient. In the open label *gBRCA* ovarian monotherapy dose-finding Study 12, three events were reported in two Olaparib treated patients.

Of the 21 reported events in Olaparib treated patients, in ten the events were non-melanoma skin cancers. There was one report of malignant melanoma. The other 10 events of new primary malignancies were breast cancer (n=2), breast cancer *in situ*, gastric cancer, lung neoplasm (plus event of recurrence of the lung carcinoma), plasma cell myeloma, colon cancer, malignant muscle neoplasm (lesion present pre-Olaparib treatment) and one fatal event of T-lymphoblastic lymphoma/leukaemia.

Of the 19 Olaparib treated patients subsequently diagnosed with a new primary malignancy, the majority were reported whilst receiving Olaparib treatment (16 patients). In 3 patients the event was reported after Olaparib discontinuation

The duration of Olaparib treatment for the 19 patients was:

- <6 months for 3 patients
- 6 to 12 months for 6 patients
- 12 to 18 months for 2 patients
- 18 to 24 months for 2 patients
- >2 years for 6 patients.

The type of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995, Fitzsimmons D et al 1999, Fong et al 2009, Fowble et al 2001, Wesolowski et al 2007), or were cancers such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates.

Ovarian cancer patients have been reported to have an increased risk of developing second primary malignancies. Patients with g*BRCA* mutations are at risk of developing other primary cancers notably breast cancer (Ginsburg et al 2010) reported higher rates of skin cancers in patients with g*BRCA1* (1.6%) and g*BRCA2* (3.0%) mutations.

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all 19 Olaparib treated patients. All patients had previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Seven of the 19 patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) and 3 patients with skin cancers had either had previous basal cell carcinoma reported or had skin lesions evident prior to study treatment) prior to the cancer under investigation in the Olaparib studies.

There is insufficient evidence for an association between Olaparib treatment and the development of new primary malignancies in the clinical trial programme to date.

1.4.2 Potential benefit

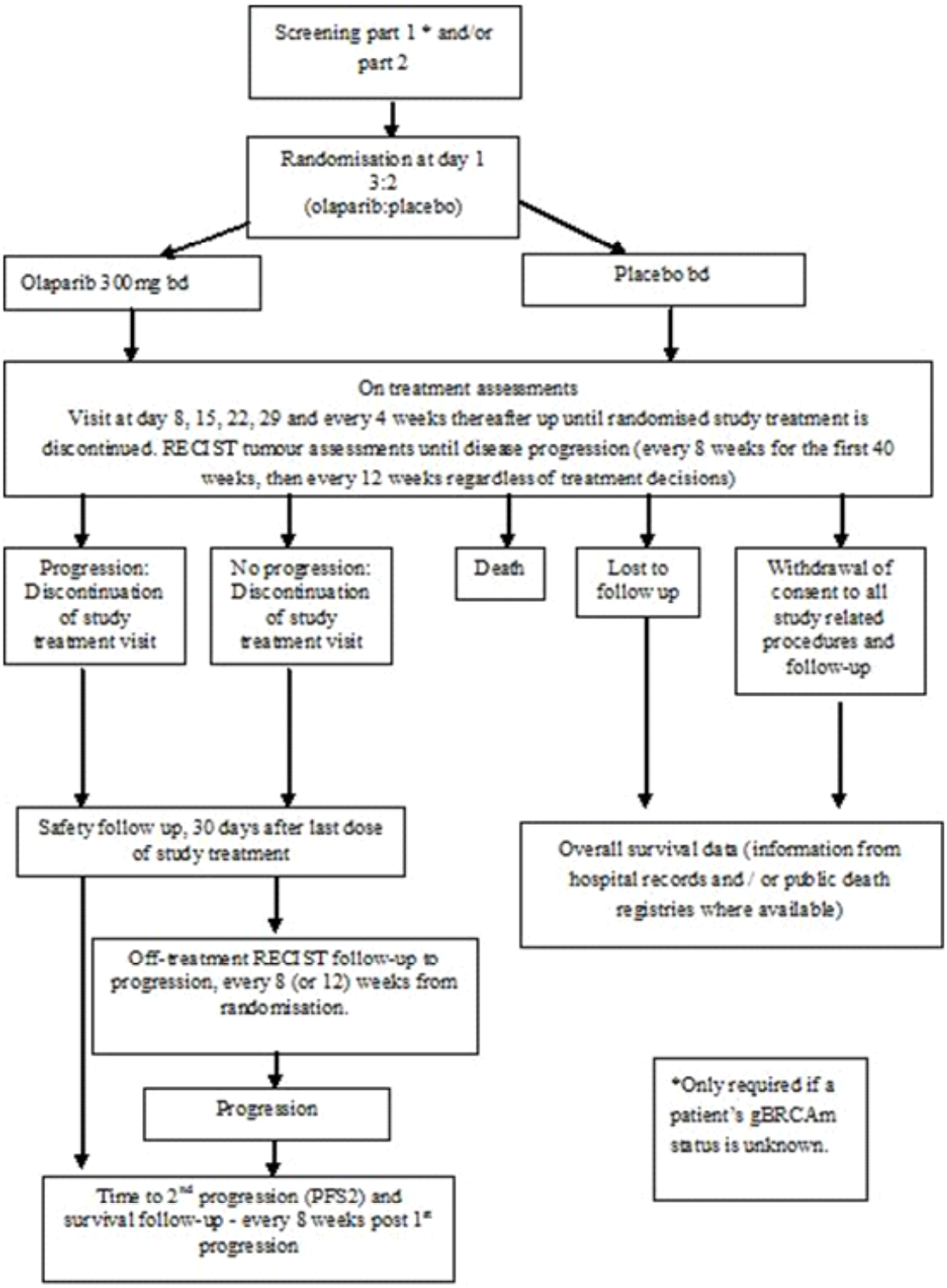
Phase II clinical studies have investigated the effect of Olaparib either as monotherapy or in combination with other chemotherapy agents in cancer patients. In patients carrying germline *BRCA* mutations, monotherapy studies in patients with heavily pre-treated breast cancer have reported an objective response rate (ORR) of up to 41%. In ovarian cancer patients, the pivotal phase II study D0810C00019 ("Study 19"), a double-blind, randomised study assessed the efficacy of Olaparib 400 mg bid capsules as a maintenance treatment following platinum-based chemotherapy in patients with platinum sensitive relapsed high grade serous ovarian cancer. The progression-free survival (PFS) following Olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.35; 95% CI: 0.25, 0.49; p<0.00001) in the overall population. In the subgroup of patients with *BRCA* mutant ovarian cancer, the effect was even greater with a PFS HR of 0.18 (95% CI: 0.11, 0.31; p<0.00001; median 11.2 versus 4.3 months). An interim analysis of OS was performed at 58% maturity. In the overall population, the analysis demonstrated a non-statistically significant numerical advantage for Olaparib-treated patients (OS HR 0.88; 95% CI 0.64-1.21; p=0.43808) and there was again a greater effect in the g*BRCA*-mutated subgroup: the OS HR was 0.74 (95% CI 0.46 to 1.19; p=0.20813) with a numerical advantage in median overall survival observed with Olaparib (median 34.9 months versus 31.9 months with placebo). Among the 62 placebo-treated patients with g*BRCA* mutations, 14 switched to a PARP inhibitor post progression. In study D0810C00042 ("Study 42')**,** a single arm phase II study of Olaparib (capsules) 400mg po bid in patients with germline *BRCA*m malignancies across multiple tumour types, 23 patients with advanced g*BRCA*m associated pancreas cancer, all previously treated with gemcitabine were enrolled. There were 1 CR and 4 PR's (ORR 22%) with a disease control rate of 57%, a PFS of 4.6 months and an OS of 9.8 mos. Patients who had not progressed on a platinum containing regimen were most likely to benefit. The results of Study 19 in ovarian cancer and Study 42 in pancreas cancer are the clinical basis for this investigation.

In this randomised double blinded study, patients who have disease control after a minimum of 16 weeks of platinum based therapy will, on the investigational arm receive monotherapy Olaparib 300 mg tablet bid (or control placebo) until disease progression or development of unacceptable toxicity. There is no intent to cap duration on Olaparib for these patients.

Based on the available data on efficacy and safety, we anticipate that in the metastatic disease setting, Olaparib will have a positive benefit risk profile for the treatment of the very small well-defined population of advanced pancreas cancer patients with g*BRCA* mutations.

1.5 Study Design

Figure 1 Study Flow Chart



This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of Olaparib maintenance monotherapy in metastatic pancreatic cancer patients with *gBRCA* mutations [documented mutation in *gBRCA1* or *gBRCA2*] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16 weeks of first line platinum based chemotherapy.

Approximately 145 patients will be randomised using an Interactive Voice Response System / Interactive Web Response System (IVR/IWR system) in a 3:2 ratio (Olaparib:placebo) to the treatments as specified below:

- Olaparib tablets *p.o.* 300 mg twice daily
- Matching placebo tablets *p.o.* twice daily

Eligible patients will be those patients with pancreas cancer previously treated for metastatic disease *gBRCA* mutated, who have not progressed following completion of at least 16 weeks (can be more) of first line platinum-based chemotherapy.

All patients must have a known deleterious or suspected deleterious germline BRCA mutation to be randomised; this may have been determined prior to enrolment into the study or may be assessed as part of the enrolment procedure for the study (via centrally provided Myriad Integrated BRAC*Analysis* test)

Patients must have completed a minimum of 16 weeks of first line platinum-based therapy (eg, oxaliplatin, carboplatin or cisplatin) given continuously before randomisation to the study and should in the opinion of the investigator have had at least disease control. There must be absence of progression by imaging done within 4 weeks of randomisation. Patients whose platinum based therapy was discontinued as a result of toxicities specifically related to their platinum containing regimen are eligible if they received at least 16 weeks of platinum therapy and have continuously received the other chemotherapy drug(s) in their regimen (for example FOLFIRI for FOLFIRINOX etc.) and fulfil all other eligibility requirements (including non-progression at the time of enrolment).

Patients known to have germline *BRCA* mutation/s prior to randomisation can enter the study based on this result provided they meet all other eligibility criteria. The type of *BRCA1/2* mutation must be reported in the eCRF. In addition the patients must consent to give 2 blood samples, the primary purpose of the first sample is for undertaking a confirmatory Myriad *gBRCA* test post randomisation and a second sample is required for assessment of current and future *BRCA* mutation assays. The patients will also submit the diagnostic pathology specimens (block or slides) if available for the exploratory portion of the study.

Patients with unknown *BRCA* status must consent to give 2 blood samples for germline *BRCA* testing by Myriad (and all local ethical procedures for such genetic testing). One sample will be used to test for *BRCA* mutations using the current commercial Myriad *BRCA* analysis test prior to study entry (Myriad Integrated BRAC*Analysis*). The second blood sample from all

tested patients (including those who do not have a *BRCA* mutation) is required for assessment of current and future *BRCA* mutation assays. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious germline *BRCA* mutation and the patient meets all other eligibility criteria, the patient can be randomised into the study. The patients will also submit the diagnostic pathology specimens (block or slides) if available.

Residual blood (or its derivatives) from both samples may be used to evaluate future *gBRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, improve the understanding of pancreas cancer and disease recurrence (including *gBRCA* mutation status and it role in response).

The 2 blood samples from patients with both known and unknown *BRCA* mutation status are needed in order to ensure sufficient information is collected in the study to enable the pre-market approval of the Myriad germline *BRCA* test as a companion diagnostic for Olaparib in the USA. In addition residual material may be used for the assessment of other current and future *BRCA* mutation diagnostic assays and/or assays that predict sensitivity to Olaparib.

Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

Following randomisation, patients will attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment.

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9.

Once a patient has discontinued study treatment, clinic visits will be reduced to every 8 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator however it is anticipated (but not required) that patients will be retreated with their platinum based regimen. Details of any further systemic anti-cancer treatment will be collected until death, loss to follow-up or withdrawal of consent. In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) to capture survival status at that point for each survival analysis. Assessments will be performed as described in Table 1.

Patients will have tumour assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to modified RECIST criteria. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decisions will be based on site

assessment of scans. After the final primary progression free survival (PFS) analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the electronic case report form (eCRF).

RECIST will be modified to assess patients with clinical CR at entry who will be assessed as having no evidence of disease (NED) until they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue, to undergo scheduled objective tumour assessments according to the study plan (see Table 1) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

Once a patient has progressed the patient will be followed for second progression (PFS2) every 8 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit for each analysis of survival.

The primary analysis of the study will occur when approximately 89 progression events have occurred, although an interim analysis for superiority will be done when 50% of the planned PFS events have occurred (see statistical Section 8). The primary analysis will be based on a blinded independent central review (BICR) of disease progression by modified RECIST; however, a sensitivity analysis will be performed using the investigator-recorded assessment. All efficacy variables including overall survival will be analysed at the time of the primary analysis (providing sufficient events are available to make the analyses meaningful).

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS)	• Progression Free Survival (PFS) by BICR using modified RECIST 1.1

2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo	• Overall Survival (observed and predicted using observed PFS and OS data) • Time from randomisation to second progression (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST). • Time from randomisation to study treatment discontinuation or death (TDT) • Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients • Disease Control Rate at 16 weeks by BICR using modified RECIST 1.1 criteria
• To assess the effect of Olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.	• Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire

2.3 Safety objectives

Safety Objective:	Outcome Measure:
• To assess the safety and tolerability of Olaparib maintenance monotherapy	• Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

2.4 Exploratory objectives

Exploratory Objective:	Outcome Measure:
• To assess the effect of Olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional and social). • To assess the effect of Olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales. • To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice • To assess change in performance status as measured by the ECOG Performance Status scale	• Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 + PAN26 symptom scales and items (pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice and on performance status measured by the ECOG Performance Status scale
• To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D
• To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement

(ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.	appraisals)
• To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.	• BRCA1 and/or BRCA2 mutation status in tumour
• To identify tumour tissue based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRCA methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches for development • Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.	• Potential tissue biomarkers identified

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

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

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

2. *Patients must be male or female ≥18 years of age

3. *Histologically or cytologically confirmed pancreas adenocarcinoma receiving initial chemotherapy for metastatic disease and without evidence of disease progression on treatment

4. Patients with measurable disease and/or non-measurable or no evidence of disease assessed at baseline by CT (or MRI where CT is contraindicated) will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline..

5. Documented mutation in *gBRCA1* or *gBRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) (See Section 1.5)

6. Patients are on treatment with a first line platinum-based (cisplatin, carboplatin or oxaliplatin) regimen for metastatic pancreas cancer, have received a minimum of 16 weeks of continuous platinum treatment and have no evidence of progression based on investigator's opinion. Patients who have received at least 16 weeks of a platinum regimen but had the platinum discontinued for toxicity but continued on the remaining drugs of their regimen are also eligible if they have no evidence of disease progression within 4 weeks of their last dose of chemotherapy.

7. Patients who have received platinum as potentially curative treatment for a prior cancer (eg ovarian cancer) or as adjuvant/neoadjuvant treatment for pancreas cancer are eligible provided at least 12 months have elapsed between the last dose of platinum-based treatment and initiation of the platinum-based chemotherapy for metastatic pancreas cancer.

8. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:

   - Haemoglobin ≥ 9.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - White blood cells (WBC) >3 x 10^9/L
   - No features suggestive of MDS/AML on peripheral blood smear
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal value unless liver metastases are present in which case they must be ≤ 5x ULN

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

9. *ECOG performance status 0-1 at date signing of informed consent

10. *Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test. Postmenopausal is defined as:

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

    - Luteinizing hormone (LH) and Follicle stimulating hormone (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

    - Surgical sterilisation (bilateral oophorectomy or hysterectomy)

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

12. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour or a metastatic site if available or 3 unstained cytology slides if available.

3.2 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 AstraZeneca staff and/or staff at the study site).

2. *gBRCA1* and/or *gBRCA2* mutations that are considered to be non detrimental (eg, “Variants of uncertain clinical significance” or “Variant of unknown significance” or “Variant, favour polymorphism” or “benign polymorphism” etc.).

3. Progression of tumour between start of first line platinum based chemotherapy for metastatic pancreas cancer and randomisation.

4. Cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days of Cycle 1 Day 1 is not permitted. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 2 weeks prior to study treatment.

5. *Previous randomisation in the present study.

6. Exposure to an investigational product within 30 days or 5 half lives (whichever is longer) prior to randomisation

7. *Any previous treatment with a PARP inhibitor, including Olaparib.

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

9. Resting ECG with QTc > 470 msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTc >470 msec, patient will be eligible only if repeat ECG demonstrates QTc ≤470 msec.

10. Concomitant use of known potent CYP3A4/5 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further detail refer to Appendix H.

11. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 3 peripheral neuropathy.

12. *Patients with myelodysplastic syndrome/acute myeloid leukaemia.

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

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

15. *Clinically significant uncontrolled medical conditions are not permitted (eg active infection requiring IV antibiotics, symptomatic congestive heart failure, unstable angina pectoris, recent (3 months) myocardial infarction, extensive bilateral interstitial lung disease, psychiatric illness that would limit ability to comply with study procedures, and any other medical condition that, in the opinion of the investigator, places the patient at unacceptable risk of toxicity. NB: Diabetes which is controlled by medication does not exclude participation in the study

16. *Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study. No history of intracranial haemorrhage or spinal cord haemorrhage. Minimum of 2 weeks between completion of radiotherapy and cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing

requirement for ≥ 10mg of prednisone per day or an equivalent dose of other corticosteroid.

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

18. *Pregnant or breast feeding women.

19. *Previous allogeneic bone marrow transplant.

20. *Patients with a known hypersensitivity to Olaparib or any of the excipients of the product.

21. *Whole blood transfusions in the last 120 days prior to enrolment to the study which may interfere with *gBRCA* testing (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.8)

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

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

The Principal Investigator will:

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

2. Assign potential patients a unique enrolment number, beginning with 'E#'. (This number will be obtained through Interactive Voice/Web Response System [IVRS/IWRS]).

3. Determine patient eligibility. See Sections 3.1 and 3.2

4. Obtain the randomisation code (patient number) through IVRS/IWRS.

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (eg, the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient unique identifier and is used to identify the patient on the eCRFs. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomised patients

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

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

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

3.5 Methods for assigning treatment groups

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised study treatment.

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

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

Patients will be identified to the Centralised Randomisation Centre using patient Ecode and month/ year of birth.

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

Eligible patients will be randomised in a 3:2 ratio (Olaparib:placebo) as specified below:

- Olaparib tablets *p.o*. 300 mg twice daily
- Placebo tablets *p.o.* twice daily

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

The IVRS/IWRS Centralised Randomisation Centre will inform the Investigator of the Kit ID number to be allocated to the patient at the randomisation visit. The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number (s).

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

3.6 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

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

3.7 Methods for unblinding

3.7.1 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

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

3.7.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists 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 randomisation. 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 SAEs 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 medical reasons, patients, investigators and study monitors in the field will have no access to the individual treatment code until final analysis.

3.8 Restrictions

3.8.1 Contraception

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception, while they are receiving study treatment and for 3 months after last dose of study drug. For details please refer to Appendix E Acceptable Birth Control Method.

3.8.2 Olaparib and CYP3A4/5

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4/5 enzyme activity (see Section 7.7.2) starting 5 days before they are randomised until 30 days after the last dose of study medication.

3.9 Discontinuation of investigational product

Patients may discontinue study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Objective radiological disease progression
- Adverse Event
- Severe non-compliance to study protocol
- Death

3.9.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.3 and 6.4); questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

Any patient discontinuing study treatment 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 treatment, 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. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study treatment at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 6.3 and 6.4). 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) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study treatment to collect and / or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Patients who discontinue treatment prior to disease progression should continue to have RECIST assessments as per the study schedule. All patients must be followed for objective progression (as per RECIST 1.1) and survival, up to the final analysis.

3.10 Criteria for withdrawal

Patients are at any time free to withdraw from study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.3 and 6.4); questionnaires (eg, for patient reported outcomes*)* and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment*
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Death

*If a patient decides at any point in the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (eg disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected on the clinical database. However if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimise the number of cases of early withdrawal the investigator should discuss the options with the patient in case they would still

be willing to undergo reduced assessments and/or reduced data collection, in which case they would remain in the study.

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

- to further participation in the study including any further follow up (eg, survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 5.6.6)

Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting.

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, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to collection of further 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.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The patient will return electronic PRO (ePRO) devices.

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

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests

4. STUDY PLAN AND TIMING OF PROCEDURES

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and in Table 1.

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

	Screen PART 1 (Patients with unknown *BRCA* status only)	**Screen PART 2** (All patients)	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Informed consent	X	X									
Randomisation [f]			X [f]								
Demographics	X	X									
Medical and surgical history, including blood transfusions [a]		X									
Prior cancer therapies including radiotherapy		X									
Inclusion/exclusion criteria	X (all * criteria) [b]	X									
Blood samples for *gBRCA* status [c]	X		X [d]								
Archival paraffin embedded tumour tissue or cytology sample [e]	X	X									
Concomitant medications		X	X	X	X	X	X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
ECOG performance status		X					X	X	X	X	
Vital signs		X [g]	X [g]				X	X	X	X	
Physical examination [h]		X					X	X	X	X	
ECG [i]		X	As clinically indicated								
Tumour assessment (modified RECIST 1.1) [j]		X (no more than 28 days before start of treatment) [j]	Every 8 weeks (± 1 week) until week 40 then every 12 weeks (±1 week), relative to the date of randomisation [j]						If patient does not have disease progression at the time of treatment discontinuation tumour assessments should be continued per the CSP schedule [k]		
Haematology/clinical chemistry		X	X [l]				X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Coagulation [m]		X	As clinically indicated								
Urinalysis [n]		X	As clinically indicated								
Pregnancy test [o]	X	X	X								
Biomarker blood sample [p]			X					X (only at progression)			
EORTC QLQ-C30 [q]		X					X	X	X	X	
EORTC QLQ-PAN26 [q]		X		X	X	X	X	X	X	X	
Euro QoL EQ5D		X	X				X	X	X	X	
Hospital Resource Use			X	X	X	X	X	X	X	X	
Adverse event [r]	SAEs related to study procedures only	X	X	X	X	X	X	X	X	X	
Study drug dispensing [s]			X				X	X			
Study drug return							X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Subsequent cancer treatment [t]										X	X
Second progression assessment [u]											X [u]
Survival status [v]											X [v]

a Include history of blood transfusion within previous 120 days from start of study treatment and the reasons eg bleeding or myelosuppression.
b These screening assessments do not need capturing on the eCRF, but they must be recorded in the patient's notes.
c Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised to the study; this can be either a local lab result or a Myriad test result. Patients for whom their *gBRCA* status is already known, should be consented to the study within 28 days prior to day 1 of study treatment. Any patient who consents to study related Myriad *gBRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future diagnostic test(s) for g*BRCA* mutations.
d Samples to be taken on Day 1 only for patients with known *gBRCA* mutation who have not completed PART 1 Screening. The screening *gBRCA* test and method performed at site must be recorded in the eCRF.
e Collection of an archival tumour sample is requested, if available, for all patients. These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test.
f Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

g Vital signs performed on day 1 before every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

h Physical examination should be performed according to the schedule. After the baseline assessment it is not necessary to record the details on the eCRF, any clinically significant changes not unequivocally related to disease progression, should be reported as adverse events.

i ECG assessments to be completed within 7 days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

j Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment and as close as possible to randomisation. A randomisation must be within 6 weeks of last chemotherapy. Treatment should be started as soon as possible but no less than 4 weeks and no more than 8 weeks after their last dose of chemotherapy. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until disease progression assessed using modified RECIST 1.1 criteria. 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. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit.

k For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1.).

l Haematology and clinical chemistry should be performed at screening and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

m Coagulation test should be performed at screening and if clinically indicated.

n Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

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

p Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

q Questionnaires to be completed prior to randomisation once eligibility has been confirmed and then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose. Questionnaires should be completed prior to dosing on all administrations.

r Adverse events must be captured from time of consent. However, in Screening PART 1 of the study only SAEs related to study procedures will be collected.

s Continuous Olaparib 300mg/ placebo twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

t All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

u Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Subsequent therapy will be collected for these patients from the time of treatment discontinuation.

v The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. 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 (see Section3.10). In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

The following assessments and procedures should be performed during screening Part 1 and Part 2 as per Table 1.

For details of the schedule and nature of assessments see below:

- Month/ year of birth, sex, race and ethnicity
- Medical and surgical history including previous cancer and radiotherapy and history of blood transfusions in previous 120 days
- Previous chemotherapy
  - If patient received a prior platinum drug, in what setting (adjuvant or advanced) and reason for discontinuation (progression on therapy, discontinuation of therapy for reason other than progression, completion of planned program without progression,)
- Current and concomitant medications including previous cancer therapies
- ECOG Performance Status
- Vital signs (blood pressure and pulse; body temperature), body weight, height
- Haematology /Clinical chemistry/Urinalysis
- Coagulation test
  - 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 (INRand APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable
- Physical examination
- CT (or MRI if CT is contraindicated) of chest, abdomen and pelvis

- ECG (within 7 days prior to the start of the study treatment)

- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be prior to performing the g*BRCA* blood test during screening part 1, within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing

- For patients with **unknown** *gBRCA* status: *gBRCA1/2* mutation status. 2 blood samples: One blood sample to test for *gBRCA* mutations using the current commercial Myriad *BRACAnalysis* test, and the second blood sample for a bridging study to validate the companion diagnostic test for Olaparib and/or assessment of current or future *BRCA* mutation assays

- Patient Reported Quality of life questionnaire: EORTC QLQ-C30 and QLQ-PAN26 should be completed prior to randomisation once eligibility is confirmed

- Adverse events must be captured from time of consent. However, in Screening Part 1 of the study only SAEs related to study procedures will be collected. In Screening Part 2 all AEs/SAEs will be collected

- Archival paraffin embedded tumour tissue sample or cytology sample requested, if available

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

4.2 Treatment period

The visit schedule is based on 28-day cycles.

Patients will attend the clinic weekly on days 1 (1st day of treatment), 8, 15, 22, 29 following the commencement of study treatment and then every 4 weeks (day 1 of every cycle) until discontinuation of treatment. The following assessments will be performed at time points specified in the study schedule (see Table 1):

- Vital signs: Day 1 of every cycle. Body weight is only required at day 1 of 1st day of study treatment, if it has not been assessed within 7 days of randomisation. Any other time as clinically indicated

- ECOG Performance Status: Day 1 of every cycle and until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose

- Haematology and clinical chemistry: Day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study treatment and which must have been 3

weeks after last dose of chemotherapy based therapy, unless the investigator believes that it is likely to have changed significantly.

- Physical examination: Day 1 before every cycle but assessments post Day 1 are not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE.

- CT of chest, abdomen and pelvis (or MRI if CT is contraindicated) performed until objective disease progression. RECIST assessments to be scheduled every 8 weeks (±1 week) from randomisation for the first 40 weeks and then every 12 weeks (±1 week). If progression is not confirmed by BICR an additional scan will be requested at the next scheduled visit. CT/MRI of chest, abdomen and pelvis to be performed until objective disease progression.

- ECG at baseline and any time if clinically indicated

- Urinalysis at baseline and any time if clinically indicated

- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day 1 of 1st day of study treatment). If the test is positive then a confirmatory test should be performed

- For patients with **known** g*BRCA* status: *gBRCA1/2* mutation status. 2 blood samples: One blood sample to test for g*BRCA* mutations using the current commercial Myriad BRAC*Analysis* test, and the second blood sample for a bridging study to validate the companion diagnostic test for Olaparib and/or assessment of current or future *BRCA* mutation assays

- AE and concomitant medications (including any blood transfusions) at every visit

- Patient Reported Quality of life questionnaire: EORTC QLQ-C30 at baseline (prior to randomisation once eligibility is confirmed), every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Patient Reported Quality of life questionnaire: QLQ-PAN26 at baseline (prior to randomisation once eligibility is confirmed), week 1, week 2, week 3 and every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Health economic data in terms of utility (EuroQoL EQ5D) at baseline and every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Health economic data in terms of hospital resource use at each visit during treatment then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Mandatory blood sample for biomarker analysis at cycle 1 day 1 (pre-dose) and disease progression (Section 5.4.1)

Once patients have discontinued study treatment, other treatment options will be at the discretion of the investigator.

4.3 Follow-up period

4.3.1 Treatment discontinuation visit due to objective radiological disease progression

Patients should be discontinued from study treatment if they have objective radiological disease progression according to modified RECIST 1.1 criteria (see Appendix F).

Following radiological disease progression patients will be followed for PFS2 and OS.

4.3.2 Treatment discontinuation visit due to any other discontinuation criteria

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 3.9). The assessments to be carried out at the visit are detailed in the study schedule (Table 1).

Patients who have discontinued from treatment but do not have radiological disease progression will continue to be followed for PFS by modified RECIST 1.1 assessments every 8 weeks (+/-1 week) from date of randomisation during the first 40 weeks and then every 12 weeks (+/-1 week) thereafter.

4.3.3 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 RECIST (see Appendix F), however, patients may be allowed to continue study treatment if the investigator believes, and AZ Study Physician concurs, that the patient could continue to receive benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. These patients will continue study procedures as per Table 1 and will be followed for OS. Safety assessment can occur with the same frequency as the visits unless more frequent testing is clinically indicated.

4.3.4 Follow-up 30 day after last dose of study treatment (follow-up visit)

A follow-up visit should be conducted 30 days after the last dose of study treatment. 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 Section 6.3). Appropriate safety evaluations should be repeated and/or additional tests

performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30 day follow up visit are detailed in the study schedule (Table 1).

4.3.5 Survival

Assessments for survival should be made every 8 weeks following objective radiological 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. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and final survival analyses to provide complete survival data.

Patients will be followed up as per Table 1 to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.

The status of patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. 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 (see Section 3.10).

4.3.6 Second Progression

Following objective progression, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review. Patients will be assessed every 8 weeks for a second progression (using the patients' status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

4.3.7 Subsequent Treatment

Following objective progression on study as per modified RECIST 1.1, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review, provided that the central read confirms progression. If progression is not confirmed, one additional scan will be required at the next scheduled visit. Following objective progression patients will be assessed every 8 weeks for survival (see Section 4.3.5) but also for nature of subsequent treatment, response to subsequent treatment and investigator assessment of time to progression on the subsequent treatment. While other than the PFS2, response and time to progression on later therapies is not a specific endpoint of the trial, the information garnered

will help determine if there is an optimal sequencing of treatments for g*BRCA*-associated pancreas cancer and for planning of future clinical studies.

The data cut-off date for the final statistical analysis for the primary objective of the study will be established when approximately 89 confirmed progression events are expected to have occurred.

Patients on study treatment at the time of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as per Section 3.9.

Patients on study treatment will be followed for core safety assessments (haematology, clinical chemistry, AEs/SAEs, concomitant medications and study treatment dosing details)

Once the primary PFS analysis has been performed the collection of RECIST data for independent central review will cease. Patients who have not had an objective disease progression at the time of the data cut off for the primary analysis should continue to have RECIST assessments until first objective disease progression is determined by the investigator. RECIST assessments should be performed every 12 weeks (± 1week) from the last assessment prior to the data cut off date. Patients will also be followed for information on vital status to obtain the data needed for the OS analysis and information on subsequent treatment.

4.4 Patient management post final analysis

The data cut-off date for the final statistical analysis of the study will be established when ~106 confirmed OS events (~75 % maturity for OS analysis) are expected to have occurred.

At this time point, the clinical study database will close to new data. Patients who are receiving 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.

AstraZeneca will continue to supply Olaparib after completion of this study until either Olaparib is licensed 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. Additionally as stated any SAE or non-serious adverse event, 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 resolve, 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

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.
The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 CT and MRI scans Tumour assessments (Modified RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to modified RECIST 1.1 should be performed every 8 weeks (±1 week) for the first 40 weeks and then every 12 weeks (± 1 week) thereafter, relative to the date of randomisation, up to objective disease progression by RECIST. Patients who are determined to have progressed according to modified RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST assessment will be requested preferably at the next scheduled RECIST visit (8 weeks from last scan).

For those patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow up radiological assessments (modified RECIST 1.1).

The imaging modalities used for RECIST assessment will be CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

Any missed copies of the scans are to be sent to an AstraZeneca appointed CRO for blinded independent central review.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of 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 radiological disease progression by modified RECIST 1.1 as per the study schedule (see Table 1), and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

5.1.2 Tumour Evaluation

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times. (The modified 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, no evidence of disease or progression of disease) are presented in Appendix F.)

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen and pelvis, with other regions as clinically indicated for the assessment of disease must be used at each subsequent follow-up assessment, see Section 4.3.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks (±1 week) up to 40 weeks then every 12 weeks (±1 week) relative to date of randomisation, according to the planned study schedule Table 1until objective radiological disease progression as defined by modified RECIST. 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 radiological disease progression as defined by modified RECIST 1.1.

Categorization of objective tumour response assessment will be based on the modified RECIST criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before randomisation.

For patients with non-measurable disease only at baseline, categorization of objective tumour response assessment will be based on the RECIST criteria of response: CR (complete response), PD (progression of disease) and Non CR/Non PD. Patients with no disease at baseline will be assessed according to modified RECIST 1.1 criteria for new lesions with responses of No Evidence of Disease (NED) or progression of disease.

If the investigator is in doubt as to whether disease progression has occurred on study therapy, 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 disease progression, then the date of the initial scan should be declared as the date of disease progression.

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

Following progression, patients should continue to be followed up for survival every 8 weeks as outlined in the study plan. It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 1.5 and CT/MRI scans in section 5.1.1.

5.1.3 Central reading of scans

An independent review of all scans used in the assessment of tumours according to modified RECIST will be conducted for data collected up to the data cut off for the primary analysis of PFS. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. Results of this independent review will not be communicated to investigators (with the exception of confirmation of progression assessments), and the management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

The primary analysis for this study will be based on the blinded independent central review (BICR) of the radiological scans.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

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).

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.

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical Chemistry (serum or plasma)**
B-Haemoglobin	S-Sodium
B-Red blood cells [RBC]	S-Potassium
B-Platelets	S-Magnesium (baseline only and if clinically indicated)
B-Mean cell volume [MCV]	S-Calcium
B-Mean cell haemoglobin concentration [MCHC]	S-Creatinine
B-Mean cell haemoglobin [MCH]	S-Total bilirubin
B-White blood cells [WBC]	S-Gamma glutamyltransferase [GGT]
B-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.	S-Aalkaline phosphatase [ALP] S-Aspartate transaminase [AST] S- alanine transaminase [ALT] S-Urea or blood urea nitrogen [BUN] S-Total protein S-Albumin S-Lactate dehydrogenase (LDH)
Urine Tests	
Urinalysis (Dipstick, baseline only and if clinically indicated)	
U-Hb/Erythrocytes/Blood	
U-Protein/Albumin	
U-Glucose	
Urinalysis (Microscopic analysis, baseline only and if clinically indicated)	

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 5.2.

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

For blood volume see Section 5.6.1.

5.2.2 Physical examination

For timing of individual measurement refer to study schedule (Table 1).

A physical examination will be performed and include 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.

5.2.3 ECOG

ECOG Performance Status is a widely used, 5-level, clinician reported outcome of the patient's performance status. Below is a description of the clinician's grading system for the ECOG Performance Status (see also Appendix G). This measure will be applied according to the study schedule (see Table 1).

Table 3 ECOG Performance Status [a]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

a As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

ECGs are required during screening within 7 days prior to starting study treatment and when clinically indicated afterwards.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. 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. The original ECG traces must be stored in the patient medical record as source data.

5.2.5 Vital signs

Height will be assessed at screening only.

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

5.2.5.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semi automatic BP recording device with an appropriate cuff size.

5.2.5.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer.

5.2.6 Other safety assessments

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).

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.

5.2.6.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential as per the study schedule. 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.

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

5.2.7 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected as clinically indicated for patients with prolonged haematological toxicities as defined in Section 6.7.1.

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.

5.3 Other assessments

5.3.1 Patient reported outcomes

5.3.1.1 EORTC QLQ-C30 and QLQ-PAN26

In this study patient reported disease related symptoms and health related quality of life will be evaluated using the validated EORTC QLQ-C30 and the PAN26 questionnaire. The EORTC QLQ-C30 was developed to assess HRQOL and functioning, and is the most commonly used cancer-specific tool in oncology. It has undergone extensive testing and validation as well as detailed cross cultural linguistic validation and has been used in pancreas cancer and gastric cancer trials (Fitzsimmons D et al 1999). The PAN26 was developed specifically for patients with pancreas cancer and has been found to be reliable and valid in this population as well as in pancreatitis patients.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following scales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social)
- 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
- A 2-item global QoL scale
- 5 single items assessing the following common cancer symptoms:
  - dyspnoea,
  - loss of appetite,
  - insomnia,
  - constipation,
  - diarrhoea
- 1 item on the financial impact of the disease.

The pancreas cancer module (PAN26) is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy. The module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreas cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).

All the EORTC scales range from 0 to 100 (through transformation of scores). 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.

5.3.1.2 Administration of PRO questionnaires

The EORTC QLQ-C30 and QLQ-PAN26 will be administered according to the study schedule (see Table 1**)**.

Questionnaires will be completed using a pencil and paper method of data collection. Each centre must allocate the responsibility for the administration (and training on ePRO device if used) of the questionnaires to a specific individual (eg, a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AZ Study Delivery 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 site staff enters the information directly into the WBDC electronic database system.

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

- The EORTC QLQ-C30 and QLQ-PAN26 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. Patients must complete the EORTC QLQ-C30 before completing the QLQ-PAN26. They must be completed in private by the patient.

- 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 (eg, is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded.

- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness.

5.4 Biomarkers

Tumour and blood samples will be collected for the biomarker work as detailed in the laboratory manual

For blood volume see Section 5.6.1.

5.4.1 Biomarker samples

The biomarker samples will be collected as described in Table 4**.**

Table 4 Samples for Biomarker Research

Sample Type	Visits
Whole blood sample for prospective germline *BRCA* testing at central laboratory for patients with unknown *gBRCA* status and for confirmation of *gBRCA* status for those with previous results	Screening Part 1 for patients with unknown *gBRCA* status Day 1 for patients with known local *gBRCA* test
Whole blood sample for assessment of current and future gBRCA mutation assay(s)	Screening Part 1 for patients with unknown *gBRCA* status Day 1 for patients with known local *gBRCA* test
Archival tumour sample (paraffin or cytology) – Requested, if available	Screening Part 1 for patients with unknown *gBRCA* status Screening Part 2 for patients with known local *gBRCA* test
Blood samples for biomarker analysis	Cycle 1 Day 1 and disease progression

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient. The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development of the drug and companion diagnostic. However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties except as required by law.

Biomarker data may be generated in real time during the study or retrospectively and will have unknown clinical significance. AstraZeneca will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

The exception to the above is the *gBRCA* status result from the Myriad assessment for patients with previously unknown local g*BRCA* status. This result will be provided to the investigator and will be collected as part of the patient's demography and medical history details.

5.4.2 Collection of blood sample for Myriad germline *BRCA1* and *BRCA2* testing

All patients must have a known deleterious or suspected deleterious *gBRCA* mutation to be randomised; this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad).

5.4.2.1 Guidance for g*BRCA* testing of patients with known g*BRCA* status.

For patients that can be randomised to the study on the basis of a pre-existing known *gBRCA* mutation test result, a blood sample for a confirmatory g*BRCA* mutation test by Myriad must be taken once the patient has consented to the study. Should the result from the Myriad test indicate the patient does not have a deleterious or suspected deleterious g*BRCA* mutation; the patient can continue in the study and can continue to receive their allocated study treatment if deemed appropriate by the investigator.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.2.2 Guidance for g*BRCA* testing of patients with unknown g*BRCA* status.

Patients that do not know their g*BRCA* status, but meet all other eligibility criteria must have a Myriad test prior to randomisation in to the study. A blood sample for the Myriad *BRCA* test can be taken once all local ethical procedures for such testing have been completed. If the result shows that the patient has a deleterious/suspected deleterious *gBRCA* mutation, the patient can then be randomised to the study. In order to limit the time that the patient is not receiving study treatment after their last dose of chemotherapy, it may be necessary for the patient to have a Myriad *BRCA* test whilst still on chemotherapy.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.2.3 Collection of blood sample for assessment of current and future g*BRCA* mutation assay(s)

All patients will be required to provide a mandatory 9 ml blood sample that will be stored for subsequent assessment of current and future g*BRCA* mutation assay(s).

Samples may be required to support subsequent analysis as part of a bridging study between the Myriad *BRCA* test to be used in this study and the “to be marketed” diagnostic test which is currently under development. Samples are required to be collected from all patients including those shown not to have a deleterious or suspected deleterious g*BRCA1* or g*BRCA2* mutation.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.3 Exploratory Biomarker Research on Archival Tumour Samples (Paraffin block or tissue cytology slides) (Requested, if available)

These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from a core biopsy from the primary tumour or a metastatic site is most desirable. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, 10-20 pre-cut sections mounted on glass slides prepared from the block can be provided. If the only diagnostic test was cytologic, a paraffin block or three unstained slides of tumour tissue should be submitted if available.

Collection of an archival tumour sample is requested if available for all patients for the assessment of tissue *BRCA* mutation status. Surplus tissue may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease progression (including tumour *BRCA* mutation status and its role in response).

Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage.

5.4.4 Exploratory Blood samples for biomarker analysis (Mandatory)

All consenting patients will be required to provide a blood sample at randomisation and disease progression for exploratory biomarker research.

Patients will be required to provide:

- 1x 6ml blood sample for preparation of serum at cycle 1 day 1 and disease progression.
- 1x 6ml blood sample for preparation of plasma at cycle 1 day 1 and disease progression.

Please refer to Investigator Laboratory Manual for further details of biomarker blood sample collection, shipping and storage.

5.5 Health economics

Hospital related resource use and health state utility

For the purposes of economic evaluation it is necessary to capture utility data and healthcare resource use related to the treatment and the underlying disease. Within the clinical trial utility data will be captured using the EuroQoL EQ5D instrument. The following hospital resource use data will be collected using the Hospital Attendance (HOSPAD) module:

1) Number of hospitalisations and attendances
2) Primary symptom/reason associated with hospitalisation or attendance
3) Length of stay, including time in intensive care.

Additional information, including medications and procedures undertaken will be derived from data captured under existing modules, for example, concomitant medications and concomitant procedures.

5.6 Biological sampling procedures

5.6.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial. The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of treatment, a treatment discontinuation visit and the 30-day follow-up visit, is 255mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

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

Table 5 Volume of blood to be drawn from each patient

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	21	105
	Haematology	5	21	105
	Coagulation	3	1	3
Whole blood sample for Myriad *BRCA* test (retrospective/prospective)		9	1	9
Whole blood sample for assessment of current and future *BRCA* mutation assay(s)		9	1	9
Serum Pregnancy test (site may use urine instead)		Site dependent	Site may use urine instead	

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Serum sample for exploratory biomarkers, cycle 1 day 1 (mandatory)	6	1	6
Plasma sample for exploratory biomarkers, cycle 1 day 1 (mandatory)	6	1	6
Serum sample for exploratory biomarkers, disease progression (mandatory)	6	1	6
Plasma sample for exploratory biomarkers, disease progression (mandatory)	6	1	6
Total			255

5.6.2 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 will be retained at AstraZeneca or a CRO, on behalf of AstraZeneca for a maximum of 15 year*s* 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.

5.6.3 Handling, storage and destruction of biological samples

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

Biological samples for future research will be retained at AstraZeneca or a CRO, on behalf of AstraZeneca for a maximum of 15 year*s* 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.

5.6.4 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria),

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

5.6.5 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site, according to local regulations or at the end of the retention period, whichever is the sooner.

5.6.6 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.

gBRCA sample: As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: If consent to use the sample is withdrawn this will not impact eligibility to study. The patient may continue in the study if the patient is already randomised.

Blood samples for biomarker analysis: Although mandatory, the patient may continue in the study if the patient is already randomised.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), 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 Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period 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 the last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any SAEs or non-serious adverse event 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.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- 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
- 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.

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

Severity of AE

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised 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 NCI website.

6.3.4 Causality collection

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

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.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormality as AE should be avoided unless one of the following is met:

- Any criterion for an SAE is fulfilled
- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The investigator believes that the abnormality should be reported as an AE

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

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

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

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 D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.7 Hy's Law

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 D for further instruction in cases of combined increase of aminotransferase and total bilirubin.

6.3.8 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. The development of local regional recurrence or distant 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 6.2). 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 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 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 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE 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

6.5 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). For other overdoses, reporting should be done within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca

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

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

If any pregnancy occurs, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **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 within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose. Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

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

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

6.7 Management of toxicity of Olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step.

6.7.1 Management of haematological toxicity Olaparib

Table 6 Management of Haematological Toxicity Olaparib

Toxicity	Study treatment dose adjustment
CTCAEa gr 1-2	Dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation
Repeat CTCAE gr 1-2	Dose interruption until recovery to CTCAE gr 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for max of 4 weeks and dose reduction to 200 mg bid
Repeat CTCAE gr 3-4	Discontinue study treatment

[a] CTCAE Version 4

6.7.1.1 Management of anaemia

Adverse events 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 (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment 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 study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

6.7.1.2 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 CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment 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 (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade 1 (ANC $\geq 1.5 \times 10^9$/L).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

6.7.1.3 Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. 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 study treatment.

If a patient develops prolonged haematological toxicity such as:

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

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks 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 patient's diagnosis of MDS and/or AML is confirmed.

6.7.2 Management of non-haematological toxicity Olaparib

6.7.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in study treatment 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 study 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.

6.7.2.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with Olaparib treatment. In Study D0810C00019 nausea was reported in 71% of the Olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the Olaparib treated patients and 14% in the placebo treated patients. They 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 for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, 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. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines, dexamethasone.

6.7.2.3 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AZ study physician.

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to Olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.7.3 Management of toxicity on placebo

Adverse events on placebo will be handled in the same manner as those arising on Olaparib (see sections 6.7)

6.8 Study governance and oversight

6.8.1 Data Monitoring Committee

This study will use an external independent data monitoring committee (IDMC) to perform interim reviews of accumulating study safety data and the interim analyses for superiority and futility based on PFS. 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.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 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 as shown below.

Investigational product	Dosage form and strength
Olaparib[a]	Tablet –100mg and 150 mg
Placebo to match Olaparib	Tablet to match each strength of Olaparib

[a] Descriptive information for Olaparib can be found in the Investigator's Brochure

7.2 Dose and treatment regimens

Study treatment is available as a green film-coated tablet containing 150 mg or 100 mg of Olaparib or matching placebo.

For all centres, Olaparib and matching placebo will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. The randomised study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. The planned dose of 300 mg bid will be made up of two (2) x 150 mg tablets bid with 100 mg tablets used to manage dose reductions. Tablets should

be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with a light meal/snack (eg, two pieces of toast or a couple of biscuits).Multiple bottles of Olaparib or matching placebo maybe required for dispensing in order to make up the desired dose.

No cross over to Olaparib will be provided in this study.

If vomiting occurs shortly after the Olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator.

7.3 Labelling

Labels for Olaparib 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, unless it is a country-specific regulatory requirement, 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.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and may only dispensed by investigator or pharmacist qualified designee. The investigational product label on the Olaparib bottle and the IB specifies the appropriate storage conditions.

7.5 Compliance

The administration of all study drugs (including Olaparib and placebo) should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their Olaparib. Patients will self-administer Olaparib. Study site 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 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 by the site staff on the eCRF.

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

7.6 Accountability

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

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

Study site personnel, will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Any discrepancies must be accounted for on the appropriate forms.

7.7 Concomitant and other treatments

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.

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.

7.7.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement 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.

7.7.2 CYP3A4/5 restrictions

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.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, Olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of Olaparib is CYP3A4/5 and 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, idnavir, saquinavir, telithromycin, clarithromycin and nelfinavir

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

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

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

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

After randomisation if the use of any potent CYP inducers or inhibitors of CYP3A4/5 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.

7.7.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.7.4 Anti-emetics/ Anti-diarrhoeals

Should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see section 6.3) and appropriate treatment of the event given.

7.7.5 Anticoagulant Therapy

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

7.7.6 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Treatment with bisphosphonates or RANKL inhibitor for the prevention of skeletal related events in patients with bone metastasis is permitted and must be started at least 5 days prior to randomisation.

7.7.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer after discontinuation of treatment, will be collected. Response to subsequent therapies and PFS on those therapies will also be collected.

The choice of subsequent systemic anticancer treatment will be entirely at the discretion of the investigator although it is expected that many/most patients upon progression on study will be treated with a platinum based regimen

8. STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION BY PAREXEL

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- A comprehensive statistical analysis plan (SAP) will be prepared and finalised before first patient in (FPI).

8.2 Definitions of analysis sets

Table 7 gives a summary of outcome variables and analysis populations

8.2.1 Full analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of Olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised 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.

In addition, key sensitivity analyses of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a g*BRCA* mutation confirmed by the Myriad test.

8.2.2 Safety analysis set

All patients who received at least one dose of randomised investigational product, Olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated Olaparib patients (those randomised to Olaparib but actually given placebo at any time) will be accounted for in the Olaparib treatment group. Erroneously treated placebo patients (those randomised to placebo but actually received at least one dose of Olaparib) will be accounted for in the Olaparib treatment group.

8.2.3 PRO analysis set

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

Table 7 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	FAS (ITT), Myriad confirmed *BRCAm* subgroup
- Secondary endpoints to be analysed: OS, PFS2, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to treatment discontinuation (TDT), time to deterioration and improvement rate of Global QoL and PAN-26 pain scale	FAS (ITT), Myriad confirmed *BRCAm* subgroup
- Secondary endpoints to be summarised: objective response rate, disease control rate	FAS (ITT), Myriad confirmed *BRCAm* subgroup
Demography	FAS (ITT)
Safety Data	
- Exposure	Safety
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

8.3 Calculation or derivation of efficacy variable(s)

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

8.3.1 Primary endpoint (PFS)

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease 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. 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 tumour assessment visits of randomisation (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) and an absolute increase of > 5 mm, or an overall non-target lesion assessment of progression or a new lesion.

The primary analysis will be based on the blinded independent central review (BICR) of the radiological scans. A charter for the BICR will be developed in advance of the start of the study. A sensitivity analysis based on the programmatically derived PFS based on Investigator-recorded assessments will be carried out.

As a supportive summary to PFS, time to start of first subsequent chemotherapy or death will be assessed (see section 8.8.3). Time to first subsequent chemotherapy or death is defined as the time from the date of randomisation to the earlier of first subsequent chemotherapy start date, or death date. Any patient not known to have had a further subsequent therapy or death will be censored at the last known time to have not received subsequent chemotherapy.

8.3.2 Secondary endpoints

8.3.2.1 Overall Survival

Overall survival is defined as the time from the date of randomisation 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) date 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.

8.3.2.2 Best overall RECIST response (BoR)

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix F. 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 F) using the following response categories: complete response (CR), partial response (PR), stable disease (SD), No Evidence of Disease (NED; applies only to those patients entering the study with no disease at baseline), progressive disease (PD) and not evaluable (NE).

Best overall response will be determined programmatically based on the RECIST criteria using BICR data.

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 ≤ 17 weeks (ie 16 weeks ±1 week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred > 17 weeks (ie 16 weeks ±1week) after randomisation then BoR will be assigned to the nonevaluable (NE) category.

Progression events that have been censored due to them being more than two missed visits 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.

The disease control rate (DCR) is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD or NED for at least 15 weeks

(ie 16 weeks ±1 week) prior to any evidence of progression. In the case of SD and NED, follow up assessments must have met the SD or NED criteria for a minimum interval of 15 weeks following randomisation.

8.3.2.3 Time from randomisation to second progression (PFS2)

Time from randomisation to second progression (PFS2) is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.

The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF. Second progression status will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie censored at the last progression assessment date if the patient has not had a second progression or death).

8.3.2.4 Time to first subsequent therapy or death (TFST)

Time to start of first subsequent therapy or death (TFST) will be assessed. TFST is defined as the time from randomisation to the earlier of first subsequent therapy start date followingstudy treatment discontinuation, or death. Subsequent therapies will be reviewed to assesswhich represent clinically important treatments intended to control ovarian cancer. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, ie the last follow-up visit where this was confirmed.

8.3.2.5 Time to second subsequent therapy or death (TSST)

Time to start of second subsequent therapy or death (TSST) will be assessed. TSST is defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received second subsequent therapy, ie the last follow-up visit where this was confirmed.

8.3.2.6 Time to study treatment discontinuation or death (TDT)

Time to study treatment discontinuation or death (TDT) will be assessed. TDT is defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment 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 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.

8.3.2.7 Disease Control Rate (DCR)

The disease control rate (DCR) is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD for at least 16 weeks (ie 17 weeks ±1 week) prior to any evidence of progression. In the case of SD, follow up assessments must have met the SD criteria for a minimum interval of 16 weeks following randomisation.

8.4 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.

8.4.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of 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.

8.5 Calculation or derivation of patient reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available.

EORTC-QLQC30 and QLQ-PAN26

The EORTC QLQ-C30 will be scored according to the EORTC scoring manual (Fayers et al 1999). Each scale will be transformed to a 100-point scale as per the manual.

Mean change from baseline in health related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 global QoL scale which includes two items from the QLQ-C30: "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall quality of life during the past week?" (Item 30)

The analysis population for PRO data will be the subset of the ITT population; patients must have a baseline score to be included in the analysis of PRO data.

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life (two items: "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall quality of life during the past week?" (Item 30)) and PAN-26 pancreatic pain (items 31, 33, 34, 35) scales . Time to global QoL and pancreatic pain scale worsening will be analysed using the same methodology and model as described for the primary analysis of PFS. However sensitivity analyses will not be performed (with the exception of attrition bias).

Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model and using the same covariates as used in the PFS analyses. If the overall response rate is < 5%, no analysis will be performed. (Note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed.) If the expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

HRQoL Visit responses

A change of at least 10 points in the global QoL score will be considered as a clinically relevant or a minimally important difference (Osoba D et al 1998).

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 1999). 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.

Scores for the QLQ-C30 will be derived using the developer instructions. Raw scores are calculated using the formula:

$$\text{RawScore} = RS\left(I_1 + I_2 + \ldots + I_n\right) n$$

A linear transformation to 0 – 100 is then applied to obtain a score (S)

Function Scale:

$$\left\{1 - \frac{(RS-1)}{range}\right\} x100$$

Symptoms Scales/items:

{(RS-1)/range}x100

Global Health Status/Quality of Life:

{(RS-1)/range}x100

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items.

The QLQ-PAN26 follows the same scoring criteria as the QLQ-C30. The QLQ-PAN26 contains 26 items which comprise 7 multi-item scales (pancreas pain (4 items), eating related items (2 items), hepatic items (2 items), altered bowel habit (2 items), body image (2 items), health care satisfaction (2 items), sexuality (2 items)), and 10 single item scales (swollen abdomen, taste changes, indigestion, flatulence, weight loss, loss of muscle strength, dry mouth, burden of treatment, fear of future health, and ability to plan future.

Within the specific module the items can be grouped into new domains rather than reporting specific items. When using this approach it is important that the correct scoring algorithm is followed.

Higher scores represent more symptoms, except for health care satisfaction scale and sexuality scale where higher scores represent greater satisfaction and sexuality. For change scores, a score of +5 is considered deterioration (except for the two scales mentioned above) and a score of -5 is considered as improvement.

Within the specific module the items can be grouped into new domains rather than reporting specific items. When using this approach it is important that the correct scoring algorithm is followed.

1. Calculate the raw score for each scale

raw score = RS = $(I_1+I_2+\ldots+I_n)/n$

2. Apply the following linear transformation for the sexuality scale:

$$\left\{1-\frac{(RS-1)}{range}\right\}x100$$

For all other scales (including the single items), apply this linear transformation:

$$\left\{\frac{(RS-1)}{range}\right\}x100$$

Where range is 3 in each case.

8.6 Calculation or derivation of pharmacogenetic variables

To be defined in an exploratory analysis plan.

8.7 Calculation or derivation of health economic variables

Responses to the EuroQoL EQ5D questionnaire will be converted into utility scores using UK EQ5D valuation set. Alternative valuation sets may be used in scenario analyses. Descriptive statistics, graphs and listings will be reported for health state utility 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.

Descriptive statistics relating to the frequency healthcare resource use items, including hospital episodes, type of contact (hospitalisation, outpatient, day case), reason, length of stay by ward type (including ICU) and procedures undertaken will be derived from the resource use information.

The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

8.8 Methods for statistical analyses

A single interim PFS analysis for futility and superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events). The interim analysis will be performed by an Independent Data Monitoring Committee (IDMC) and full details will be provided in the IDMC charter. A final PFS analysis will be performed when approximately 89 progression events have occurred (~60% maturity). No further analyses of PFS are planned beyond this point unless requested by health authorities.

Timing of the statistical analyses are given in Table 8.

Table 8 Timing of statistical analyses

Timing of analyses	Outcome Variable
	Efficacy Data
Interim PFS analyses (~ 45 PFS events)	- PFS
Final PFS (~ 89 PFS events)	- PFS, PFS2, TDT, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pain scale

Timing of analyses	Outcome Variable
	Efficacy Data
Final OS analyses (~ 106 OS events)	- PFS2, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pain scale

** Only if superiority is met for PFS at the PFS interim analyses, will analyses of the following endpoints be performed: PFS2, TDT, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pain scale.

The treatment comparison is Olaparib 300 mg bid vs. placebo to Olaparib 300 mg bid.

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 subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint

Table 9 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: log-rank test using BICR data Key sensitivity analysis[a]: log rank test using BICR data in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS) Additional sensitivity analyses: 1) Evaluation time bias analysis; log-rank test using BICR data 2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data 3) Ascertainment bias analysis; log-rank test using investigator data 4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
Overall Survival (Time from randomisation to death due to any cause)	Primary analysis: log-rank test Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)

Endpoints Analysed	Notes
	Supportive analysis: KM plot of time to censoring for OS
Second Progression Free Survival (PFS2)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to treatment discontinuation (TDT)	Primary analysis: Stratified log rank test of time from randomisation to treatment discontinuation
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to first subsequent therapy (TFST)	Primary analysis: Stratified log rank test of time from randomisation to first subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to second subsequent therapy (TSST)	Primary analysis: Stratified log rank test of time from randomisation to second subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to deterioration in global QoL (as measured by the global QOL score from the EORTC-QLQ-C30 questionnaire)	Primary analysis: Stratified log rank test of time from randomisation to deterioration in global QOL

[a] See Section 8.8.3 for further details

8.8.1 Multiplicity strategy for primary and key secondary endpoints

In order to describe the nature of the benefits of Olaparib maintenance treatment, PFS, PFS2 and OS will be tested at a 1-sided significance level of 2.5%.

However, in order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure will also be employed across the primary endpoint and secondary endpoints intended for key label claims (ie OS).

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha 5% 2 sided) and the key secondary endpoint of OS will then be

tested using a multiple testing procedure with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 2).

Figure 2 Multiple Testing Procedures

At the interim analyses for PFS, 1% of alpha will be spent; statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26%. (Stone 2010). If PFS is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. Two interim analyses for OS will be performed; the first at the time of the interim PFS analysis (approximately 45 PFS events) and the second at the time of the final PFS analysis (approximately 89 PFS events). A final analysis of OS will be performed when approximate 106 death events have occurred. Statistical significance for OS will be declared the first at interim analyses for OS if the null hypothesis for PFS is rejected and the observed p-value for OS is $p<0.005$. If the null hypothesis for OS is not rejected at this time, then statistical significance for OS will be declared at the next interim analyses (final analysis of PFS) if the null hypothesis for PFS has been rejected and the observed 1-sided p-value for OS is < 0.01499. The final significance level will be determined accounting for the actual correlation between the interim and final OS analyses. To ensure that the type I error will be controlled at the 2.5% 1-sided level, if the interim analyses occur at exactly 30% and 57% of events respectively and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final analysis would be 1.53%

All planned analyses will be performed, regardless of the outcome of the MTP.

8.8.2 Analysis of the primary variable (s)

A single interim PFS analysis for superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on the BICR. A final PFS analysis will be performed when approximately 89 progression events have occurred (~60% maturity) based on the BICR. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

PFS will be analysed using a log rank test. The hazard ratio (HR) and confidence interval will be estimated from the U and V statistics obtained directly from the LIFETEST model (and using the Breslow approach for handling ties).

The HR and its confidence interval will be estimated from the log-rank as follows (Berry et al 1999 and Sellke et al 1983)

$$HR = \exp(U/V)$$

$$95\%\ CI\ for\ HR = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96/\sqrt{V}\})$$

Where $U = \sum_i (d_{1i} - e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic as produced in the LIFETEST output.

The HR (Olaparib vs. placebo) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib).

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment arm.

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 producing 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 primary analysis will be based on the programmatically derived PFS based on BICR overall visit assessments (ie Individual tumour measurements will not be used) and using all scans regardless of whether they were scheduled or not.

The estimated PFS rates 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 they had not progressed and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, the HR and associated confidence interval calculated from a Cox Proportional Hazards model containing treatment and these additional demographic variables, may be reported.

Subgroup analyses will be conducted comparing PFS between treatments. 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 PFS will not be formally analysed. In this case, only descriptive summaries will be provided

The following subgroups of the full analysis set will be analysed for PFS:

- Type of chemotherapy (doublets vs triplets)
- Time on first line treatment till randomisation (≤6 months vs >6 months)
- Best response on first line treatment (SD vs PR/CR)
- Measurable versus non measurable disease /no evidence of disease at baseline
- *BRCA* mutation type, eg *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation (>=65 vs. <65)
- Race
- Sex

Other baseline variables may also be assessed if there is clinical justification.

For each subgroup, the HRs (Olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor and treatment-by-factor interaction term. 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).

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

A further analysis of PFS (using Investigator assessed RECIST) may be performed at the time of the OS analyses, if requested by Health authorities.

8.8.3 Sensitivity analysis for the primary endpoint

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used as for the primary analysis of PFS and the HR and associated 95% CI will be reported.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (ie, 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.

8.8.3.1 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 stratified log rank test, 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). This approach will use the BICR RECIST assessments.

8.8.3.2 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 presented.

8.8.3.3 Ascertainment bias

A log-rank test will be repeated using the programmatically derived RECIST using Investigator assessed PFS. The HR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using Investigator assessments, then the proportion of patients with site but no central confirmation of progression will be summarised. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the Investigator review as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the Investigator review as a proportion of all discrepancies.

8.8.3.4 Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A log-rank test will be repeated using the BICR RECIST data, using the same ties as described for the primary analysis of PFS. The HR and 95% CI will be presented.

8.8.4 Analysis of the secondary variable(s)

8.8.4.1 Analysis of OS endpoint

OS data will be analysed at the time of the interim (if PFS null hypothesis rejected) and final analyses of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

The sensitivity analysis outlined in Section 8.8.3 will not be repeated for OS with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS is reversed.

To assist in quantifying the PFS effect, at the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data (Chen and Sun 2011). The estimate of the treatment effect for OS at the final analysis is defined as $\hat{\Delta}_I = w\hat{\Delta}_F + (1-w)\hat{\Delta}_P$ where $\hat{\Delta}_F$ is the observed treatment effect for OS at the time of the PFS analysis and $\hat{\Delta}_P = \hat{\rho}\hat{\Delta}_I$ is the estimated treatment effect for OS based on the observed treatment effect for PFS, where $\hat{\rho}$ represents the estimated slope relating PFS to OS from historical trials. The weightings (w) are based on the inverse of the variance (ie those with more uncertainty are given less weight). The variance is dependent on the correlation between the two endpoints. Details of the methodology will be provided in the statistical analysis plan (SAP).

8.8.4.2 Analysis of PFS2 endpoint

The analyses of PFS2 will use the same methodology and model as the primary analysis of PFS. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF. Second progression status

will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie censored at the last progression assessment date if the patient has not had a second progression or death)

As a key sensitivity, the analysis of PFS2 will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

A KM plot of the time to censoring where the censoring indicator of the primary PFS2 is reversed will be produced.

Time from second progression to previous assessment will be summarised by treatment arm.

8.8.4.3 Analysis of TDT endpoint

Time to study treatment discontinuation or death (TDT) will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

As a key sensitivity, the analyses of TDT will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TDT in this subset of patients will be presented by treatment group.

8.8.4.4 Analysis of TFST endpoint

Time to first subsequent therapy or death (TFST) will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. In addition, the time between progression and starting subsequent therapy will be assessed.

As a key sensitivity, the analyses of TFST will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TFST in this subset of patients will be presented by treatment group.

8.8.4.5 Analysis of TSST endpoint

Time to first second subsequent therapy or death (TSST) will be analysed analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm.

Summary tables of first and second subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm.

As a key sensitivity, the analyses of TSST will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TSST in this subset of patients will be presented by treatment group.

8.8.4.6 Analysis of PRO endpoints

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales.

Time to global QoL and pancreatic pain scale deterioration will be analysed using the same methodology and model as described for the primary analysis of PFS. However sensitivity analyses will not be performed (with the exception of attrition bias).

Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model. If the overall response rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Supportive analyses (of time to deterioration and improvement rates) will be performed for the individual QLQC30 domains (physical, role, cognitive, emotional, social). Treatment estimates and 95% CI for each domain will be presented on forest plots (one for Time to deterioration and one for improvement rate). P-values will not be calculated for these supportive analyses. These additional sub-scales are considered exploratory to support the primary QLQC30 global QoL and will be used to assess whether any observed differences in the global measure are driven by particular domains of functioning, symptoms or group of symptoms.

Descriptive statistics and graphs will be reported for the Global QoL item and the pancreatic pain scale by visits as well as change in these scores from baseline. Summary tables of QLQC30 best change rates will be provided (improvement, worsening, no change).

As supportive analyses, change from baseline in global QoL and pancreatic pain scale scores will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, pooled centre, visit and treatment by visit interaction as explanatory variables and the baseline score as a covariate. Treatment, visit and

treatment by visit interaction will be fixed effects in the model; centre will be a random effect. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. If there are still issues with the fit of the model or estimation of the treatment effects, CENTRE will be treated as a fixed effect.

The adjusted mean estimates and corresponding 95% confidence intervals will be presented by visit for each treatment group.

No formal testing will be done on the global QoL and pancreatic pain scale data. Data will be descriptive and plots will be used to visualise the adjusted mean global QoL score across time for each treatment arm.

Compliance

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 QoL score, divided by the number of patients randomised. Compliance over time is calculated separately for each visit, including baseline, as the number of patients providing an evaluable assessment for the global QoL score at that visit divided by the number of patients expected to have provided an assessment.

QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

8.8.4.7 Summary of Best overall RECIST Response (BoR) and ORR

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

The objective response rate (ORR) will be summarised (ie, number of patients (%)) by treatment group in patients in the FAS (ITT population) with measurable disease at baseline. Any patients who experienced CR or PR which was first observed whilst receiving subsequent therapy after discontinuation of Olaparib/placebo will be identified. The denominator for the response rate will be measurable disease as defined by the BICR data

ORR and BOR will be presented based on the BICR data and also summarised in a similar way using the investigator recorded data.

8.8.4.8 Summary of DCR

The disease control rate (DCR) will be summarised (ie, number of patients (%)) by treatment group in patients in the FAS (ITT population).

DCR will be presented based on the BICR data and also the investigator recorded data.

8.8.5 Exploratory analysis

8.8.5.1 Exploratory analysis of PRO endpoints (PAN-26 symptom scales and items)

Exploratory analyses, examining improvement rates and time to worsening, will be performed for the individual PAN-26 symptom scales and items (with a particular focus on fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice), and presented on forest plots (showing treatment estimates and 95% CI for each domain). P-values will not be calculated for these exploratory analyses.

Descriptive statistics and graphs will be reported for the symptom scales and items (specifically fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite and jaundice). Summary tables of PAN26 best change rates will be provided (improvement, worsening, no change).

Change from baseline in QLQC30 functioning domain scores and PAN-26 scales and items may be analysed using the same MMRM model described in Section 8.8.4.6 for Global QoL score and the pancreatic pain score.

Descriptive summaries for individual symptom items within the PAN-26 will also be provided.

8.8.5.2 Analysis of Healthcare Resource Use

A health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance.

Descriptive statistics, graphs and listings will be reported for health state utility 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.

The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

8.8.5.3 Analysis of ECOG Performance status

Shift tables will be provided showing best and then worst on treatment change in performance status vs baseline, by treatment.

Change from baseline in levels of ECOG performance status at each post randomisation time point will be reported descriptively (n, %) by treatment group, as well as the proportion of patients with ECOG status of 0 at baseline (ie cannot improve).

8.8.6 Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. 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 patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan. These analyses are intended to support reimbursement appraisals.

8.8.7 Exploratory translational science endpoints

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

8.8.8 Biomarkers

Biomarker data will be summarised descriptively using tables and plots. If the data is available at the time of developing the CSR then the biomarker data will be included in the CSR. Otherwise the biomarker data will be reported in a separate addendum to the CSR (if applicable). Further details on the data summaries and plots for the biomarker data for the CSR will be provided in the SAP.

BRCA status will be summarised for all patients based on the central myriad test result. This will highlight any patients with a negative *BRCA* result from the central test.

8.9 Sample Size Determination

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately 89 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on BICR.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and 2.26% alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median OS for placebo. At the interim

analyses, 0.5% of alpha (1-sided) will be spent, and controlling the type I error across the two time points, 89 PFS events will be required at the final analyses.

Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. Assuming 45 PFS events at the interim, a HR ≤ 0.46 would equate to a 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26%. (Stone 2010). Assuming 89 PFS events, a HR ≤ 0.65 would equate to a 1-sided p-value <0.0226.

Patients are to be followed for the final analysis of OS (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6 month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

Assuming that the study accrual period will be approximately 15 months, 89 progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that 45 PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 death events will occur approximately 31 months after first patient in.

8.9.1 Interim analysis

A single interim PFS analysis for superiority and futility will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

Section 8.8.1 details the spending function used to account for multiplicity introduced by including interim analyses for superiority.

Interim analyses of OS will be performed at the time of the interim analyses of PFS (~89 PFS events),and again at the final analyses at the final analyses of PFS (~89 events), and when approximately 106 OS events have occurred.

If the interim PFS results indicate superiority, then analyses of all other endpoints would be performed and the results of these analyses will form the basis for submissions for regulatory approval. Patients would continue to be followed for PFS and survival until ~89 PFS events had occurred, and then followed for survival until 106 patients had died.

The futility analyses on PFS will be used to guide decisions on stopping the study for futility or continuing the study. Details will be documented in the IDMC charter.

9. STUDY AND DATA MANAGEMENT BY PAREXEL

9.1 Training of study site personnel

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

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

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

9.2 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 CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

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

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q2 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.

9.4 Data management by PAREXEL

Data management will be performed by PAREXEL. .

The data collected through third party sources will be obtained and reconciled against study data.

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

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

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

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

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Data from external providers (eg 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, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including 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.

Exploratory 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 analyse samples. The results from this exploratory genetic research will not be reported in the CSR.

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.

Site staff will enter PRO booklet data into Medidata Rave exactly as reported by the patient.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

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**.**

The exception to the above is the result of the Myriad *BRCA* test. This will be made available to the Investigator and patient.

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.

10.3 Ethics and regulatory review

An Institutional Review Board (IRB)/Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

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

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

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

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study

- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File

- Ensure a copy of the signed Informed Consent Form is given to the patient

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

10.5 Changes to the protocol and informed consent form

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

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

The amendment is to be approved by the relevant Ethics Committee 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 Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

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

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any

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

11. LIST OF REFERENCES

Alexandrov et al 2013
Alexandrov et al. Signatures of mutational processes in human cancer Nature 2013;500;7463;415-21

American Cancer Society 2013
American Cancer Society. Cancer Facts and Figures 2013. Atlanta, Georgia: American Cancer Society, 2013. http://www.cancer.org

Audeh et al 2010
Audeh, M.W., Carmichael, J, Penson R.T. et al., Oral poly(ADP-ribose) polymerase inhibitor Olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet, 2010. **376**(9737): p. 245-51.PMID: 20609468

Bang et al 2013
Bang et al. Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: A randomized, double-blind phase II study. J Clin Oncol 31, 2013 (suppl; abstr 4013)

Bergfeldt et al 1995
Bergfeldt K, Einhorn S, Rosendahl I & Hall P. Increased risk of second primary malignancies in patients with gynecological cancer. A Swedish record-linkage study. Acta Oncol. 1995;34(6):771-7.

Berry et al 1999
Berry G, Kitchin RM & Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-755

Bryant et al 2005
Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature, 2005. **434**(7035): p. 913-7. PMID: 15829966

Chen and Sun 2011
Quantification of PFS Effect for Accelerated Approval of Oncology Drugs. Statistics in Biopharmaceutical Research 2011, Vol. 3, No. 3DOI: 10.1198/sbr.2011.09046

Cole and Strair 2010
Cole M, & Strair R. Acute myelogenous leukemia and myelodysplasia secondary to breast cancer treatment: case studies and literature review. Am J Med Sci 2010;339(1):36-40.

Conroy et al 2011
Conroy T. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer, 2011 NEngl J Med 364; 1817-25

Cowley et al 2013
Cowley et al Understanding pancreas cancer genomes. J Hepatobiliary Pancreat Sci (2013) 20:549–556

Fayers et al 1999
Fayers P, Aaronson N, Bjordal K & Sullivan M (1999). EORTC QLQC30, Scoring Manual. Belgium: EORTC Data Center.

Ferrone CR et al 2009
Ferrone CR. et al.BRCA Germline Mutations in Jewish Patients With Pancreatic Adenocarcinoma. Journal of Clinical Oncology, Vol 27, No 3 (January 20), 2009: pp. 433-438

Fitzsimmons D et al 1999
Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur. J. Cancer 35: 939-941, 1999.

Fong et al 2009
Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med. 2009;361(2):123-34.

Fowble et al 2001
Fowble B, Hanlon A, Freedman G, Nocolaou N, Anderson P. Second cancers after conservative surgery and radiation for stages I-II breast cancer : identifying a subset of women at increased risk. Int J Radiat Oncol, Biol, Phys. 2001; 51 (3);679-690.

Gaymes et al 2008
Gaymes TJ, Shall S, MacPherson LJ, Twine NA, Lea NC, Farzaneh F, and Mufti GJ. Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes. Haematologica 2009; 94:638-646. doi:10.3324/haematol.2008.00193

Ginsburg et al 2010
Ginsburg et al *BRCA1* and *BRCA2* families and the risk of skin cancer Springer Science+Business Media B.V. 2010

Goggins M. et al 1996
Germline M et al BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996 Dec 1;56(23):5360-4

Hay et al 2009
Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res. 2009;69(9):3850-5.

Hahn et al 2003
Hahn et al BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003 Feb 5;95(3):214-21.

Helleday 2011
Helleday T. The underlying mechanism for the PARP and *BRCA* synthetic lethality: Clearing up the misunderstandings. Molecular Oncology 2011; 5: 387-393.

Jemal A et al 2011
Jemal A et al. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90

Kaufman B et al 2013
Kaufman B, Shapira-Frommer R Schmutzler RK, Audeh MW, et al. Olaparib monotherapy in patients with advanced cancer and a germline *BRCA1/2* mutation: An open label phase II study. J Clin Oncol 31, 2013 (suppl; abstr 11024)

Kim et al 2014
Kim et al. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poor prognosis. Clin Cancer Res Published Online First January 31, 2014

Ledermann et al 2013
Ledermann, J Clin Oncol 31, 2013. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (SOC) and a *BRCA* mutation (*BRCAm*)

Lowery M et al 2011
Lowery M et al.An Emerging Entity: Pancreatic Adenocarcinoma Associated with a Known BRCA Mutation: Clinical Descriptors, Treatment Implications, and Future Directions The Oncologist 2011, 16:1397-1402.

Murai et al 2012
Murai J, Huang SN, Das BB, Renaud A, Zhnag, Y, Doroshow, JH, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. AACR; 72(21); 5588–99.

Murphy KM et al 2002
Evaluation of Candidate Genes MAP2K4, MADH4, ACVR1B, and Mutations in 17% BRCA2 in Familial Pancreatic Cancer: Deleterious BRCA2. Cancer Res 2002;62:3789-3793.

Osoba D et al 1998
Osoba D, Rodrigues G, Myles J, Zee B and Pater J. Interpreting the significance of changes in health-related quality-of-life scores. JCO January 1998 vol. 16 no. 1 139-144

Ozcelik et al 1997
Ozcelik et al Germline *BRCA2* 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients Nature Genetics 16, 17 - 18 (1997)

Rahma et al 2013
Rahma et al Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Annals of Oncology 2013 Aug;24(8):1972-9.

Robins et al 1991
Robins JM, Tsiatis AA. Correcting for noncompliance in randomized trials using rank preserving structural failure time models. Communications in Statistics - Theory and Methods 1991; 20:2609-2631.

Robins 1993
Robins J. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. Proceedings of the Biopharmaceutical Section, American Statistical Association 1993; 24-33.

Rottenberg et al 2008
Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of *BRCA1*-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci. 2008;105(44):17079-84.

Roy et al 2012
Roy, R., J. Chun, and S.N. Powell, *BRCA1* and *BRCA2*: different roles in a common pathway of genome protection. Nat Rev Cancer, 2012. **12**(1): p. 68-78. PMID: 22193408

Sadler ZK. 2012
Sadler ZK. 2012. BRCA and Pancreatic Cancer: Selection of Chemotherapy Journal of the Pancreas JOP. J Pancreas (Online) 2012 Mar 10; 13(2):180-181

Sellke et al 1983
Sellke, T. and Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 70: 315-326, 1983

Stone 2010
Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. Pharm. Statistics 5 (2010) 151-161

Sun and Chen 2010
Sun X, Chen C: Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. Stat Biopharm Research 2:97-108, 2010

The Breast Cancer Linkage Consortium 1999
The Breast Cancer Linkage Consortium: 1999 J Natl Cancer 91:1310-16

Tutt A et al 2010
Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel J et al,. Oral poly(ADP-ribose) polymerase inhibitor Olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 376: 235–44

Von Hoff et al 2013
Daniel D. Von Hoff, M.D. et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine N Engl J Med 2013; 369:1691-1703

Wesolowski et al 2007
Wesolowski R, Choueiri TK, Rybicki L, Shealy AG, Casey G, Weng D, et al. BRCA mutation status and risk of secondary malignancy following chemotherapy for breast cancer. J Clin Oncol, 2007;ASCO Annual Meeting Proceedings Part I. Vol (25);No. 18S (June 20 Supplement):11017.

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Clinical Study Protocol Appendix A	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014
Protocol Dated	31 March 2014

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with g*BRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

June 16th 2014
Date
(Day Month Year)

Jane Robertson
Medical Science Director
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Macclesfield
Cheshire SK10 4TG, UK

ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with g*BRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

13-Jun-2014

Date
(Day Month Year)

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ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with g*BRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

24/06/2014
Date
(Day Month Year)

Helen Mann
Global Product Statistician
AstraZeneca
90T 169-3 East Wing, Parklands
Alderly Park, Macclesfield
Cheshire SK10 4TG, UK

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with g*BRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Signature:

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with g*BRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Signature:

ISRAEL

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Clinical Study Protocol Appendix B	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

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.

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Clinical Study Protocol Appendix C	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

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/dgr/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/dgr/Pages/infectious_substances.aspx)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

Appendix D
Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

TABLE OF CONTENTS PAGE

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. Hy's Law 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 Product (IP).

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)

A Potential Hy's Law (PHL) case is defined as a study subject with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

A Hy's Law (HL) case is defined as a study subject with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

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

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

- 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:

- 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 patient's 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 3 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 were 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 IP. 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 IP:

- 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 (including the 30-day follow-up period) 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 subsequent 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 such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. 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 (including the 30-day follow-up period) 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 subsequent 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, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. 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

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Clinical Study Protocol Appendix E	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

Appendix E
Acceptable Birth Control Methods

1. 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 in combination while they are receiving study treatment and for 3 months after last dose of study drug.

Acceptable Non-hormonal birth control methods include

- Total/True abstinence: when the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for 3 months after the last dose of study drug. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom
- IUD plus male condom. Provided coils are copper-banded

Acceptable hormonal methods

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

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Clinical Study Protocol Appendix F	
Drug Substance	Olaparib
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Appendix F
Guidelines for Evaluation of Objective Tumour Response Using Modified RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of modified RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009) for the study D081FC00001 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 measurable disease and/or non measurable disease or no evidence of disease assessed at baseline by CT (or MRI where CT is contraindicated) will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at base-line.

Measurable lesions

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

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

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

- Previously irradiated lesions. Localised post-radiation changes which affect lesion size, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

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 non-cystic lesions should be selected as target lesions (TLs).

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 TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

3. METHODS OF MEASUREMENT

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

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, 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
	X-ray, Chest x-ray	X-ray, Chest x-ray, Clinical examination
	Clinical examination	Ultrasound
		Bone scan
		FDG-PET

3.1 CT and MRI

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

In study D081FC00001 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 contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

3.2 Clinical examination

In study D081FC00001 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-rays

3.3.1 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.3.2 Plain X-ray

In study D081FC00001 plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs 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

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment 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 the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs 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 NTLs and followed by the same method as per baseline assessment.

In the D081FC00001 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 D081FC00001 study FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed every 8 weeks (±1 week) for 40 weeks and then every 12 weeks ± 1 week relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1. See Table 1: Study Schedule from Study Protocol for further information. 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.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule, until objective radiological disease progression, irrespective of reasons for discontinuation of treatment.

4.2 Target lesions

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 TLs 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 millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs 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 TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

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

4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, 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 TLs, 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 TLs 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 (NE) as a TL response

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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 NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

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

Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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

4.4 New Lesions

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

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

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

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

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of Overall Visit Response and Best Overall 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
NA	NA	No	NED

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NED = no evidence of disease, NA = not applicable (relevant when no TLs/NTLs at baseline)

5. CENTRAL REVIEW

All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. After the final Progression Free Survival (PFS) analysis, central review of scans will no longer be required. Patients should continue to receive study treatment until objective radiological disease progression as per modified RECIST 1.1 as assessed by the investigator, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The CRO appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J.

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

Appendix G
ECOG Performance Status

1. ECOG PERFORMANCE STATUS

1.1 Example of Performance Status (ECOG SCALE)

DESCRIPTION	ECOG GRADE
Fully active, able to carry on all pre-disease performance without restriction.	0
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
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Clinical Study Protocol Appendix H	
Drug Substance	Olaparib
Study Code	D081FC00001
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Appendix H
CYP3A4/5 Restrictions

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LIST OF TABLES

GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

NB. While this is not an exhaustive list, it covers the known potent inhibitors and inducers, which have most often previously been reported to be associated with clinically significant drug interactions. Please contact the Medical Monitor or AstraZeneca physician if further clarification is required.

1. POTENT INHIBITORS OF CYP3A4/5

In vitro data has shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and consequently, to ensure patient safety, **the following inhibitors of CYP3A4/5 must not be used during this study.**

Table 1 Competitive inhibitors of CYP3A4/5

Drug	Minimum washout period prior to starting olaparib
Ketoconazole	1 Week
Itraconazole	
Indinavir	
Saquinavir	
Telithromycin	
Nelfinavir	

Table 2 Time dependent inhibitors of CYP3A4/5

Drug	Minimum washout period prior to starting olaparib
Clarithromycin	1 Week
Ritonavir	

2. INDUCERS OF CYP

In addition, to avoid potential reductions in exposure due to drug interactions, **the following CYP3 inducers should be avoided:**

Table 3 Inducers of CYP

Drug	Minimum washout period prior to starting olaparib
Carbamazepine	3 Weeks

Table 3 Inducers of CYP

Drug	Minimum washout period prior to starting olaparib
Modafinil	
Nevirapine	
Phenytoin	
Rifabutin	
Rifampicin	
Rifapentin	
St John's Wort (Hypericum perforatum)	
Phenobarbitone	5 Weeks

After randomisation if the use of any potent CYP inducers or inhibitors of CYP3A4/5 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.

3. NATURAL / HERBAL PRODUCTS

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

4. INTERACTIONS WITH P450

Olaparib is an investigational drug for which no data on in vivo interactions is currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity.

Clinical Study Protocol Appendix I	
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Appendix I
Patient Reported Outcomes EORTC QLQ-C30, QLQ-PAN26, EQ-5D-5L

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

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 - PAN26

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 abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

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

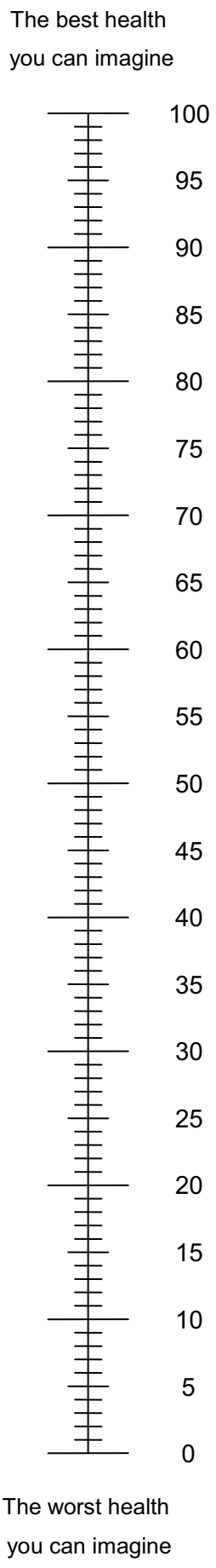
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



Revised Clinical Study Protocol_Global	
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Date	28 February 2015

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

27-Mar-2015

May Lien — Date

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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	14 October 2014		
2	28 Feburary 2015		

PROTOCOL SYNOPSIS

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Study centre(s) and number of patients planned: Approximately 80 centres worldwide will be initiated to randomise approximately 145 patients with germline *BRCA1/2* mutations and metastatic adenocarcinoma of the pancreas (hereafter referred to as pancreas cancer). Additional countries and centres may be added dependent on recruitment rates.

Study period		**Phase of development**
Estimated date of first patient enrolled	Q2 2014	III
Estimated date of last patient completed	Q2 2017	

Besides the main study, an exploratory study looking at the feasibility of assaying for and determining the prevalence of tumour tissue biomarkers (including but not limited to somatic *BRCA1/2* mutations, methylation and/or other HRD biomarkers) will be done on tissue samples submitted by patients screened for *gBRCA*. The information from this exploratory analysis may potentially guide future pancreas cancer Olaparib studies.

Objectives

Primary Objective:	**Outcome Measure:**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS)	• Progression Free Survival (PFS) by BICR using modified RECIST 1.1

Secondary Objective:	**Outcome Measure:**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo	• Overall Survival (observed and predicted using observed PFS and OS data) • Time from randomisation to second progression (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST). • Time from randomisation to study treatment discontinuation or death (TDT) • Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients • Disease Control Rate at 16 weeks by BICR using modified RECIST 1.1 criteria
• To assess the effect of Olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.	• Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire

Safety Objective:	**Outcome Measure:**
• To assess the safety and tolerability of Olaparib maintenance monotherapy	• Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

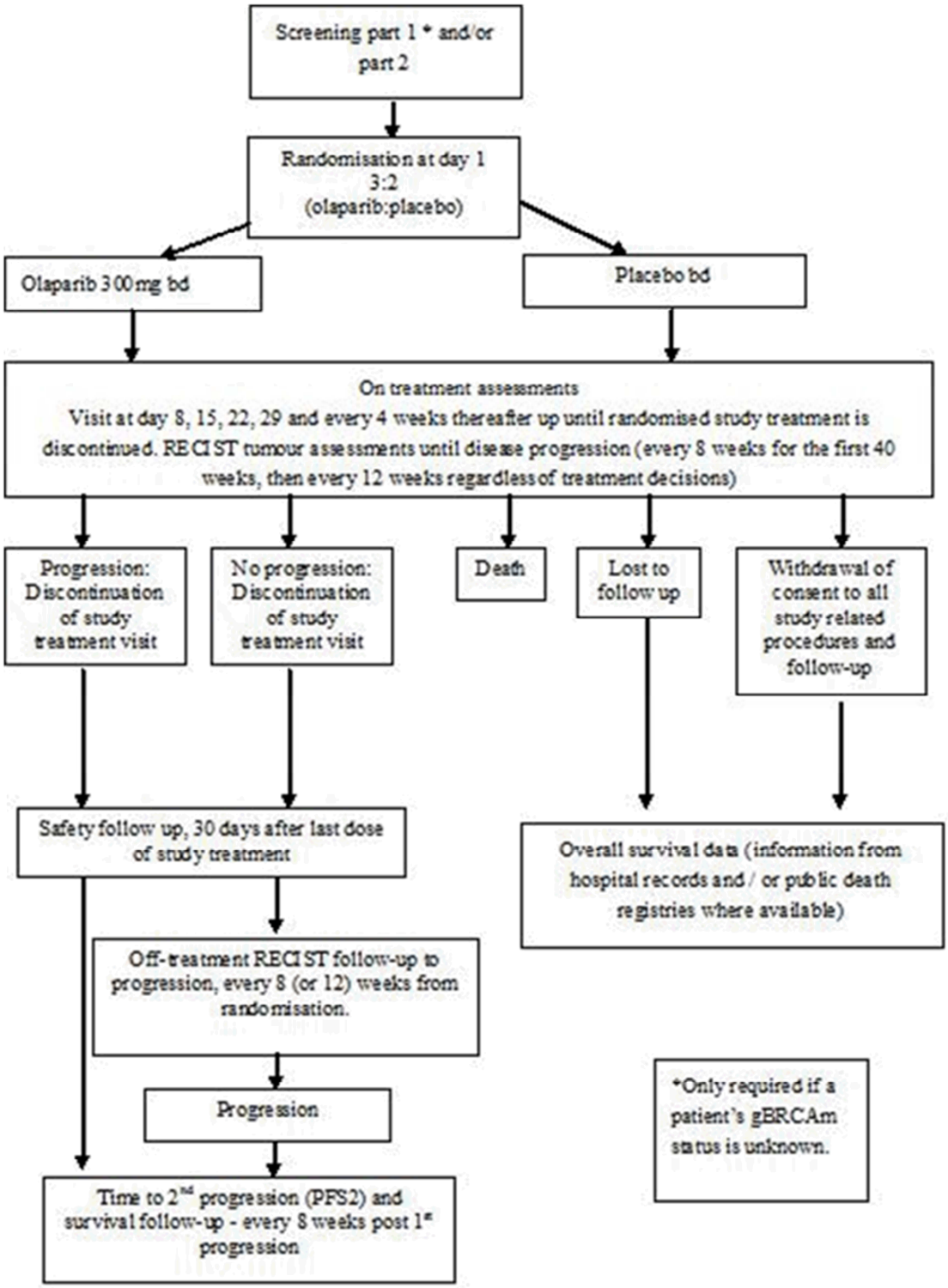
Exploratory Objective:	**Outcome Measure:**
• To assess the effect of Olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical,	• Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 + PAN26

role, cognitive, emotional and social). • To assess the effect of Olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales. • To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice • To assess change in performance status as measured by the ECOG Performance Status scale	symptom scales and items (pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice and on performance status measured by the ECOG Performance Status scale
• To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D
• To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement appraisals)
• To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.	• BRCA1 and/or BRCA2 mutation status in tumour
• To identify tumour tissue based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRCA methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches	• Potential tissue biomarkers identified

for development • Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.	

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

Study Flow Chart



Target Patient population

All patients randomised in the study will be selected based on the following 2 principles:

- **Genetic selection**: Documented germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Patients with g*BRCA1* and/or g*BRCA2* mutations that are considered to be non detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism," etc) will not be eligible for the study.

- **Treatment setting:** All eligible patients must have metastatic *gBRCAm* pancreas cancer, must have received a minimum of 16 weeks of platinum based treatment and must have no evidence of progression based on investigator's opinion. Study treatment will be started after randomisation as soon as possible but no less than 4 and no more than 8 weeks after last dose of first line chemotherapy. Tumour response during study treatment will be assessed using modified RECIST 1.1. Baseline assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis and should be performed no more than 28 days prior to start of study treatment, and as close as possible to randomisation. Follow-up assessments should be performed every 8 weeks (±1 week) for 40 weeks and then every 12 weeks ± 1 week relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1.

An exploratory study looking at the feasibility of assaying for and determining the prevalence of tumour tissue biomarkers (including but not limited to somatic *BRCA1/2* mutations, methylation and/or other HRD biomarkers) will be done on tissue samples submitted by patients screened for *gBRCA*. The information from this exploratory analysis may potentially guide future pancreas cancer Olaparib studies.

After confirmation of eligibility, patients will be randomised (using an IVRS) in a 3:2 ratio (Olaparib:placebo) to the treatments as specified below:

- Olaparib tablets po. 300 mg twice daily

- Placebo tablets twice daily

Investigational product, dosage and mode of administration

Olaparib is available as a green film-coated tablet containing 150 mg or 100 mg of Olaparib. Patients will be administered study treatment orally at a dose of 300 mg twice daily (bid). The planned dose of 300 mg bid will be made up of two x 150 mg tablets bid with 100 mg tablets used to manage dose reductions.

Comparator, dosage and mode of administration

Placebo will be available as green film-coated tablets matching the Olaparib tablets. These should be taken as per instructions for Olaparib tablets.

Duration of treatment

Patients should continue to receive study treatment until objective radiological disease progression per modified RECIST 1.1 as assessed by the investigator or unacceptable toxicity and they do not meet any other discontinuation criteria. Patients who are determined to have progressed according to modified RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review one additional RECIST assessment will be requested preferably at the next scheduled RECIST visit. Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. It is expected that many if not most patients will be restarted on a platinum based regimen at progression on study therapy. Whatever the regimen, they will be assessed for PFS2 and followed for survival.

Statistical methods

Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately **87** PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for futility will be performed when 50% of the final number of progression **event**s needed for the **primary PFS analysis** has been reached (approximately **44** PFS events). The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and **2.5**% alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo.

Assuming that the study accrual period will be approximately 15 months, 87 progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that 44 PFS events will occur approximately 13 to 14 months after the first patient enters the trial.

Patients are to be followed for the final analysis of OS (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 2.5% level (1-sided) if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6 month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

The primary statistical analysis of the efficacy of Olaparib will include all randomised patients (Full Analysis Set; FAS) and will compare the treatment groups on the basis of randomised

treatment, regardless of the treatment actually received. In addition, key sensitivity analyses of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a g*BRCA* mutation confirmed by the Myriad test. When assessing safety and tolerability, summaries will be produced based on the Safety Analysis Set. This will include all patients who receive at least one dose of randomised treatment (Olaparib or placebo). The safety data will be summarised descriptively and will not be formally analysed.

PFS will be analysed using a log rank test. The HR together with its 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib). The primary analysis will be based on a blinded independent central review (BICR) of disease progression by modified RECIST 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

Subgroup analyses will be conducted to assess consistency of treatment effect across potential prognostic factors (see Section 8.8.2 for all predefined subgroups). An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (ie, if there are less than 20 events in a subgroup).

OS analyses will be performed at the same time as the **primary** analysis of PFS and will use the same methodology and model as PFS. A final analysis of OS will be performed when approximately 106 death events have occurred and a multiplicity adjustment will be made to account for the different analyses. At the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data.

Exploratory analyses of OS which attempt to adjust for any potential confounding impact of subsequent use of PARP inhibitors on the control arm may be performed if an appropriate proportion of patient's on the control arm receive such treatments and sufficient information is collected on subsequent therapy use.

PFS2 analyses will be performed at the same time as the **primary** analys**i**s of PFS, and at the time of the final analysis of OS. PFS2 will be analysed using the same methodology and model as PFS.

In order to describe the nature of the benefits of Olaparib maintenance treatment, PFS, PFS2 and OS will be tested at a 1-sided significance level of 2.5%. However, in order to strongly control the type I error, a multiple testing procedure will also be employed where PFS is tested first using the full test mass and OS will be tested if the null hypothesis for PFS is rejected.

Secondary analyses of time to treatment discontinuation, time to first subsequent therapy or death, and time to second subsequent therapy or death will be provided, using the same methodology as specified for the primary analyses of PFS; however no multiplicity adjustment will be applied as these are viewed as supportive endpoints.

Objective tumour response rates and disease control rates (based on central review) will be summarised for the two treatment arms. In addition, the investigator reported response rates will also be summarised.

Patient Reported Outcomes

The impact of olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC QLQ-C30 global quality of life **(QoL)** and **QLQ-**PAN26 pancreatic pain scales. **Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. As a supportive analysis,** global **QoL** improvement rate will be analysed using a logistic regression model.

An exploratory analysis will examine adjusted mean change from baseline on EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, social) and on EORTC QLQ-C30 and QLQ-PAN26 symptom scales/items (including pancreatic pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice).

EORTC QLQ-C30 and **QLQ-**PAN26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Health Economics

An exploratory health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance. For utility, descriptive statistics, graphs and listings will be reported for health state utility by visit 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.

Biomarkers

The most important biomarker research will be done on non-randomised and randomised patients. Screened patients will submit tumour samples for t*BRCA/BRCA* methylation/ HRD analyses. A combination of evaluability, prevalence and sensitivity for known g*BRCA* will be used to determine the feasibility of investigating Olaparib in future studies.

Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

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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 6.1)
ALP	Alkaline phophatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboblastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
Baseline	Refers to the most recent assessment of any variable prior to dosing with study treatment
BICR	Blinded Independent Central Review
bid	Bis in die (twice daily)
BoR	Best Overall RECIST Response
BP	Blood pressure
gBRCA	germline Breast Cancer susceptibility gene
BRCA mutation or *BRCAm*	Breast Cancer susceptibility gene mutation (see *gBRCA* mutation or *gBRCAm*)
BUN	Blood urea nitrogen
CHO	Chinese hamster ovary
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form (electronic/paper)
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DCIS	ductal carcinoma in situ

DCO	Data Cut Off
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DSB	Double strand break
ECG	Electrocardiogram
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
E-code	Enrolment code (allocated by IVRS/IWRS)
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing
eCRF	Electronic Case Report form
EORTC QLQ-C30	The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients
EORTC QLQ-PAN26	The EORTC QLQ-PAN26 module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes)
EQ-5D-5L/ EQ-5D	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FSH	Follicle stimulating hormone
gBRCA mutation or *gBRCAm*	The term "*gBRCA* mutation" is used to refer to a germline *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
gBRCA wt	gBRCA wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practice
GRand	AZ Global Randomisation system
Hb	Haemoglobin
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus

HR	Hazard Ratio
HRD	Homologous recombination repair deficiencies
HRQoL	Health-related Quality of Life
IATA	International Air Transport Association
IB	Investigator's brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IDMC	Independent Data Monitoring Committee
INR	International Normalised Ratio
IPCW	Inverse Probability of Censoring Weighting
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KM	Kaplan Meier
LDH	Lactic dehydrogenase
LH	Luteinizing hormone
LIMS	Laboratory Information Management System
m	Metre
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MDS	Myelodysplastic syndrome
mg	Milli-gram
MRI	Magnetic resonance imaging
nab	nanoparticle albumen bound
NCI	National Cancer Institute
NE	Not evaluable
NTL	Non-target lesions
OAE	Other Significant Adverse Event (see definition in Section 8.4.1)
ORR	Objective response rates
OS	Overall survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation

PD	Progressive disease
PFS	Progression Free Survival
p.o.	Per os (by mouth, orally)
PR	Partial response
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious adverse event (see definition in Section 6.2
SAP	Statistical Analysis Plan
SD	Stable disease
SSB	Single strand break
SUSARs	Suspected Unexpected Serious Adverse Reactions
Study treatment	Olaparib or control arm chemotherapy
tBRCA mutation or *tBRCAm*	The term "*tBRCA* mutation" is used to refer to a somatic tumour *BRCA1* or *BRCA2* mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants
TL	Target lesions
US	United States
WBC	White blood cells
WBDC	Web Based Data Capture
wt	Wildtype (patients without evidence of *BRCA1* or *BRCA2* deleterious or suspected deleterious mutations)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Pancreas cancer and its treatment

Pancreas cancer is a life-threatening disease and is the fourth leading cause of cancer death in the West. In 2013, it is estimated that there were 45,220 newly diagnosed pancreas cancer cases in the US, and approximately 38,460 people deaths from pancreas cancer (American Cancer Society 2013). Worldwide, it was estimated that 266,000 people died of pancreas cancer in 2008 (.

Fitzsimmons D et al 1999
Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur. J. Cancer 35: 939-941, 1999.

Fong et al 2009
Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med. 2009;361(2):123-34.

Fowble et al 2001
Fowble B, Hanlon A, Freedman G, Nocolaou N, Anderson P. Second cancers after conservative surgery and radiation for stages I-II breast cancer : identifying a subset of women at increased risk. Int J Radiat Oncol, Biol, Phys. 2001; 51 (3);679-690.

Gaymes et al 2008
Gaymes TJ, Shall S, MacPherson LJ, Twine NA, Lea NC, Farzaneh F, and Mufti GJ. Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes. Haematologica 2009; 94:638-646. doi:10.3324/haematol.2008.00193

Ginsburg et al 2010
Ginsburg et al *BRCA1* and *BRCA2* families and the risk of skin cancer Springer Science+Business Media B.V. 2010

Goggins M. et al 1996
Germline M et al BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996 Dec 1;56(23):5360-4

Hay et al 2009
Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res. 2009;69(9):3850-5.

Hahn et al 2003
Hahn et al BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003 Feb 5;95(3):214-21.

Helleday 2011
Helleday T. The underlying mechanism for the PARP and *BRCA* synthetic lethality: Clearing up the misunderstandings. Molecular Oncology 2011; 5: 387-393.

Jemal A et al 2011).

The poor prognosis of pancreas cancer (~90% of patients who are diagnosed will die of the disease) is a function of late presentation of the disease when inoperable/ locally advanced or metastatic. Furthermore treatment of metastatic pancreas cancer even with the most "active" regimens such as FOLFIRINOX (Conroy et al 2011) or gemcitabine + nab paclitaxel (Von Hoff et al 2013) is associated with median survivals of less than one year, and for single agent treatments at best only 6 months. Unfortunately the toxicity of the most active combination chemotherapy regimens limits the duration of exposure to patients even if benefiting from the treatment. The neurotoxicity of both FOLFIRINOX and gemcitabine + nab paclitaxel in the former case generally leads to discontinuation of some or all of the drugs at or before 6 months of treatment and in the later case dose attenuation. The FOLFIRINOX study recommended no more than a total of 6 months of chemotherapy for patients who had a response (Conroy et al 2011).Furthermore there are few if any established second line regimens available (American Cancer Society 2013) and benefit if any, is at most a few months of survival (Rahma et al 2013). Despite the development of more "active" regimens for first treatment of metastatic pancreatic cancer in the last decade, their limited absolute benefit and significant toxicity strongly suggest that improving the results of initial therapy of metastatic pancreas cancer constitutes an unmet medical need. Furthermore to date there has been no marker, clinical or molecular that would predict for increased likelihood of benefit from systemic therapies for pancreas cancer.

Although carriers of deleterious germline mutations of the *BRCA1* and particularly gene are known to have an increased risk of developing pancreas cancer (The Breast Linkage Consortium 1999, Goggins M. et al 1996), the prevalence of g*BRCA*m in the unselected cases of pancreas cancer is unclear but likely less than 5 % In a tissue based 7% of patients with resected pancreas cancer or human xenografts had "germline" in their tumour (Goggins M. et al 1996) but this cohort may not represent the typical unselected cases and the prevalence is likely somewhat lower. There are specific however, where the association is much stronger. In Ashkenazi Jewish patients with cancer, the prevalence of g*BRCA*m is 6-10% in unselected patients (Fayers et al 2001
Fayers et al. EORTC QLQ-C30 Scoring Manual (Third Edition). Belgium: EORTC Quality of Life Group, 2001.

Ferrone CR et al 2009, Ozcelik et al 1997) and 15% in patients with a family history of the disease (Sadler ZK. 2012). In pancreas cancer patients with a family history of the disease, reported prevalence of carrying a germline *BRCA2* mutation may be as high as 17-19% (Murphy KM et al 2002, Hahn et al 2003).Given the small size of the g*BRCA*m

subpopulation in pancreas cancer, information comparing the natural history of this group with the overall pancreas cancer population is minimal. One study of the natural history of Ashkenazi Jews with pancreas cancer treated with surgery (most of whom eventually died of the disease) could find no difference in survival between those who had germline *BRCA*m (n=8) vs. those who did not (n=137). The study however did not extend beyond 2004 and did not include patients treated with more modern chemotherapies (Fayers et al 2001
Fayers et al. EORTC QLQ-C30 Scoring Manual (Third Edition). Belgium: EORTC Quality of Life Group, 2001.

Ferrone CR et al 2009). In a large study of the natural history of *BRCAm* associated pancreas cancer, the median all–stage overall survival (OS) for 58 patients was 14 months (95% CI 10-23 months). Median OS for patients with stage 1-2 disease has not been reached at 60 months. Median OS for stage 3-4 was 12 months (95% CI 6-15). Superior OS was observed for patients with stage III and IV disease treated with platinum versus those treated with non-platinum chemotherapies (22 vs 9 months; p=0.039 (Golan *et al* unpublished data). There are no approved treatments for patients with germline *BRCA1/2* mutations and these patients are treated with regimens used for standard advanced pancreas (Lowery M et al 2011).

Recent data suggest there may also be a number of pancreas cancer patients' tumours with ATM defects or a g*BRCA*-like or HRD phenotype (Cowley et al 2013). The development of a test to identify such tumours may broaden the patient population which could benefit from PARP inhibitors. Obtaining tumour tissue to look for the prevalence these other potential markers of drug sensitivity is another unmet need in advancing therapy of this serious illness.

1.1.2 Chemotherapy use in advanced pancreas cancer

Chemotherapy for metastatic pancreas cancer has modest, at best, impact on PFS and OS. The "best" regimens for use as initial treatment of metastatic disease, FOLFIRINOX or gemcitabine + nab paclitaxel have respectively PFS's of 6.4 and 5.5 mos. and OS's of 11.1 and 8.5 mos. (Conroy et al 2011, Von Hoff et al 2013). Toxicity particularly on the platinum based regimen was substantial (80% had hematologic toxicity, 45% ≥grade 3; 70% had peripheral neurotoxicity, 9% ≥grade 3) and led to dose reductions and treatment discontinuations. It is of note that median number of FOLFIRINOX cycles given was 10 (ie. ~5 months of treatment) but the median PFS was 6.4 months suggesting some discontinuation prior to the planned 12 cycles and evidence of progression. Nevertheless platinum based regimens are widely used as first line therapy of metastatic pancreas cancer.

1.1.3 PARP inhibition as a target for *BRCA* mutation positive cancer

Investigators should be familiar with the current Olaparib (AZD2281) Investigator Brochure (IB).

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an

oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair. Tumours with homologous recombination deficiencies (HRD), such as ovarian cancers in patients with g*BRCA1/2* mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, Olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

gBRCA1 and g*BRCA2* defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo Rottenberg et al 2008, Hay et al 2009) and in the clinic (.

Fitzsimmons D et al 1999, Fong et al 2009, Fowble et al 2001). The mechanism of action for Olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011, Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by homologous repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knockout models, either as a stand-alone treatment or in combination with established chemotherapies.

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 eg, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

Rodent and dog toxicology studies have indicated that the primary target organ of toxicity is the bone marrow with recovery seen following withdrawal of Olaparib. *Ex vivo* studies have confirmed that Olaparib is cytotoxic to human bone marrow cells.

Olaparib was not mutagenic in the Ames test but was clastogenic in the Chinese hamster ovary (CHO) chromosome aberration test *in vitro*. When dosed orally, Olaparib also induced micronuclei in the bone marrow of rats. This profile is consistent with the potential for genotoxicity in man.

Reproductive toxicology data indicate that Olaparib can have adverse effects on embryofoetal survival and development at dose levels that do not induce significant maternal toxicity.

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

1.1.6 Clinical experience with Olaparib

Below is an outline of the monotherapy Olaparib studies conducted in pancreas cancer patients.

1.1.6.1 Olaparib monotherapy studies in pancreas cancer patients

Study D0810C00042

Study 42 was a single arm phase II study of Olaparib (capsules) 400mg po bid in patients with germline *BRCA*m malignancies across multiple tumour types. Twenty three patients with germline *BRCA*m-associated advanced pancreas cancer after therapy with gemcitabine were treated with Olaparib capsules 400mg po bid. All patients had seen a prior gemcitabine regimen and over half a prior platinum containing regimen. The ORR was 22%, DCR 57%, PFS 4.6 mos. and OS 9.8 mos (Kaufman B et al 2013). This level of activity compares favourably with that reported for other therapies reported in advanced previously treated pancreas cancer (Rahma et al 2013). A retrospective analysis of the patient data from study 42 suggested greatest benefit from Olaparib in those (15) patients whose tumours had not progressed on a prior platinum treatment (ORR 33%, DCR 66%, PFS 6.4 mos., OS 13.1 mos.).

1.2 Research hypothesis

Single agent Olaparib tablet 300 mg bid has superior efficacy and acceptable tolerability profile as compared with placebo in patients with deleterious or suspected deleterious germline mutation in *BRCA1* and/or *BRCA2* and metastatic pancreas cancer who have achieved disease control(absence of objective progression) after receiving a minimum of 16 weeks of first line platinum based chemotherapy. The efficacy in this study will be assessed by the primary analysis of PFS defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST1.1 criteria, or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to disease progression. To reduce bias, primary analysis of PFS will be based on blinded, independent central review of RECIST scans. Secondary endpoints include overall survival, DCR at 16 weeks, ORR (in patients with baseline evaluable disease), PFS2, safety assessments and patient-reported symptoms, functioning and health related quality of life.

1.3 Rationale for study design, doses and control group

Mutations in g*BRCA1* and g*BRCA2* are a very rare but definable molecular subgroup of pancreas cancer which may be found in some identifiable populations with a prevalence as high as 15%. Cells that lack g*BRCA1/2* function, such as cancer cells from patients with germline mutations in these genes, are deficient in their ability to repair double-strand DNA breaks through homologous recombination (Roy et al 2012). This deficiency is presumed to underlie the observation that g*BRCA1/2*-deficient cells are sensitive to interventions that promote double strand DNA breaks or cross-links, such as ionizing radiation and platinum-

based chemotherapeutic agents. Platinum based regimens are increasingly being used early in the treatment of advanced g*BRCA*-mutated breast and pancreas cancer, in addition to their established use in ovarian cancer. It is also presumed to underlie the observation that *gBRCA1/2*-deficient cells are sensitive to treatment with inhibitors of poly-(ADP-ribose)-polymerases (PARP inhibitors) (Bryant et al 2005) which are presumed to force repair of single-strand breaks towards the homologous repair pathway rather than the pathways that usually address single-strand breaks. Phase I and proof-of-concept phase II studies have shown that PARP inhibitors have significant activity with limited toxicity when used as single agents in the treatment of g*BRCA1/2* mutation-associated breast and ovarian cancer (Tutt A et al 2010; Audeh et al 2010) and pancreas cancer (Kaufman B et al 2013). The present trial is an important step in defining the role of Olaparib as a PARP inhibitor in patients with deleterious germline *BRCA1/2* mutations and metastatic pancreas cancer and the strategy of switch maintenance to prolong disease control after beneficial effect of a platinum regimen as has been suggested for *gBRCA*-mutated ovarian cancer (Kim et al 2014, Ledermann et al 2013). The study will assess the efficacy of Olaparib relative to placebo as maintenance therapy after documentation of disease control(absence of progression) on an initial platinum based regimen for metastatic g*BRCA* pancreas cancer. The preliminary analysis of study 42 suggests selecting patients with tumours which are not known to be platinum resistant would increase the likelihood of benefit. Because of data to suggest that "sporadic" pancreas cancers may have tumour tissue *BRCA* mutations (Goggins M. et al 1996), an exploratory analysis of tumour tissue will be done to assess the prevalence and feasibility of assaying tumour tissue for *BRCA* mutations and/or other markers of HRD. In the future it may be possible to extend the use of PARPi to patients with tumours having non-*BRCA* deficiencies in dsDNA repair. Olaparib has shown activity in ATM negative gastric cancer (Bang et al 2013) and there is suggestion of a similar sub-population in pancreas cancer (Kim et al 2014). Furthermore, independent groups have also identifed genomic signatures in pancreas cancer predicted to be associated with sensitivity to PARP inhibitors (Alexandrov et al 2013; Cowley et al 2013). In order to further understand candidate methods for identifying these patients in future clinical trials we are asking all patients to donate a tumour sample at screening. In order to understand the prevalence and relationship of these markers to *BRCA* status it is important that we are able to test samples from patients with and without *gBRCA* mutations.

If the trial is successful it will give patients a relatively non-toxic oral therapeutic which will delay progression after stopping first line platinum based chemotherapy.

1.3.1 Rationale for using Myriad Genetics

The FDA has indicated that the g*BRCA1* and g*BRCA2* mutation assay will need to be approved as a companion diagnostic in the US.

Myriad Genetics has been chosen as a partner in developing a companion diagnostic for g*BRCA1* and g*BRCA2* testing because it has extensive experience of g*BRCA1* and *gBRCA2* mutation detection. Myriad keeps a comprehensive database on g*BRCA1* and g*BRCA2* gene mutations and their clinical relevance. Furthermore, Myriad has an established laboratory

infrastructure, which supports high volume testing with turnaround times that can meet the needs of a clinical trial.

1.4 Benefit/risk and ethical assessment

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumours are estimated to have received treatment with Olaparib across the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of Olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the Olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given Olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to Olaparib capsule for ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term Olaparib (capsule) monotherapy exposure.

Additionally statistical analysis of the pooled QT/QTc data from 2 studies in a total of 109 patients for the primary multiple dose analysis and 119 patients for the supportive single dose analysis showed that following multiple dosing of olaparib (300 mg bd), the upper confidence limit of the 2-sided 90% confidence interval (CI) around the mean treatment effect for QT Fridericia Correction Formula (QTcF) was <10 ms at all time points. Furthermore, the supportive analysis showed that following a single dose of olaparib, of either 100mg or 300mg the upper confidence limit of the 2-sided 90%CI around the mean treatment effect for QTcF was also <10 ms at all time points.

In conclusion, there was no indication of a clinically relevant effect of olaparib on cardiac repolarisation (as determined by prolongation of QTcF) following multiple dosing (300 mg bd) or following single dosing.

As a further supporting analysis, concentration-effect modelling of the pooled QT/QTc data from the same patients was conducted. Predictions, from the concentration-effect relationship obtained of the likely magnitude of effect of olaparib on ΔQTcF, showed that at the range of plasma concentrations achieved following the 300 mg bd tablet dose, olaparib would not be expected to cause prolongation of QTc interval of a magnitude that would be of clinical concern or which would cross the threshold for regulatory concern as described in ICH E14.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate

(CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

1.4.1 Important potential risks

1.4.1.1 Myelodysplastic syndrome/acute myeloid leukaemia

There have been 16 reports of myelodysplastic syndrome (MDS) and/or acute myeloid leukaemia (AML) in patients treated with Olaparib as of 02 Oct 2013; 11 cases in Olaparib monotherapy trials and 5 cases in Olaparib combination studies with carboplatin and paclitaxel (n=4) or cediranib (n=1). A total of 2103 patients are estimated to have received Olaparib, giving a cumulative incidence of 0.76% for MDS/AML, similar to the cumulative incidence reported from control arms of Olaparib randomised studies 0.7% (2/304 patients). All 16 patients had primary ovarian or peritoneal cancer and 12 of them were g*BRCA1/2* positive (3 cases g*BRCA* status unknown; 1 case negative). It has been hypothesised that a deficiency in the expression of *BRCA* genes may leave patients more vulnerable to the adverse effects of chemotherapy, and therefore, at an increased risk of MDS/AML as a result of cancer treatment (Cole and Strair 2010). Most patients had been treated with extensive previous chemotherapy ranging from 6 to 95 cycles over periods of 3.5 months to 15 years, including platinum agents, topoisomerase II inhibitors, alkylating agents and taxanes. The median time from diagnosis of cancer to onset of MDS was 5.3 yrs (range 2.9 -12.7). The median time from start of Olaparib treatment to onset of MDS was 0.9 years (0.1 to 4.8 years). The reported events of MDS/AML occurred post discontinuation of Olaparib treatment in 8 of the 16 patients following a median of 0.1 years post treatment discontinuation (range: 0.1 to 1 years). Half of the patients (n=8) had received Olaparib for ≤ 12 months (5 patients had ≤ 6 months exposure) and the other 8 cases occurred following longer than 12 month Olaparib exposure (3 patients following 12-18 months exposure and 5 patients following >2 years exposure to Olaparib).

Since bone marrow is known to be a target organ for Olaparib toxicity, a risk of MDS/AML with long-term exposure to Olaparib cannot be excluded, but there is insufficient data at present to evaluate the strength, if any, of this relationship. Moreover, while non-clinical data suggest bone marrow progenitor cell populations are reduced temporarily following Olaparib treatment, there is no evidence to date linking Olaparib treatment to the generation of abnormal bone marrow precursors. Furthermore, all patients who developed MDS/AML had extensive prior chemotherapy and while it is not possible to exclude the contribution of Olaparib, it is also considered that there were other potential contributing factors in all cases. Preclinical data also suggest potential benefit with PARP inhibitors in MDS/AML and clinical trials are now underway to assess this effect (Gaymes et al 2008).

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every **4** weeks during the rest of the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

1.4.1.2 Pneumonitis

As of 2nd of Oct 2013, 10 patients out of a total of 2103 patients estimated to have received Olaparib have reported pneumonitis, giving a cumulative incidence of 0.5% for pneumonitis. Pneumonitis was also reported for 2 patients (0.7%) of 304 patients that received placebo or comparator in the Olaparib trial programme (1 patient on placebo in Study 19 and 1 patient on paclitaxel in Study 39). The patients were treated with Olaparib for breast cancer (n=2), ovarian cancer (n=2), non-small cell lung cancer (n=2), small cell lung cancer (n=1), pancreas cancer (n=1), gastric cancer (n=1) and thymic cancer (n=1). Five of the 10 patients had a history of tobacco smoking. The majority of patients had received prior radiotherapy and/or chemotherapy. The majority of patients had relevant medical histories including pneumonitis, interstitial lung fibrosis, dyspnoea, haemoptysis, chest infection, allergic asthma, pleural effusion, and pleural metastases.

Investigation of any new or worsening pulmonary symptoms has been implemented as a safety management plan (section 6.7.2).

1.4.1.3 New Primary Malignancies

Overall, the number of reports of new primary malignancies is low, with 21 events (in 19 patients) being reported in 02 Oct 2103 Olaparib treated patients (0.9%) and one event (bladder cancer) reported in the placebo arm of the double-blind Study 19. In randomised controlled studies, 5 events of new primary malignancies have been reported in four Olaparib treated patients and one event in a placebo treated patient:

In the double blind maintenance Study 19, two events of new primary malignancies have been reported in Olaparib treated patients and one event in a placebo treated patient. In the open label *gBRCA* ovarian monotherapy dose-finding Study 12, three events were reported in two Olaparib treated patients.

Of the 21 reported events in Olaparib treated patients, in ten the events were non-melanoma skin cancers. There was one report of malignant melanoma. The other 10 events of new primary malignancies were breast cancer (n=2), breast cancer *in situ*, gastric cancer, lung neoplasm (plus event of recurrence of the lung carcinoma), plasma cell myeloma, colon cancer, malignant muscle neoplasm (lesion present pre-Olaparib treatment) and one fatal event of T-lymphoblastic lymphoma/leukaemia.

Of the 19 Olaparib treated patients subsequently diagnosed with a new primary malignancy, the majority were reported whilst receiving Olaparib treatment (16 patients). In 3 patients the event was reported after Olaparib discontinuation

The duration of Olaparib treatment for the 19 patients was:

- <6 months for 3 patients
- 6 to 12 months for 6 patients

- 12 to 18 months for 2 patients
- 18 to 24 months for 2 patients
- >2 years for 6 patients.

The type of new primary cancers reported were generally in line with secondary cancers observed in ovarian and breast cancer populations reported in the literature (Bergfeldt et al 1995, .

Fitzsimmons D et al 1999, Fong et al 2009, Fowble et al 2001, Wesolowski et al 2007), or were cancers such as skin cancer, known to be the most common cancer in the general population and associated with high cure rates.

Ovarian cancer patients have been reported to have an increased risk of developing second primary malignancies. Patients with g*BRCA* mutations are at risk of developing other primary cancers notably breast cancer (Ginsburg et al 2010) reported higher rates of skin cancers in patients with g*BRCA1* (1.6%) and g*BRCA2* (3.0%) mutations.

There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all 19 Olaparib treated patients. All patients had previously received various chemotherapy agents including multiple cycles of DNA damaging platinum containing chemotherapies, taxanes, anthracyclines and other alkylating and DNA damaging agents. Four patients were reported to have had prior radiotherapy. Seven of the 19 patients had previous medical histories of cancer (ovarian, cervix, breast, peritoneal) and 3 patients with skin cancers had either had previous basal cell carcinoma reported or had skin lesions evident prior to study treatment) prior to the cancer under investigation in the Olaparib studies.

There is insufficient evidence for an association between Olaparib treatment and the development of new primary malignancies in the clinical trial programme to date.

1.4.2 Potential benefit

Phase II clinical studies have investigated the effect of Olaparib either as monotherapy or in combination with other chemotherapy agents in cancer patients. In patients carrying germline *BRCA* mutations, monotherapy studies in patients with heavily pre-treated breast cancer have reported an objective response rate (ORR) of up to 41%. In ovarian cancer patients, the pivotal phase II study D0810C00019 (“Study 19”), a double-blind, randomised study assessed the efficacy of Olaparib 400 mg bid capsules as a maintenance treatment following platinum-based chemotherapy in patients with platinum sensitive relapsed high grade serous ovarian cancer. The progression-free survival (PFS) following Olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.35; 95% CI: 0.25, 0.49; $p<0.00001$) in the overall population. In the subgroup of patients with *BRCA* mutant ovarian cancer, the effect was even greater with a PFS HR of 0.18 (95% CI: 0.11, 0.31; $p<0.00001$; median 11.2 versus 4.3 months). An interim analysis of OS was performed at 58% maturity.

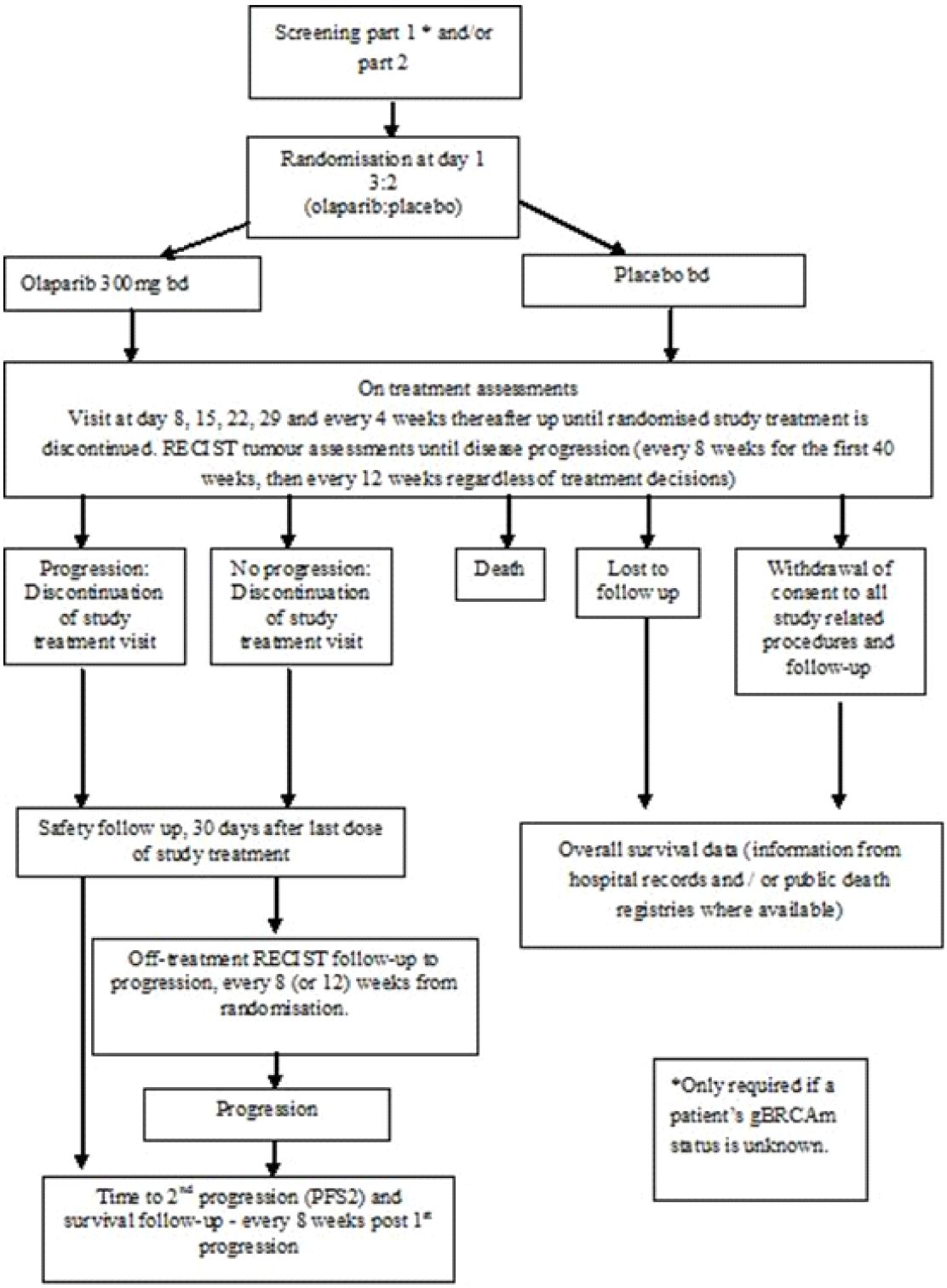
In the overall population, the analysis demonstrated a non-statistically significant numerical advantage for Olaparib-treated patients (OS HR 0.88; 95% CI 0.64-1.21; p=0.43808) and there was again a greater effect in the g*BRCA*-mutated subgroup: the OS HR was 0.74 (95% CI 0.46 to 1.19; p=0.20813) with a numerical advantage in median overall survival observed with Olaparib (median 34.9 months versus 31.9 months with placebo). Among the 62 placebo-treated patients with g*BRCA* mutations, 14 switched to a PARP inhibitor post progression. In study D0810C00042 ("Study 42'), a single arm phase II study of Olaparib (capsules) 400mg po bid in patients with germline *BRCA*m malignancies across multiple tumour types, 23 patients with advanced g*BRCA*m associated pancreas cancer, all previously treated with gemcitabine were enrolled. There were 1 CR and 4 PR's (ORR 22%) with a disease control rate of 57%, a PFS of 4.6 months and an OS of 9.8 mos. Patients who had not progressed on a platinum containing regimen were most likely to benefit. The results of Study 19 in ovarian cancer and Study 42 in pancreas cancer are the clinical basis for this investigation.

In this randomised double blinded study, patients who have disease control after a minimum of 16 weeks of platinum based therapy will, on the investigational arm receive monotherapy Olaparib 300 mg tablet bid (or control placebo) until disease progression or development of unacceptable toxicity. There is no intent to cap duration on Olaparib for these patients.

Based on the available data on efficacy and safety, we anticipate that in the metastatic disease setting, Olaparib will have a positive benefit risk profile for the treatment of the very small well-defined population of advanced pancreas cancer patients with g*BRCA* mutations.

1.5 Study Design

Figure 1 Study Flow Chart



This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of Olaparib maintenance monotherapy in metastatic pancreatic cancer patients with *gBRCA* mutations [documented mutation in *gBRCA1* or *gBRCA2*] that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16 weeks of first line platinum based chemotherapy.

Approximately 145 patients will be randomised using an Interactive Voice Response System / Interactive Web Response System (IVR/IWR system) in a 3:2 ratio (Olaparib:placebo) to the treatments as specified below:

- Olaparib tablets *p.o.* 300 mg twice daily
- Matching placebo tablets *p.o.* twice daily

Eligible patients will be those patients with pancreas cancer previously treated for metastatic disease *gBRCA* mutated, who have not progressed following completion of at least 16 weeks (can be more) of first line platinum-based chemotherapy.

All patients must have a known deleterious or suspected deleterious germline BRCA mutation to be randomised; this may have been determined prior to enrolment into the study or may be assessed as part of the enrolment procedure for the study (via centrally provided Myriad Integrated BRAC*Analysis* test)

Patients must have completed a minimum of 16 weeks of first line platinum-based therapy (eg, oxaliplatin, carboplatin or cisplatin) given continuously before randomisation to the study and should in the opinion of the investigator have had at least disease control. There must be absence of progression by imaging done within 4 weeks of randomisation. Patients whose platinum based therapy was discontinued as a result of toxicities specifically related to their platinum containing regimen are eligible if they received at least 16 weeks of platinum therapy and have continuously received the other chemotherapy drug(s) in their regimen (for example FOLFIRI for FOLFIRINOX etc.) and fulfil all other eligibility requirements (including non-progression at the time of enrolment).

Patients known to have germline *BRCA* mutation/s prior to randomisation can enter the study based on this result provided they meet all other eligibility criteria. The type of *BRCA1/2* mutation must be reported in the eCRF. In addition the patients must consent to give 2 blood samples, the primary purpose of the first sample is for undertaking a confirmatory Myriad *gBRCA* test post randomisation and a second sample is required for assessment of current and future *BRCA* mutation assays. The patients will also submit the diagnostic pathology specimens (block or slides) <u>if available</u> for the exploratory portion of the study.

Patients with unknown *BRCA* status must consent to give 2 blood samples for germline *BRCA* testing by Myriad (and all local ethical procedures for such genetic testing). One sample will be used to test for *BRCA* mutations using the current commercial Myriad *BRCA* analysis test prior to study entry (Myriad Integrated BRAC*Analysis*). The second blood sample from all

tested patients (including those who do not have a *BRCA* mutation) is required for assessment of current and future *BRCA* mutation assays. When the result from the Myriad test indicates the patient does have a deleterious or suspected deleterious germline *BRCA* mutation and the patient meets all other eligibility criteria, the patient can be randomised into the study. The patients will also submit the diagnostic pathology specimens (block or slides) if available.

Residual blood (or its derivatives) from both samples may be used to evaluate future *gBRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, improve the understanding of pancreas cancer and disease recurrence (including *gBRCA* mutation status and it role in response).

The 2 blood samples from patients with both known and unknown *BRCA* mutation status are needed in order to ensure sufficient information is collected in the study to enable the pre-market approval of the Myriad germline *BRCA* test as a companion diagnostic for Olaparib in the USA. In addition residual material may be used for the assessment of other current and future *BRCA* mutation diagnostic assays and/or assays that predict sensitivity to Olaparib.

Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

Following randomisation, patients will attend clinic visits weekly for the first 4 weeks of treatment (Days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment.

Patients should continue to receive study treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria as outlined in Section 3.9.

Once a patient has discontinued study treatment, clinic visits will be reduced to every 8 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator however it is anticipated (but not required) that patients will be retreated with their platinum based regimen. Details of any further systemic anti-cancer treatment will be collected until death, loss to follow-up or withdrawal of consent. In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) to capture survival status at that point for each survival analysis. Assessments will be performed as described in Table 1.

Patients will have tumour assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to modified RECIST criteria. All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. All treatment decisions will be based on site

assessment of scans. After the final primary progression free survival (PFS) analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review. Ongoing collection of site review tumour assessment is required and must be recorded in the electronic case report form (eCRF).

RECIST will be modified to assess patients with clinical CR at entry who will be assessed as having no evidence of disease (NED) until they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue, to undergo scheduled objective tumour assessments according to the study plan (see Table 1) in order to assess objective radiological progression of disease. Failure to do so may result in bias to the study results.

Once a patient has progressed the patient will be followed for second progression (PFS2) every 8 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit for each analysis of survival.

The primary analysis of the study will occur when approximately **87** progression events have occurred, although an interim analysis for **futility** will be done when 50% of the planned PFS events have occurred (see statistical Section 8).

The primary analysis will be based on a blinded independent central review (BICR) of disease progression by modified RECIST; however, a sensitivity analysis will be performed using the investigator-recorded assessment. All efficacy variables including overall survival will be analysed at the time of the primary analysis (providing sufficient events are available to make the analyses meaningful).

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS)	• Progression Free Survival (PFS) by BICR using modified RECIST 1.1

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure :**
• To determine the efficacy of Olaparib maintenance monotherapy compared to placebo	• Overall Survival (observed and predicted using observed PFS and OS data) • Time from randomisation to second progression (PFS2) • Time from randomisation to first subsequent therapy or death (TFST) • Time from randomisation to second subsequent therapy or death (TSST). • Time from randomisation to study treatment discontinuation or death (TDT) • Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients • Disease Control Rate at 16 weeks by BICR using modified RECIST 1.1 criteria
• To assess the effect of Olaparib on the Health-related Quality of Life (HRQoL) as measured by EORTC QLQ-C30 global QoL scale.	• Adjusted mean change from baseline in global QoL score from the EORTC-QLQ-C30 questionnaire

2.3 Safety objectives

Safety Objective:	**Outcome Measure:**
• To assess the safety and tolerability of Olaparib maintenance monotherapy	• Adverse event (AE), physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology

2.4 Exploratory objectives

Exploratory Objective:	**Outcome Measure:**
• To assess the effect of Olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional and social). • To assess the effect of Olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales. • To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), jaundice • To assess change in performance status as measured by the ECOG Performance Status scale	• Adjusted mean change from baseline on EORTC-QLQ-C30 functioning domains (physical, role, cognitive, emotional, social), on EORTC-QLQ-C30 + PAN26 symptom scales and items (pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice and on performance status measured by the ECOG Performance Status scale
• To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility	• Number, type and reason of hospitalisations and hospital attendances, procedures undertaken and hospital length of stay. • Health state utility derived from the HRQL instrument, the EuroQoL EQ5D
• To explore methods of estimating overall survival (OS) adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose [poly	• Overall survival adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents (if appropriate, to support reimbursement

(ADP ribose)] polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.	appraisals)
• To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.	• BRCA1 and/or BRCA2 mutation status in tumour
• To identify tumour tissue based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRCA methylation and/or other HRD biomarkers) that could be used to guide future patient segmentation approaches for development • Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.	• Potential tissue biomarkers identified

The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

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

3.1 Inclusion criteria

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

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

2. *Patients must be male or female ≥18 years of age

3. *Histologically or cytologically confirmed pancreas adenocarcinoma receiving initial chemotherapy for metastatic disease and without evidence of disease progression on treatment

4. Patients with measurable disease and/or non-measurable or no evidence of disease assessed at baseline by CT (or MRI where CT is contraindicated) will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at baseline..

5. Documented mutation in *gBRCA1* or *gBRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) (See Section 1.5)

6. Patients are on treatment with a first line platinum-based (cisplatin, carboplatin or oxaliplatin) regimen for metastatic pancreas cancer, have received a minimum of 16 weeks of continuous platinum treatment and have no evidence of progression based on investigator's opinion. Patients who have received at least 16 weeks of a platinum regimen but had the platinum discontinued for toxicity but continued on the remaining drugs of their regimen are also eligible if they have no evidence of disease progression within 4 weeks of their last dose of chemotherapy.

7. Patients who have received platinum as potentially curative treatment for a prior cancer (eg ovarian cancer) or as adjuvant/neoadjuvant treatment for pancreas cancer are eligible provided at least 12 months have elapsed between the last dose of platinum-based treatment and initiation of the platinum-based chemotherapy for metastatic pancreas cancer.

8. Patients must have normal organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:

   - Haemoglobin ≥ 9.0 g/dL with no blood transfusions (packed red blood cells and platelet transfusions) in the past 28 days
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - White blood cells (WBC) >3 x 10^9/L
   - No features suggestive of MDS/AML on peripheral blood smear
   - Platelet count ≥ 100 x 10^9/L
   - Total bilirubin ≤ 1.5 x institutional upper limit of normal
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal value unless liver metastases are present in which case they must be ≤ 5x ULN

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

9. *ECOG performance status 0-1 at date signing of informed consent

10. *Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test. Postmenopausal is defined as:

    - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone (LH) and Follicle stimulating hormone (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
    - Surgical sterilisation (bilateral oophorectomy or hysterectomy)

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

12. Formalin fixed, paraffin embedded (FFPE) tumour sample from the primary tumour or a metastatic site if available or 3 unstained cytology slides if available.

3.2 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 AstraZeneca staff and/or staff at the study site).

2. *gBRCA1* and/or *gBRCA2* mutations that are considered to be non detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favour polymorphism" or "benign polymorphism" etc.).

3. Progression of tumour between start of first line platinum based chemotherapy for metastatic pancreas cancer and randomisation.

4. Cytotoxic chemotherapy or non-hormonal targeted therapy within 28 days of Cycle 1 Day 1 is not permitted. Palliative radiotherapy must have been completed 14 or more days before Cycle 1 Day 1. The patient can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 2 weeks prior to study treatment.

5. *Previous randomisation in the present study.

6. Exposure to an investigational product within 30 days or 5 half lives (whichever is longer) prior to randomisation

7. *Any previous treatment with a PARP inhibitor, including Olaparib.

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

9. Resting ECG with QTC **≥ 450** msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTC **≥ 450** msec, patient will only be eligible if repeat ECG demonstrates QTC ≤ **450** msec.

10. Concomitant use of known potent CYP3A4/5 inhibitors such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For further detail refer to Appendix H.

11. Persistent toxicities (≥CTCAE grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE grade 3 peripheral neuropathy.

12. *Patients with myelodysplastic syndrome/acute myeloid leukaemia.

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

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

15. *Clinically significant uncontrolled medical conditions are not permitted (eg active infection requiring IV antibiotics, symptomatic congestive heart failure, unstable angina pectoris, recent (3 months) myocardial infarction, extensive bilateral interstitial lung disease, psychiatric illness that would limit ability to comply with study procedures, and any other medical condition that, in the opinion of the investigator, places the patient at unacceptable risk of toxicity. NB: Diabetes which is controlled by medication does not exclude participation in the study

16. *Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study. No history of intracranial haemorrhage or spinal cord haemorrhage. Minimum of 2 weeks between completion of radiotherapy and cycle 1 Day 1 and recovery from significant (Grade ≥3) acute toxicity with no ongoing

requirement for ≥ 10mg of prednisone per day or an equivalent dose of other corticosteroid.

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

18. *Pregnant or breast feeding women.

19. *Previous allogeneic bone marrow transplant.

20. *Patients with a known hypersensitivity to Olaparib or any of the excipients of the product.

21. *Whole blood transfusions in the last 120 days prior to enrolment to the study which may interfere with *gBRCA* testing (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria no.8)

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment and randomisation

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

The Principal Investigator will:

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

2. Assign potential patients a unique enrolment number, beginning with 'E#'. (This number will be obtained through Interactive Voice/Web Response System [IVRS/IWRS]).

3. Determine patient eligibility. See Sections 3.1 and 3.2

4. Obtain the randomisation code (patient number) through IVRS/IWRS.

As patients are screened for the study, they must be allocated an enrolment code (E-code). The E-code is a 7-digit number made up of the centre number and the patient number within that particular centre (eg, the first patient screened at centre number 0001 would be assigned the E-code E0001001, the second patient screened would be E0001002 and so on). This number is the patient unique identifier and is used to identify the patient on the eCRFs. If a patient withdraws from participation in the study, then his/her enrolment/randomisation code cannot be reused.

3.4 Procedures for handling incorrectly enrolled or randomised patients

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

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

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

3.5 Methods for assigning treatment groups

Patient eligibility will be established before treatment randomisation. Once the eligibility of a patient has been confirmed, the Investigator (or nominated assistant) should contact the IVRS/IWRS Centralised Randomisation Centre for allocation of randomised study treatment.

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

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

Patients will be identified to the Centralised Randomisation Centre using patient Ecode and month/ year of birth.

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

Eligible patients will be randomised in a 3:2 ratio (Olaparib:placebo) as specified below:

- Olaparib tablets *p.o*. 300 mg twice daily
- Placebo tablets *p.o.* twice daily

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

The IVRS/IWRS Centralised Randomisation Centre will inform the Investigator of the Kit ID number to be allocated to the patient at the randomisation visit. The Investigator will call/log in to the IVRS/IWRS for each subsequent dispensing visit for assignment of a new Kit ID number (s).

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

3.6 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

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

3.7 Methods for unblinding

3.7.1 Methods for ensuring blinding

Olaparib and placebo treatment will be blinded.

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

3.7.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists 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 randomisation. 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 SAEs 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 medical reasons, patients, investigators and study monitors in the field will have no access to the individual treatment code until final analysis.

3.8 Restrictions

3.8.1 Contraception

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of two highly effective forms of contraception, while they are receiving study treatment and for 3 months after last dose of study drug. For details please refer to Appendix E Acceptable Birth Control Method.

3.8.2 Olaparib and CYP3A4/5

Patients should avoid concomitant use of drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4/5 enzyme activity (see Section 7.7.2) starting 5 days before they are randomised until 30 days after the last dose of study medication.

3.9 Discontinuation of investigational product

Patients may discontinue study treatment in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Objective radiological disease progression
- Adverse Event
- Severe non-compliance to study protocol
- Death

3.9.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator(s). Adverse events will be followed up (See Sections 6.3 and 6.4); questionnaires and all study drugs should be returned by the patient.

If a patient is withdrawn from study, see Section 3.10.

Any patient discontinuing study treatment 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 treatment, 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. Patients will be required to attend the treatment discontinuation visit. The patient should return all study medication.

After discontinuation of the study treatment at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the patients underlying disease, or the patient is lost to follow up (see Sections 6.3 and 6.4). 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) and followed to resolution as above. Patients should be seen at least 30 days after discontinuing study treatment to collect and / or complete AE information. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Patients who discontinue treatment prior to disease progression should continue to have RECIST assessments as per the study schedule. All patients must be followed for objective progression (as per RECIST 1.1) and survival, up to the final analysis.

3.10 Criteria for withdrawal

Patients are at any time free to withdraw from study (study treatment and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an investigator. Adverse events will be followed up (See Sections 6.3 and 6.4); questionnaires (eg, for patient reported outcomes*)* and all study drugs should be returned by the patient.

Withdrawn patients will not be replaced.

Reasons for withdrawal from the study:

- Voluntary withdrawal by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment*
- Incorrectly enrolled patients ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Death

*If a patient decides at any point in the trial that they do not wish to continue with the full study schedule of assessments but are still willing to provide important study information (eg disease recurrence information and/or survival status information) then the patient should continue in the study and information should continue to be collected on the clinical database. However if a patient does not wish to have any further data collected, only then should they be considered as withdrawing consent from the study. To minimise the number of cases of early withdrawal the investigator should discuss the options with the patient in case they would still

be willing to undergo reduced assessments and/or reduced data collection, in which case they would remain in the study.

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

- to further participation in the study including any further follow up (eg, survival calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples (see Section 5.6.5)

Data obtained prior to withdrawal of consent will be maintained in the clinical database and used in the study reporting.

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, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to collection of further 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.

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Incorrect Enrolment' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up AEs outside of the clinical study. The patient will return electronic PRO (ePRO) devices.

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

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests

4. STUDY PLAN AND TIMING OF PROCEDURES

A study initiation visit must be conducted at the centre prior to the commencement of any study activities requiring informed consent. A schedule for the tests and evaluations to be conducted in this study is contained in this section and in Table 1.

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

	Screen PART 1 (Patients with unknown *BRCA* status only)	**Screen PART 2** (All patients)	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Informed consent	X	X									
Randomisation [f]			X [f]								
Demographics	X	X									
Medical and surgical history, including blood transfusions [a]		X									
Prior cancer therapies including radiotherapy		X									
Inclusion/exclusion criteria	X (all * criteria) [b]	X									
Blood samples for *gBRCA* status [c]	X		X [d]								
Archival paraffin embedded tumour tissue or cytology sample [e]	X	X									
Concomitant medications		X	X	X	X	X	X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
ECOG performance status		X					X	X	X	X	
Vital signs		X [g]	X [g]				X	X	X	X	
Physical examination [h]		X					X	X	X	X	
ECG [i]		X	As clinically indicated								
Tumour assessment (modified RECIST 1.1) [j]		X (no more than 28 days before start of treatment) [j]	Every 8 weeks (± 1 week) until week 40 then every 12 weeks (±1 week), relative to the date of randomisation [j]						If patient does not have disease progression at the time of treatment discontinuation tumour assessments should be continued per the CSP schedule [k]		
Haematology/clinical chemistry		X	X [l]	**X**	**X**	**X**	X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Coagulation [m]		X	As clinically indicated								
Urinalysis [n]		X	As clinically indicated								
Pregnancy test [o]	X	X	X								
Biomarker blood sample [p]			X					X (only at progression)			
EORTC QLQ-C30 [q]		X					X	X	X	X	
EORTC QLQ-PAN26 [q]		X		X	X	X	X	X	X	X	
Euro QoL EQ5D		X	X				X	X	X	X	
Hospital Resource Use			X	X	X	X	X	X	X	X	
Adverse event [r]	SAEs related to study procedures only	X	X	X	X	X	X	X	X	X	
Study drug dispensing [s]			X				X	X			
Study drug return							X	X	X	X	

	Screen PART 1 **(Patients with unknown *BRCA* status only)**	**Screen PART 2** **(All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Subsequent cancer treatment [t]										X	X
Second progression assessment [u]											X [u]
Survival status [v]											X [v]

a Include history of blood transfusion within previous 120 days from start of study treatment and the reasons eg bleeding or myelosuppression.
b These screening assessments do not need capturing on the eCRF, but they must be recorded in the patient's notes.
c Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised to the study; this can be either a local lab result or a Myriad test result. Patients for whom their *gBRCA* status is already known, should be consented to the study within 28 days prior to day 1 of study treatment. Any patient who consents to study related Myriad *gBRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future diagnostic test(s) for g*BRCA* mutations.
d Samples to be taken on Day 1 only for patients with known *gBRCA* mutation who have not completed PART 1 Screening. The screening *gBRCA* test and method performed at site must be recorded in the eCRF.
e Collection of an archival tumour sample is requested, if available, for all patients. These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test.
f Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last infusion) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.
g Vital signs performed on day 1 before every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

h Physical examination should be performed according to the schedule. After the baseline assessment it is not necessary to record the details on the eCRF, any clinically significant changes not unequivocally related to disease progression, should be reported as adverse events.

i ECG assessments to be completed within **14** days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

j Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment and as close as possible to randomisation. A randomisation must be within 6 weeks of last chemotherapy. Treatment should be started as soon as possible but no less than 4 weeks and no more than 8 weeks after their last dose of chemotherapy. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until disease progression assessed using modified RECIST 1.1 criteria. 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. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit.

k For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1.).

l Haematology and clinical chemistry should be performed at screening, cycle 1 day 1, 8, 15, 22 and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

m Coagulation test should be performed at screening and if clinically indicated.

n Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

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

p Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

q Questionnaires to be completed prior to randomisation once eligibility has been confirmed and then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose. Questionnaires should be completed prior to dosing on all administrations.

r Adverse events must be captured from time of consent.**-Only SAE's related to blood sampling for the Myriad *gBRCA* test will be collected at this visit.**

s Continuous Olaparib 300mg/ placebo twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

t All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

u Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Subsequent therapy will be collected for these patients from the time of treatment discontinuation.

v The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. 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 (see Section 3.10). In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut off date) for each survival analysis.

4.1 Enrolment/screening period

Procedures will be performed according to the Study Plan.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

The following assessments and procedures should be performed during screening Part 1 and Part 2 as per Table 1.

For details of the schedule and nature of assessments see below:

- Month/ year of birth, sex, race and ethnicity
- Medical and surgical history including previous cancer and radiotherapy and history of blood transfusions in previous 120 days
- Previous chemotherapy
  - If patient received a prior platinum drug, in what setting (adjuvant or advanced) and reason for discontinuation (progression on therapy, discontinuation of therapy for reason other than progression, completion of planned program without progression,)
- Current and concomitant medications including previous cancer therapies
- ECOG Performance Status
- Vital signs (blood pressure and pulse; body temperature), body weight, height
- Haematology /Clinical chemistry/Urinalysis
- Coagulation test
  - 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 (INRand APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable
- Physical examination
- CT (or MRI if CT is contraindicated) of chest, abdomen and pelvis

- ECG (within **14** days prior to the start of the study treatment)

- Menopausal status; serum or urine pregnancy test for women of childbearing potential. The pregnancy test should be prior to performing the g*BRCA* blood test during screening part 1, within 28 days prior to the start of study treatment and confirmed on day 1 prior to dosing

- For patients with **unknown** *gBRCA* status: *gBRCA1/2* mutation status. 2 blood samples: One blood sample to test for *gBRCA* mutations using the current commercial Myriad *BRACAnalysis* test, and the second blood sample for a bridging study to validate the companion diagnostic test for Olaparib and/or assessment of current or future *BRCA* mutation assays

- Patient Reported Quality of life questionnaire: EORTC QLQ-C30 and QLQ-PAN26 should be completed prior to randomisation once eligibility is confirmed

- Adverse events must be captured from time of consent. **Only SAE's related to blood sampling for the Myriad *gBRCA* test will be collected at this visit. In Screening Part 2 all AEs/SAEs will be collected**

- Archival paraffin embedded tumour tissue sample or cytology sample requested, if available

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

4.2 Treatment period

The visit schedule is based on 28-day cycles.

Patients will attend the clinic weekly on days 1 (1st day of treatment), 8, 15, 22, 29 following the commencement of study treatment and then every 4 weeks (day 1 of every cycle) until discontinuation of treatment. The following assessments will be performed at time points specified in the study schedule (see Table 1):

- Vital signs: Day 1 of every cycle. Body weight is only required at day 1 of 1st day of study treatment, if it has not been assessed within 7 days of randomisation. Any other time as clinically indicated

- ECOG Performance Status: Day 1 of every cycle and until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose

- Haematology and clinical chemistry: cycle 1 day 1, 8, 15, 22 and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study

treatment and which must have been 3 weeks after last dose of chemotherapy based therapy, unless the investigator believes that it is likely to have changed significantly.

- Physical examination: Day 1 before every cycle but assessments post Day 1 are not required to be captured on an eCRF, however any significant changes from baseline must be reported as an AE.

- CT of chest, abdomen and pelvis (or MRI if CT is contraindicated) performed until objective disease progression. RECIST assessments to be scheduled every 8 weeks (±1 week) from randomisation for the first 40 weeks and then every 12 weeks (±1 week). If progression is not confirmed by BICR an additional scan will be requested at the next scheduled visit. CT/MRI of chest, abdomen and pelvis to be performed until objective disease progression.

- ECG at baseline and any time if clinically indicated

- Urinalysis at baseline and any time if clinically indicated

- Serum or urine pregnancy test for women of childbearing potential (prior to treatment on day 1 of 1st day of study treatment). If the test is positive then a confirmatory test should be performed

- For patients with **known** g*BRCA* status: *gBRCA1/2* mutation status. 2 blood samples: One blood sample to test for g*BRCA* mutations using the current commercial Myriad BRAC*Analysis* test, and the second blood sample for a bridging study to validate the companion diagnostic test for Olaparib and/or assessment of current or future *BRCA* mutation assays

- AE and concomitant medications (including any blood transfusions) at every visit

- Patient Reported Quality of life questionnaire: EORTC QLQ-C30 at baseline (prior to randomisation once eligibility is confirmed), every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Patient Reported Quality of life questionnaire: QLQ-PAN26 at baseline (prior to randomisation once eligibility is confirmed), week 1, week 2, week 3 and every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Health economic data in terms of utility (EuroQoL EQ5D) at baseline and every 4 weeks until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Health economic data in terms of hospital resource use at each visit during treatment then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose.

- Mandatory blood sample for biomarker analysis at cycle 1 day 1 (pre-dose) and disease progression (Section 5.4.1)

Once patients have discontinued study treatment, other treatment options will be at the discretion of the investigator.

4.3 Follow-up period

4.3.1 Treatment discontinuation visit due to objective radiological disease progression

Patients should be discontinued from study treatment if they have objective radiological disease progression according to modified RECIST 1.1 criteria (see Appendix F).

Following radiological disease progression patients will be followed for PFS2 and OS.

4.3.2 Treatment discontinuation visit due to any other discontinuation criteria

- Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled (see Section 3.9). The assessments to be carried out at the visit are detailed in the study schedule (Table 1).

Patients who have discontinued from treatment but do not have radiological disease progression will continue to be followed for PFS by modified RECIST 1.1 assessments every 8 weeks (+/-1 week) from date of randomisation during the first 40 weeks and then every 12 weeks (+/-1 week) thereafter.

4.3.3 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 RECIST (see Appendix F), however, patients may be allowed to continue study treatment if the investigator believes, and AZ Study Physician concurs, that the patient could continue to receive benefit, the patient is not experiencing serious toxicity, and there is no available better alternative treatment that could benefit the patient. These patients will continue study procedures as per Table 1 and will be followed for OS. Safety assessment can occur with the same frequency as the visits unless more frequent testing is clinically indicated.

4.3.4 Follow-up 30 day after last dose of study treatment (follow-up visit)

A follow-up visit should be conducted 30 days after the last dose of study treatment. 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 Section 6.3). Appropriate safety evaluations should be repeated and/or additional tests

performed at any time when clinically indicated, or at the discretion of the investigator, until resolution, unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the eCRF. The assessments to be carried out at the 30 day follow up visit are detailed in the study schedule (Table 1).

4.3.5 Survival

Assessments for survival should be made every 8 weeks following objective radiological 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. Survival data will be collected up to the time of the final overall survival (OS) analysis. In addition, patients should be contacted in the week following the data cut-off for the primary PFS and final survival analyses to provide complete survival data.

Patients will be followed up as per Table 1 to the point of the final analysis. At this point investigators will be notified that no further data collection for the study is required. Monitoring and recording of SAEs will continue as per Section 6.4.

The status of patients at the time of an overall survival analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. 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 (see Section 3.10).

4.3.6 Second Progression

Following objective progression, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review. Patients will be assessed every 8 weeks for a second progression (using the patients' status at first progression as the reference for assessment of second progression). A patient's progression status is defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

4.3.7 Subsequent Treatment

Following objective progression on study as per modified RECIST 1.1, copies of the patient's radiological scans are no longer required to be sent for blinded independent central review, provided that the central read confirms progression. If progression is not confirmed, one additional scan will be required at the next scheduled visit. Following objective progression patients will be assessed every 8 weeks for survival (see Section 4.3.5) but also for nature of subsequent treatment, response to subsequent treatment and investigator assessment of time to progression on the subsequent treatment. While other than the PFS2, response and time to progression on later therapies is not a specific endpoint of the trial, the information garnered

will help determine if there is an optimal sequencing of treatments for g*BRCA*-associated pancreas cancer and for planning of future clinical studies.

The data cut-off date for the final statistical analysis for the primary objective of the study will be established when approximately **87** confirmed progression events are expected to have occurred.

Patients on study treatment at the time of the data cut-off will continue to receive study treatment until they meet any discontinuation criteria as per Section 3.9.

Patients on study treatment will be followed for core safety assessments (haematology, clinical chemistry, AEs/SAEs, concomitant medications and study treatment dosing details)

Once the primary PFS analysis has been performed the collection of RECIST data for independent central review will cease. Patients who have not had an objective disease progression at the time of the data cut off for the primary analysis should continue to have RECIST assessments until first objective disease progression is determined by the investigator. RECIST assessments should be performed every 12 weeks (± 1week) from the last assessment prior to the data cut off date. Patients will also be followed for information on vital status to obtain the data needed for the OS analysis and information on subsequent treatment.

4.4 Patient management post final analysis

The data cut-off date for the final statistical analysis of the study will be established when ~106 confirmed OS events (~75 % maturity for OS analysis) are expected to have occurred.

At this time point, the clinical study database will close to new data. Patients who are receiving 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.

AstraZeneca will continue to supply Olaparib after completion of this study until either Olaparib is licensed 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. Additionally as stated any SAE or non-serious adverse event, 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 resolve, 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

5. STUDY ASSESSMENTS

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided.
The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

5.1 Efficacy assessments

5.1.1 CT and MRI scans Tumour assessments (Modified RECIST 1.1)

Following the baseline assessment, subsequent tumour assessments according to modified RECIST 1.1 should be performed every 8 weeks (±1 week) for the first 40 weeks and then every 12 weeks (± 1 week) thereafter, relative to the date of randomisation, up to objective disease progression by RECIST. Patients who are determined to have progressed according to modified RECIST 1.1 criteria by the Investigator will have scans centrally reviewed for confirmation of objective disease progression. If disease progression is not confirmed at central review an additional RECIST assessment will be requested preferably at the next scheduled RECIST visit (8 weeks from last scan).

For those patients with no evidence of disease at baseline, following a clinical complete response to chemotherapy, progression is defined by the detection of new lesions on follow up radiological assessments (modified RECIST 1.1).

The imaging modalities used for RECIST assessment will be CT (MRI where CT is contraindicated) scans of the chest, abdomen and pelvis with other regions as clinically indicated for the assessment of disease. Any other sites at which new disease is suspected should also be appropriately imaged. The methods of assessment of tumour burden used at baseline must be used at each subsequent follow-up assessment.

Radiological examinations performed in the conduct of this study should be retained at site as source data.

Any missed copies of the scans are to be sent to an AstraZeneca appointed CRO for blinded independent central review.

All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required and investigators will be advised when to stop sending copies of the scans to the CRO conducting the central review.

It is important to follow the assessment schedule as closely as possible. If scans are performed outside of 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 radiological disease progression by modified RECIST 1.1 as per the study schedule (see Table 1), and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations, unless they withdraw consent.

5.1.2 Tumour Evaluation

Modified RECIST 1.1 criteria will be used to assess patient response to treatment by determining progression free survival (PFS) times. (The modified 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, no evidence of disease or progression of disease) are presented in Appendix F.)

The methods of assessment of tumour burden used at baseline - CT or MRI scans of chest, abdomen and pelvis, with other regions as clinically indicated for the assessment of disease must be used at each subsequent follow-up assessment, see Section 4.3.

Following the baseline assessment, efficacy for all patients will be assessed by objective tumour assessments every 8 weeks (±1 week) up to 40 weeks then every 12 weeks (±1 week) relative to date of randomisation, according to the planned study schedule Table 1 until objective radiological disease progression as defined by modified RECIST. 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 radiological disease progression as defined by modified RECIST 1.1.

Categorization of objective tumour response assessment will be based on the modified RECIST criteria of response: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD), no evidence of disease (NED) and not evaluable (NE). Target lesion (TL) progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of a best response of progression, tumour response (CR, PR, SD) will be calculated in comparison to the baseline tumour measurements obtained before randomisation.

For patients with non-measurable disease only at baseline, categorization of objective tumour response assessment will be based on the RECIST criteria of response: CR (complete response), PD (progression of disease) and Non CR/Non PD. Patients with no disease at baseline will be assessed according to modified RECIST 1.1 criteria for new lesions with responses of No Evidence of Disease (NED) or progression of disease.

If the investigator is in doubt as to whether disease progression has occurred on study therapy, 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 disease progression, then the date of the initial scan should be declared as the date of disease progression.

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

Following progression, patients should continue to be followed up for survival every 8 weeks as outlined in the study plan. It is important to follow the assessment schedule as closely as possible. Please refer to the study plan in Section 1.5 and CT/MRI scans in section 5.1.1

5.1.3 Central reading of scans

An independent review of all scans used in the assessment of tumours according to modified RECIST will be conducted for data collected up to the data cut off for the primary analysis of PFS. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (CRO) for central analysis. Results of this independent review will not be communicated to investigators (with the exception of confirmation of progression assessments), and the management of patients will be based solely upon the results of the RECIST assessment conducted by the investigator.

The primary analysis for this study will be based on the blinded independent central review (BICR) of the radiological scans.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

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).

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.

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin	S-Sodium
B-Red blood cells [RBC]	S-Potassium
B-Platelets	S-Magnesium (baseline only and if clinically indicated)
B-Mean cell volume [MCV]	S-Calcium
B-Mean cell haemoglobin concentration [MCHC]	S-Creatinine
B-Mean cell haemoglobin [MCH]	S-Total bilirubin
B-White blood cells [WBC]	S-Gamma glutamyltransferase [GGT]
B-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.	S-Aalkaline phosphatase [ALP] S-Aspartate transaminase [AST] S- alanine transaminase [ALT] S-Urea or blood urea nitrogen [BUN] S-Total protein S-Albumin S-Lactate dehydrogenase (LDH)
Urine Tests	
Urinalysis (Dipstick, baseline only and if clinically indicated)	
U-Hb/Erythrocytes/Blood	
U-Protein/Albumin	
U-Glucose	
Urinalysis (Microscopic analysis, baseline only and if clinically indicated)	

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 5.2.

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

For blood volume see Section 5.6.1.

5.2.2 Physical examination

For timing of individual measurement refer to study schedule (Table 1).

A physical examination will be performed and include 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.

5.2.3 ECOG

ECOG Performance Status is a widely used, 5-level, clinician reported outcome of the patient's performance status. Below is a description of the clinician's grading system for the ECOG Performance Status (see also Appendix G). This measure will be applied according to the study schedule (see Table 1).

Table 3 ECOG Performance Status [a]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

a As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

ECGs are required during screening within **14** days prior to starting study treatment and when clinically indicated afterwards.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. 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. The original ECG traces must be stored in the patient medical record as source data.

5.2.5 Vital signs

Height will be assessed at screening only.

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

5.2.5.1 Pulse and blood pressure

Blood pressure and pulse rate will be measured preferably using a semi automatic BP recording device with an appropriate cuff size.

5.2.5.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer.

5.2.6 Other safety assessments

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).

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.

5.2.6.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential as per the study schedule. 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.

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

5.2.7 Bone marrow or blood cytogenetic samples

Bone marrow or blood cytogenetic samples may be collected as clinically indicated for patients with prolonged haematological toxicities as defined in Section 6.7.1

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.

5.3 Other assessments

5.3.1 Patient reported outcomes

5.3.1.1 EORTC QLQ-C30 and QLQ-PAN26

In this study patient reported disease related symptoms and health related quality of life will be evaluated using the validated EORTC QLQ-C30 and the PAN26 questionnaire. The EORTC QLQ-C30 was developed to assess HRQOL and functioning, and is the most commonly used cancer-specific tool in oncology. It has undergone extensive testing and validation as well as detailed cross cultural linguistic validation and has been used in pancreas cancer and gastric cancer trials (.

Fitzsimmons D et al 1999). The PAN26 was developed specifically for patients with pancreas cancer and has been found to be reliable and valid in this population as well as in pancreatitis patients.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following scales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social)
- 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
- A 2-item global QoL scale
- 5 single items assessing the following common cancer symptoms:
  - dyspnoea,
  - loss of appetite,
  - insomnia,
  - constipation,
  - diarrhoea
- 1 item on the financial impact of the disease.

The pancreas cancer module (PAN26) is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy. The module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreas cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).

All the EORTC scales range from 0 to 100 (through transformation of scores). 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.

5.3.1.2 Administration of PRO questionnaires

The EORTC QLQ-C30 and QLQ-PAN26 will be administered according to the study schedule (see Table 1**)**.

Questionnaires will be completed using a pencil and paper method of data collection. Each centre must allocate the responsibility for the administration (and training on ePRO device if used) of the questionnaires to a specific individual (eg, a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The AZ Study Delivery 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 site staff enters the information directly into the WBDC electronic database system.

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

- The EORTC QLQ-C30 and QLQ-PAN26 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. Patients must complete the EORTC QLQ-C30 before completing the QLQ-PAN26. They must be completed in private by the patient.

- 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 (eg, is blind or illiterate) the questionnaire may be read out by trained clinic staff and responses recorded.

- On completion of the questionnaire it should be handed back to the person responsible for questionnaires who should check for completeness.

5.4 Biomarkers

Tumour and blood samples will be collected for the biomarker work as detailed in the laboratory manual

For blood volume see Section 5.6.1.

5.4.1 Biomarker samples

The biomarker samples will be collected as described in Table 4**.**

Table 4 Samples for Biomarker Research

Sample Type	Visits
Whole blood sample for prospective germline *BRCA* testing at central laboratory for patients with unknown *gBRCA* status and for confirmation of *gBRCA* status for those with previous results	Screening Part 1 for patients with unknown *gBRCA* status Day 1 for patients with known local *gBRCA* test
Whole blood sample for assessment of current and future gBRCA mutation assay(s)	Screening Part 1 for patients with unknown *gBRCA* status Day 1 for patients with known local *gBRCA* test
Archival tumour sample (paraffin or cytology) – Requested, if available	Screening Part 1 for patients with unknown *gBRCA* status Screening Part 2 for patients with known local *gBRCA* test
Blood samples for biomarker analysis	Cycle 1 Day 1 and disease progression

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient enrolment number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the investigator will be able to link the biomarker sample to the individual patient. The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development of the drug and companion diagnostic. However, the samples and any results will remain the responsibility of AstraZeneca at all times. AstraZeneca will not give samples, sample derivatives or data derived from the samples to any other parties except as required by law.

Biomarker data may be generated in real time during the study or retrospectively and will have unknown clinical significance. AstraZeneca will not provide biomarker results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party unless required to do so by law. The patient's samples will not be used for any other purpose other than those described in the protocol.

The exception to the above is the *gBRCA* status result from the Myriad assessment for patients with previously unknown local g*BRCA* status. This result will be provided to the investigator and will be collected as part of the patient's demography and medical history details.

5.4.2 Collection of blood sample for Myriad germline *BRCA1* and *BRCA2* testing

All patients must have a known deleterious or suspected deleterious *gBRCA* mutation to be randomised; this may have been determined prior to study entry or may be assessed as part of the enrolment procedure for the study (via Myriad).

5.4.2.1 Guidance for g*BRCA* testing of patients with known g*BRCA* status.

For patients that can be randomised to the study on the basis of a pre-existing known *gBRCA* mutation test result, a blood sample for a confirmatory g*BRCA* mutation test by Myriad must be taken once the patient has consented to the study. Should the result from the Myriad test indicate the patient does not have a deleterious or suspected deleterious g*BRCA* mutation; the patient can continue in the study and can continue to receive their allocated study treatment if deemed appropriate by the investigator.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.2.2 Guidance for g*BRCA* testing of patients with unknown g*BRCA* status.

Patients that do not know their g*BRCA* status, but meet all other eligibility criteria must have a Myriad test prior to randomisation in to the study. A blood sample for the Myriad *BRCA* test can be taken once all local ethical procedures for such testing have been completed. If the result shows that the patient has a deleterious/suspected deleterious *gBRCA* mutation, the patient can then be randomised to the study. In order to limit the time that the patient is not receiving study treatment after their last dose of chemotherapy, it may be necessary for the patient to have a Myriad *BRCA* test whilst still on chemotherapy.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.2.3 Collection of blood sample for assessment of current and future g*BRCA* mutation assay(s)

All patients will be required to provide a mandatory 9 ml blood sample that will be stored for subsequent assessment of current and future g*BRCA* mutation assay(s).

Samples may be required to support subsequent analysis as part of a bridging study between the Myriad *BRCA* test to be used in this study and the “to be marketed” diagnostic test which is currently under development. Samples are required to be collected from all patients including those shown not to have a deleterious or suspected deleterious g*BRCA1* or g*BRCA2* mutation.

Residual blood (or its derivatives) may be used to evaluate future g*BRCA* companion diagnostic tests and for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of pancreas cancer and disease recurrence (including g*BRCA* mutation status and its role in response).

5.4.3 Exploratory Biomarker Research on Archival Tumour Samples (Paraffin block or tissue cytology slides) (Requested, if available)

These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test. An adequately sized (minimum of 2 mm x 2 mm) historical tumour tissue paraffin block from a core biopsy from the primary tumour or a metastatic site is most desirable. This sample will have been collected anytime since the time of original diagnosis but prior to study entry. Alternatively, 10-20 pre-cut sections mounted on glass slides prepared from the block can be provided. If the only diagnostic test was cytologic, a paraffin block or three unstained slides of tumour tissue should be submitted if available.

Collection of an archival tumour sample is requested if available for all patients for the assessment of tissue *BRCA* mutation status. Surplus tissue may be used for additional exploratory work, to elucidate the mechanism of response, understand the mode of action of study treatment, and improve the understanding of disease progression (including tumour *BRCA* mutation status and its role in response).

Please refer to Investigator Laboratory Manual for further details of archival tissue collection, shipping and storage.

5.4.4 Exploratory Blood samples for biomarker analysis (Mandatory)

All consenting patients will be required to provide a blood sample at randomisation and disease progression for exploratory biomarker research.

Patients will be required to provide:

- 1x 6ml blood sample for preparation of serum at cycle 1 day 1 and disease progression.
- 1x 6ml blood sample for preparation of plasma at cycle 1 day 1 and disease progression.

Please refer to Investigator Laboratory Manual for further details of biomarker blood sample collection, shipping and storage.

5.5 Health economics

Hospital related resource use and health state utility

For the purposes of economic evaluation it is necessary to capture utility data and healthcare resource use related to the treatment and the underlying disease. Within the clinical trial utility

data will be captured using the EuroQoL EQ5D instrument. The following hospital resource use data will be collected using the Hospital Attendance (HOSPAD) module:

1. Number of hospitalisations and attendances

2. Primary symptom/reason associated with hospitalisation or attendance

3. Length of stay, including time in intensive care.

Additional information, including medications and procedures undertaken will be derived from data captured under existing modules, for example, concomitant medications and concomitant procedures.

5.6 Biological sampling procedures

5.6.1 Volume of blood

The volume of blood that will be drawn from each patient will vary, dependent upon the length of time that the patient remains in the trial. The total volume of blood to be drawn from each patient in the study, assuming they complete screening, 6 cycles of treatment, a treatment discontinuation visit and the 30-day follow-up visit, is 255mL.

Safety laboratory assessments will be performed locally at each centre's laboratory by means of their established methods. The number of samples/blood volumes is therefore patient to site-specific change. Extra blood samples may also be collected if, for example, additional samples are required for repeat safety assessments.

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

Table 5 Volume of blood to be drawn from each patient

Assessment		**Sample volume (mL)**	**No. of samples**	**Total volume (mL)**
Safety	Clinical chemistry	5	21	105
	Haematology	5	21	105
	Coagulation	3	1	3
Whole blood sample for Myriad *BRCA* test (retrospective/prospective)		9	1	9
Whole blood sample for assessment of current and future *BRCA* mutation assay(s)		9	1	9
Serum Pregnancy test (site may use urine instead)		Site dependent	Site may use urine instead	
Serum sample for exploratory biomarkers, cycle 1 day 1 (mandatory)		6	1	6

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Plasma sample for exploratory biomarkers, cycle 1 day 1 (mandatory)	6	1	6
Serum sample for exploratory biomarkers, disease progression (mandatory)	6	1	6
Plasma sample for exploratory biomarkers, disease progression (mandatory)	6	1	6
Total			255

5.6.2 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 will be retained at AstraZeneca or a 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.

5.6.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria),

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

5.6.4 Chain of custody of biological samples

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

The Principal Investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

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

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

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site, according to local regulations or at the end of the retention period, whichever is the sooner.

5.6.5 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.

gBRCA sample: As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

Archival tumour sample: If consent to use the sample is withdrawn this will not impact eligibility to study. The patient may continue in the study if the patient is already randomised.

Blood samples for biomarker analysis: Although mandatory, the patient may continue in the study if the patient is already randomised.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory (ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the

abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), 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 Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period 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 the last dose of study medication must be followed to resolution. After any interim analysis, any ongoing AEs/SAEs need to be unlocked and followed for resolution.

SAEs will be recorded from the time of informed consent.

6.3.2 Follow-up of unresolved adverse events

Any SAEs or non-serious adverse event 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.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- 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
- 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.

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

Severity of AE

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

The grading scales found in the National Cancer Institute (NCI) CTCAE version 4.0 will be utilised 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 NCI website.

6.3.4 Causality collection

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

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.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The reporting of laboratory/vital signs/ECG abnormality as AE should be avoided unless one of the following is met:

- Any criterion for an SAE is fulfilled

- Causes study treatment discontinuation
- Causes study treatment interruption
- Causes study treatment dose reduction
- The investigator believes that the abnormality should be reported as an AE

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

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

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

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 D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

6.3.7 Hy's Law

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 D for further instruction in cases of combined increase of aminotransferase and total bilirubin.

6.3.8 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. The development of local regional recurrence or distant 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 6.2). 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 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 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 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives 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 adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE 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

6.5 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). For other overdoses, reporting should be done within 30 days.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

Women of childbearing potential are not allowed to be included in this study. Should a pregnancy still occur, the investigational product should be discontinued immediately and the pregnancy reported to AstraZeneca

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

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous

miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day ie, immediately but **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 within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 3 months following the last dose. Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

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

To capture information about a pregnancy from the partner of a male patient, the male patient's partner consent must be obtained to collect information related to the pregnancy and outcome; the male patient should not be asked to provide this information. A consent form specific to this situation must be used.

6.7 Management of toxicity of Olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step.

6.7.1 Management of haematological toxicity Olaparib

Table 6 Management of Haematological Toxicity Olaparib

Toxicity	Study treatment dose adjustment
CTCAEa gr 1-2	Dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation
Repeat CTCAE gr 1-2	Dose interruption until recovery to CTCAE gr 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step

Toxicity	Study treatment dose adjustment
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for max of 4 weeks and dose reduction to **250 mg bid as first step and 200 mg bid as second step**
Repeat CTCAE gr 3-4	Discontinue study treatment **if 2 dose reductions are not able to manage the anaemia**

[a] CTCAE Version 4

6.7.1.1 Management of anaemia

Patients can enter the study with a haemoglobin value of > 9g/dl, this should be taken into account when considering the management of anaemia. Adverse events 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 (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment can be restarted a**t a reduced dose (see Table 4)** 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 **a further** study treatment dose reduction to 200 mg bid.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose **if bone marrow recovers.**

6.7.1.2 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 CTC grade 3 or worse neutropenia occurs. Primary prophylaxis with Granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment 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 (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leucopenia have been recovered up to CTCAE grade 1 (ANC $\geq 1.5 \times 10^9$/L).

Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

6.7.1.3 Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. 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 study treatment.

If a patient develops prolonged haematological toxicity such as:

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

Weekly differential blood counts including reticulocytes and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks 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 patient's diagnosis of MDS and/or AML is confirmed.

6.7.2 Management of non-haematological toxicity Olaparib

6.7.2.1 Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (eg, dyspnoea) or radiological abnormality occurs, an interruption in study treatment 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 study 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.

6.7.2.2 Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with Olaparib treatment. In Study D0810C00019 nausea was reported in 71% of the Olaparib treated patients and 36% in the

placebo treated patients and vomiting was reported in 34% of the Olaparib treated patients and 14% in the placebo treated patients. They 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 for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, 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. As per international guidance on antiemetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered eg dopamine receptor antagonist, antihistamines, dexamethasone.

6.7.2.3 Interruptions for intercurrent non-toxicity related events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with AZ study physician.

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

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Because the AEs related to Olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

6.7.3 Management of toxicity on placebo

Adverse events on placebo will be handled in the same manner as those arising on Olaparib (see sections 6.7)

6.8 Study governance and oversight

6.8.1 Data Monitoring Committee

This study will use an external independent data monitoring committee (IDMC) to perform interim reviews of accumulating study safety data and the interim analyses for futility based on PFS.

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.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 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 as shown below.

Investigational product	Dosage form and strength
Olaparib[a]	Tablet –100mg and 150 mg
Placebo to match Olaparib	Tablet to match each strength of Olaparib

[a] Descriptive information for Olaparib can be found in the Investigator's Brochure

7.2 Dose and treatment regimens

Study treatment is available as a green film-coated tablet containing 150 mg or 100 mg of Olaparib or matching placebo.

For all centres, Olaparib and matching placebo will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. The randomised study treatment will be dispensed to patients. Each dosing container will contain sufficient medication for at least each treatment period plus overage. The planned dose of 300 mg bid will be made up of two (2) x 150 mg tablets bid with 100 mg tablets used to manage dose reductions. Tablets should be taken at the same times each morning and evening of each day, approximately 12 hours apart with approximately 240 mL of water. The Olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with a light meal/snack (eg, two pieces of toast or a couple of biscuits).Multiple bottles of Olaparib or matching placebo maybe required for dispensing in order to make up the desired dose.

No cross over to Olaparib will be provided in this study.

If vomiting occurs shortly after the Olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg, as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose

time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

Once patients have been discontinued from study treatment, other treatment options will be at the discretion of the investigator.

7.3 Labelling

Labels for Olaparib 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, unless it is a country-specific regulatory requirement, 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.

7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and may only dispensed by investigator or pharmacist qualified designee. The investigational product label on the Olaparib bottle and the IB specifies the appropriate storage conditions.

7.5 Compliance

The administration of all study drugs (including Olaparib and placebo) should be recorded in the appropriate sections of the eCRF.

Patients should be given clear instructions on how and when to take their Olaparib. Patients will self-administer Olaparib. Study site 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 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 by the site staff on the eCRF.

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

7.6 Accountability

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

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

Study site personnel, will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed. Any discrepancies must be accounted for on the appropriate forms.

7.7 Concomitant and other treatments

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.

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.

7.7.1 Medications that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement 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 days 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.

7.7.2 CYP3A4/5 restrictions

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.

Olaparib is an investigational drug for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data, Olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of Olaparib is CYP3A4/5 and 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, idnavir, saquinavir, telithromycin, clarithromycin and nelfinavir

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

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

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

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

After randomisation if the use of any potent CYP inducers or inhibitors of CYP3A4/5 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.

7.7.3 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

7.7.4 Anti-emetics/ Anti-diarrhoeals

Should a patient develop nausea, vomiting and/or diarrhoea, then these symptoms should be reported as AEs (see section 6.3) and appropriate treatment of the event given.

7.7.5 Anticoagulant Therapy

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

7.7.6 Administration of other anti-cancer agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment.

Treatment with bisphosphonates or RANKL inhibitor for the prevention of skeletal related events in patients with bone metastasis is permitted and must be started at least 5 days prior to randomisation.

7.7.7 Subsequent therapies for cancer

Details of first and subsequent therapies for cancer after discontinuation of treatment, will be collected. Response to subsequent therapies and PFS on those therapies will also be collected.

The choice of subsequent systemic anticancer treatment will be entirely at the discretion of the investigator although it is expected that many/most patients upon progression on study will be treated with a platinum based regimen

8. STATISTICAL ANALYSIS AND SAMPLE SIZE DETERMINATION BY PAREXEL

8.1 Statistical considerations

- All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators identified.
- Analyses will be performed by AstraZeneca or its representatives.
- A comprehensive statistical analysis plan (SAP) will be prepared and finalised before first patient in (FPI).

8.2 Definitions of analysis sets

Table 7 gives a summary of outcome variables and analysis populations

8.2.1 Full analysis set

Intention to treat (ITT): The primary statistical analysis of the efficacy of Olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. Patients who were randomised 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.

In addition, key sensitivity analyses of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a g*BRCA* mutation confirmed by the Myriad test.

8.2.2 Safety analysis set

All patients who received at least one dose of randomised investigational product, Olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, erroneously treated Olaparib patients (those randomised to Olaparib but actually given placebo at any time) will be accounted for in the Olaparib treatment group. Erroneously treated placebo patients (those randomised to placebo but actually received at least one dose of Olaparib) will be accounted for in the Olaparib treatment group.

8.2.3 PRO analysis set

The analysis population for PRO data will be the subset of the FAS (ITT) population **who** have **evaluable** baseline **EORTC QLQ-C30 and QLQ-PAN26 forms.**

Table 7 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	FAS (ITT), Myriad confirmed *BRCAm* subgroup
- Secondary endpoints to be analysed: OS, PFS2, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to treatment discontinuation (TDT)	FAS (ITT), Myriad confirmed *BRCAm* subgroup
-Adjusted mean change from baseline in EORTC QLQ-C30 global QoL score	**PRO (subset of the FAS (ITT) who have evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms)**
-Secondary endpoints to be summarised:	
-Objective response rate	FAS (ITT) **(patients with measurable disease at baseline only)**, Myriad confirmed *BRCAm* subgroup
-Disease control rate	**FAS (ITT), Myriad confirmed *BRCAm* subgroup**
Demography	FAS (ITT)
Safety Data	
- Exposure	Safety
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

8.3 Calculation or derivation of efficacy variable(s)

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

8.3.1 Primary endpoint (PFS)

PFS is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease 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. 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 tumour assessment visits of randomisation (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) and an absolute increase of > 5 mm, or an overall non-target lesion assessment of progression or a new lesion.

The primary analysis will be based on the blinded independent central review (BICR) of the radiological scans. A charter for the BICR will be developed in advance of the start of the study. A sensitivity analysis based on the programmatically derived PFS based on Investigator-recorded assessments will be carried out.

8.3.2 Secondary endpoints

8.3.2.1 Overall Survival

Overall survival is defined as the time from the date of randomisation 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) date 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.

8.3.2.2 Best overall RECIST response (BoR)

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix F. It is the best response a patient has had **after randomisation but prior to starting any subsequent cancer and prior to** 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 F)

using the following response categories: complete response (CR), partial response (PR), stable disease (SD), No Evidence of Disease (NED; applies only to those patients entering the study with no disease at baseline), progressive disease (PD) and not evaluable (NE).

Best overall response will be determined programmatically based on the RECIST criteria using BICR data. **In addition, this will also be reported using investigator-recorded 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 ≤ 17 weeks (ie 16 weeks ±1 week) after randomisation then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST assessments, if the death occurred □□17 weeks (ie 16 weeks ±1week) after randomisation then BoR will be assigned to the nonevaluable (NE) category.

Progression events that have been censored due to them being more than two missed visits 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.

The disease control rate (DCR) is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD or NED for at least 15 weeks (ie 16 weeks ±1 week) prior to any evidence of progression. In the case of SD and NED, follow up assessments must have met the SD or NED criteria for a minimum interval of 15 weeks following randomisation.

8.3.2.3 Time from randomisation to second progression (PFS2)

Time from randomisation to second progression (PFS2) is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.

The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF. Second progression status will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and

without a second disease progression, ie censored at the last progression assessment date if the patient has not had a second progression or death).

8.3.2.4 Time to first subsequent therapy or death (TFST)

Time to start of first subsequent therapy or death (TFST) will be assessed. TFST is defined as the time from randomisation to the earlier of first subsequent **cancer** start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, ie the last follow-up visit where this was confirmed.

8.3.2.5 Time to second subsequent therapy or death (TSST)

Time to start of second subsequent therapy or death (TSST) will be assessed. TSST is defined as the time from randomisation to the earlier of the second subsequent **cancer** start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received second subsequent therapy, ie the last follow-up visit where this was confirmed.

8.3.2.6 Time to study treatment discontinuation or death (TDT)

Time to study treatment discontinuation or death (TDT) will be assessed. TDT is defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment 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 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.

8.3.2.7 Disease Control Rate (DCR)

The disease control rate (DCR) is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD for at least 16 weeks (ie 17 weeks ±1 week) prior to any evidence of progression. In the case of SD, follow up assessments must have met the SD criteria for a minimum interval of 16 weeks following randomisation.

8.4 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.

8.4.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and DAEs. Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of 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.

8.5 Calculation or derivation of patient reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines or the developer's guidelines, if published guidelines are not available.

EORTC QLQ-C30 and QLQ-PAN26

The EORTC QLQ-C30 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.

HRQoL Visit responses

A change of at least 10 points in the global QoL score will be considered as a clinically relevant or a minimally important difference (Osoba D et al 1998).

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 1999). 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.

Scores for the QLQ-C30 will be derived using the developer instructions. Raw scores are calculated using the formula:

Raw Score = RS $(I_1 + I_2 + ... + I_n)$ n

A linear transformation to 0 – 100 is then applied to obtain a score (S)

Function Scale:

$$\left\{1 - \frac{(RS-1)}{range}\right\} x100$$

Symptoms Scales/items:

{(RS-1)/range}x100

Global Health Status/Quality of Life:

{(RS-1)/range}x100

Range is the difference between the maximum possible value of *RS* and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of *RS* equals the range of the item values. Most items are scored 1 to 4, giving *range* = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6, and the initial yes/no items.

The QLQ-PAN26 follows the same scoring criteria as the QLQ-C30. The QLQ-PAN26 contains 26 items which comprise 7 multi-item scales (pancreas pain (4 items), eating related items (2 items), hepatic items (2 items), altered bowel habit (2 items), body image (2 items), health care satisfaction (2 items), sexuality (2 items)), and 10 single item scales (swollen abdomen, taste changes, indigestion, flatulence, weight loss, loss of muscle strength, dry mouth, burden of treatment, fear of future health, and ability to plan future.

Within the specific module the items can be grouped into new domains rather than reporting specific items. When using this approach it is important that the correct scoring algorithm is followed.

Higher scores represent more symptoms, except for health care satisfaction scale and sexuality scale where higher scores represent greater satisfaction and sexuality.

The threshold for a clinically important deterioration is outlined below (Table 8):

Table 8 Visit Response in EORTC QLQ-C30 Global QoL Score

Score	Change from baseline	Visit response
EORTC QLQ-C30 global QoL score	**≥ +10**	**Improved**
	≤ -10 or patient too ill to complete measure	**Deterioration**
	Otherwise	**No change**

Further detail will be provided in the SAP.

Best overall QoL response

A patient's best overall QoL response will be derived as the best QoL response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. The criteria in Table 9 will

be used to assign a best QoL response for HRQoL based on the 2-item global QoL score. Improvement rate will be defined as the proportion of patients whose best overall QoL response was "Improved".

Table 9 Best QoL Response in EORTC QLQ-C30 Global QoL Score

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 qualify for overall score response of "improved". A visit response of "deterioration" without response of "improved" or "no change" within 21 days.**
Other	**Does not qualify for one of the above.**

Compliance

Summary measures of overall compliance and compliance over time will be derived for the EORTC QLQ-C30 and QLQ-PAN26 questionnaires. These will be based upon:

- **Received forms = number of EORTC QLQ-C30 / QLQ-PAN26 questionnaire forms received back plus the number not received back where the reason was 'Subject too affected by symptoms of disease under investigation'.**
- **Expected forms = number of patients still under QoL follow-up at the specified assessment time excluding patients in countries with no available translation.**
- **Evaluable forms = subset of expected EORTC QLQ-C30 / QLQ-PAN26 questionnaire forms with at least one subscale that can be determined; or where the reason questionnaire not completed is ticked as 'Subject too affected by symptoms of disease under investigation'.**

Thus the compliance rate for QLQ-C30 and for QLQ-PAN26 is defined as the number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline EORTC QLQ-C30 / QLQ-PAN26 questionnaire form. In addition, an overall compliance rate defined as number of patients with an evaluable baseline and at least one evaluable follow-up, divided by the number of patients expected to have completed at least a baseline for both, the EORTC QLQ-C30 AND QLQ-PAN26 questionnaire form, will be calculated.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

Within the specific module the items can be grouped into new domains rather than reporting specific items. When using this approach it is important that the correct scoring algorithm is followed.

1. Calculate the raw score for each scale

Raw score = RS = $(I_1+I_2+\ldots+I_n)/n$

2. Apply the following linear transformation for the sexuality scale:

$$\left\{1-\frac{(RS-1)}{range}\right\}x100$$

For all other scales (including the single items), apply this linear transformation:

$$\left\{\frac{(RS-1)}{range}\right\}x100$$

Where range is 3 in each case.

8.6 Calculation or derivation of pharmacogenetic variables

To be defined in an exploratory analysis plan.

8.7 Calculation or derivation of health economic variables

Responses to the EuroQoL EQ5D questionnaire will be converted into utility scores using UK EQ5D valuation set. Alternative valuation sets may be used in scenario analyses. Descriptive statistics, graphs and listings will be reported for health state utility 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.

Descriptive statistics relating to the frequency healthcare resource use items, including hospital episodes, type of contact (hospitalisation, outpatient, day case), reason, length of stay by ward type (including ICU) and procedures undertaken will be derived from the resource use information.

The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

8.8 Methods for statistical analyses

A single interim PFS analysis for futility will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events). The interim analysis will be performed by an Independent Data Monitoring Committee (IDMC) and full details will be provided in the IDMC charter. A final PFS analysis will be performed when approximately **87** progression events have occurred (**60%** maturity). No further analyses of PFS are planned beyond this point unless requested by health authorities

Timing of the statistical analyses are given in Table 10

Table 10 Timing of statistical analyses

Timing of analyses	**Outcome Variable**
	Efficacy Data
Interim PFS analyses (~ 4**4** PFS events)	- PFS
Final PFS (~ 8**7** PFS events)	- PFS, PFS2, TDT, TFST, TSST, OS, **adjusted mean change from baseline in** global QoL **score**
Final OS analyses (~ 106 OS events)	- PFS2, TFST, TSST, OS, **adjusted mean change from baseline in** global QoL **score**

The treatment comparison is Olaparib 300 mg bid vs. placebo to Olaparib 300 mg bid.

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 subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint

Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: log-rank test using BICR data Key sensitivity analysis[a]: log rank test using BICR data in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)

Endpoints Analysed	Notes
	Additional sensitivity analyses:
	1) Evaluation time bias analysis; log-rank test using BICR data
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data
	4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
Overall Survival (Time from randomisation to death due to any cause)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
	Supportive analysis: KM plot of time to censoring for OS
Second Progression Free Survival (PFS2)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to treatment discontinuation (TDT)	Primary analysis: log rank test of time from randomisation to treatment discontinuation
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to first subsequent therapy (TFST)	Primary analysis: log rank test of time from randomisation to first subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to second subsequent therapy (TSST)	Primary analysis: log rank test of time from randomisation to second subsequent therapy or death
	Primary analysis: log rank test of time from randomisation to treatment discontinuation

Endpoints Analysed	Notes
Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire	**Primary analysis: mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit** **Supportive analysis: logistic regression on global QoL score improvement rate.**

[a] **See Section 8.8.3 for further details**

8.8.1 Multiplicity strategy for primary and key secondary endpoints

In order to describe the nature of the benefits of Olaparib maintenance treatment, PFS, PFS2 and OS will be tested at a 1-sided significance level of 2.5%.

However, in order to strongly control the type I error at 2.5% 1-sided, a multiple testing procedure will also be employed across the primary endpoint and secondary endpoints intended for key label claims (ie OS).

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha 5% 2 sided) and the key secondary endpoint of OS will then be tested using a multiple testing procedure with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 2).

Figure 2 Multiple Testing Procedures

OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. **One** interim analysis for OS will be performed at the time of the final PFS analysis (approximately **87** PFS events). A final analysis of OS will be performed when approximately 106 death events have occurred. **The Lan and DeMets approach that approximates the O'Brien & Fleming spending function will be employed to preserve the overall 1-sided type I error rate of 2.5% (**Lan and DeMets 1983**). If the interim analysis for OS occurs at exactly 57% of the 106 OS events,** statistical significance for OS will be declared if the null hypothesis for PFS is rejected and the observed p-value for OS is p<0.00**3, which equates to a HR ≤ 0.49. The significance level at the final analysis will be determined based on the exact number of events at the time of the interim and final analyses.** If the interim analysis **for OS** occurs at exactly 57% of events and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final analysis **will** be **2.4**%. **Statistical significance for OS will be declared if the observed p-value for OS is p<0.024, which equates to a HR ≤ 0.68.**

All planned analyses will be performed, regardless of the outcome of the MTP.

8.8.2 Analysis of the primary variable (s)

The primary PFS analysis will be performed when approximately **87** progression events have occurred (**60%** maturity) based on the BICR. No further analyses of PFS are planned beyond this point unless requested by Health Authorities

PFS will be analysed using a log rank test. The hazard ratio (HR) and confidence interval will be estimated from the U and V statistics obtained directly from the LIFETEST model (and using the Breslow approach for handling ties).

The HR and its confidence interval will be estimated from the log-rank as follows (Berry et al 1999 and Sellke et al 1983)

$$HR = \exp(U/V)$$

$$95\%\ CI\ for\ HR = (\exp\{U/V - 1.96/\sqrt{V}\}, \exp\{U/V + 1.96/\sqrt{V}\})$$

Where $U = \sum_i (d_{1i} - e_{1i})$ is the log-rank test statistic (with d_{1i} and e_{1i} the observed and expected events in group 1) and $\sqrt{V}$ the standard deviation of the log-rank test statistic as produced in the LIFETEST output.

The HR (Olaparib vs. placebo) together with its corresponding 95% confidence interval (CI) and p-value will be presented (a HR less than 1 will favour Olaparib).

A Kaplan-Meier (KM) plot of PFS will be presented by treatment group. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST or death) will be provided along with median PFS for each treatment arm.

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 producing 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 primary analysis will be based on the programmatically derived PFS based on BICR overall visit assessments (ie Individual tumour measurements will not be used) and using all scans regardless of whether they were scheduled or not.

The estimated PFS rates 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 they had not progressed and the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date.

Subgroup analyses will be conducted comparing PFS between treatments. 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 PFS will not be formally analysed. In this case, only descriptive summaries will be provided

The following subgroups of the full analysis set will be analysed for PFS:

- **Previous chemotherapy (FOLFIRINOX variants vs gemcitabine/cisplatin)**
- **Presence or absence of biliary stent**
- Type of **previous** chemotherapy (doublets vs triplets)
- Time on first line treatment till randomisation (≤6 months vs >6 months)
- Best response on first line treatment (SD vs PR/CR)
- Measurable versus non measurable disease /no evidence of disease at baseline
- *BRCA* mutation type, eg *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation (>=65 vs. <65)
- Race
- Sex

Other baseline variables may also be assessed if there is clinical justification.

For each subgroup, the HRs (Olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (ties = Efron) that contains the treatment term, factor and treatment-by-factor interaction term. 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).

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

A further analysis of PFS (using Investigator assessed RECIST) may be performed at the time of the OS analyses, if requested by Health authorities.

8.8.3 Sensitivity analysis for the primary endpoint

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a *gBRCA* mutation status confirmed by the Myriad test. The same methodology and model will be used as for the primary analysis of PFS and the HR and associated 95% CI will be reported.

Sensitivity analyses will be performed to assess the possible presence of time-assessment bias (ie, 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.

8.8.3.1 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 stratified log rank test, 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). This approach will use the BICR RECIST assessments.

8.8.3.2 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 subjects who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, subjects who take subsequent therapy prior to **their last evaluable RECIST assessment or** 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 presented.

8.8.3.3 Ascertainment bias

A log-rank test will be repeated using the programmatically derived RECIST using Investigator assessed PFS. The HR and 95% Confidence Interval will be presented.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using Investigator assessments, then the proportion of patients with site but no central confirmation of progression will be summarised. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the Investigator review

as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the Investigator review as a proportion of all discrepancies.

8.8.3.4 Deviation bias (if meaningful to do)

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with deviations that may affect the efficacy of the trial therapy will be performed if > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A log-rank test will be repeated using the BICR RECIST data, using the same ties as described for the primary analysis of PFS. The HR and 95% CI will be presented.

8.8.4 Analysis of the secondary variable(s)

8.8.4.1 Analysis of OS endpoint

OS data will be analysed at the time of the final analyses of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

The sensitivity analysis outlined in Section 8.8.3 will not be repeated for OS with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of the primary OS is reversed.

To assist in quantifying the PFS effect, at the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data (Chen and Sun 2011). The estimate of the treatment effect for OS at the final analysis is defined as $\hat{\Delta}_j = w\hat{\Delta}_F + (1-w)\hat{\Delta}_P$ where $\hat{\Delta}_F$ is the observed treatment effect for OS at the time of the PFS analysis and $\hat{\Delta}_P = \hat{\gamma}\hat{\Delta}_I$ is the estimated treatment effect for OS based on the observed treatment effect for PFS, where $\hat{\gamma}$ represents the estimated slope relating PFS to OS from historical trials. The weightings (w) are based on the inverse of the variance (ie those with more uncertainty are given less weight). The variance is dependent on the correlation between the two endpoints. Details of the methodology will be provided in the statistical analysis plan (SAP).

8.8.4.2 Analysis of PFS2 endpoint

The analyses of PFS2 will use the same methodology and model as the primary analysis of PFS. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

The date of second progression will be recorded by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic

progression or death. RECIST measurements will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF. Second progression status will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie censored at the last progression assessment date if the patient has not had a second progression or death)

As a key sensitivity, the analysis of PFS2 will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

A KM plot of the time to censoring where the censoring indicator of the primary PFS2 is reversed will be produced.

Time from second progression to previous assessment will be summarised by treatment arm.

8.8.4.3 Analysis of TDT endpoint

Time to study treatment discontinuation or death (TDT) will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

As a key sensitivity, the analyses of TDT will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TDT in this subset of patients will be presented by treatment group.

8.8.4.4 Analysis of TFST endpoint

Time to first subsequent therapy or death (TFST) will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm. In addition, the time between progression and starting subsequent therapy will be assessed.

As a key sensitivity, the analyses of TFST will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TFST in this subset of patients will be presented by treatment group.

8.8.4.5 Analysis of TSST endpoint

Time to first second subsequent therapy or death (TSST) will be analysed analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment arm.

Summary tables of first and second subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm.

As a key sensitivity, the analyses of TSST will be repeated in those patients whose *gBRCAm* status is confirmed by the Myriad test. A KM plot of TSST in this subset of patients will be presented by treatment group.

8.8.4.6 Analysis of PRO endpoints

The analysis population for PRO data will be the **PRO analysis set including patients with evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms.**

The impact of olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales.

Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive.

The adjusted mean change from baseline estimates and corresponding 95% CIs will be presented by visit for each treatment group and corresponding plots over time will be presented.

As a supportive analysis, EORTC QLQ-C30 global QoL **score** improvement rate will be analysed using a logistic regression model. If the overall response rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC QLQ-C30 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Descriptive statistics and graphs will be reported for the global QoL **score** by visits as well as **unadjusted** change in these scores from baseline. Summary tables of **EORTC** QLQ-C30

best **overall QoL response as defined in Table 9** will be provided (improvement, **deterioration, no change**).

An exploratory analysis will examine adjusted mean change from baseline on QLQ-PAN26 symptom scales/items (including pancreatic pain). This is detailed in Section 8.8.5.1.

8.8.4.7 Summary of Best overall RECIST Response (BoR) and ORR

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

The objective response rate (ORR) will be summarised (ie, number of patients (%)) by treatment group in patients in the FAS (ITT population) with measurable disease at baseline. Any patients who experienced CR or PR which was first observed whilst receiving subsequent therapy after discontinuation of Olaparib/placebo will be identified. The denominator for the response rate will be measurable disease as defined by the BICR data

ORR and BOR will be presented based on the BICR data and also summarised in a similar way using the investigator recorded data.

8.8.4.8 Summary of DCR

The disease control rate (DCR) will be summarised (ie, number of patients (%)) by treatment group in patients in the FAS (ITT population).

DCR will be presented based on the BICR data and also the investigator recorded data.

8.8.5 Exploratory analysis

8.8.5.1 Exploratory analysis of PRO endpoints (QLQ-PAN-26 symptom scales and items)

Exploratory analyses examining **adjusted mean change from baseline** will be performed **for EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, social) and** for the individual **EORTC QLQ-C30 and QLQ-PAN26** symptom scales/items (with a particular focus on **pancreatic pain,** fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice), **using the same MMRM model described in Section 8.8.4.6 for the global QoL score.**

Descriptive statistics and graphs will be reported for the **EORTC QLQ-C30 functioning domains and EORTC QLQ-C30 and QLQ-PAN26** symptom scales/items (specifically **pancreatic pain,** fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite) and jaundice).

EORTC QLQ- PAN26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

8.8.5.2 Analysis of Healthcare Resource Use

A health economic analysis of resource use will be estimated, including descriptive statistics relating frequency of hospitalisations and hospital admission, type of attendance, length of stay and procedures undertaken, and the primary symptom/reason for the attendance.

Descriptive statistics, graphs and listings will be reported for health state utility 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.

The evaluable population will comprise all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.

8.8.5.3 Analysis of ECOG Performance status

Shift tables will be provided showing best and then worst on treatment change in performance status vs baseline, by treatment.

Change from baseline in levels of ECOG performance status at each post randomisation time point will be reported descriptively (n, %) by treatment group, as well as the proportion of patients with ECOG status of 0 at baseline (ie cannot improve).

8.8.6 Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analyses

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. 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 patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the analyses. Further detail will be provided in the SAP and Payer Analysis Plan. These analyses are intended to support reimbursement appraisals.

8.8.7 Exploratory translational science endpoints

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

8.8.8 Biomarkers

Biomarker data will be summarised descriptively using tables and plots. If the data is available at the time of developing the CSR then the biomarker data will be included in the CSR. Otherwise the biomarker data will be reported in a separate addendum to the CSR (if

applicable). Further details on the data summaries and plots for the biomarker data for the CSR will be provided in the SAP.

BRCA status will be summarised for all patients based on the central myriad test result. This will highlight any patients with a negative *BRCA* result from the central test.

8.9 Sample Size Determination

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately **87** PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for **futility** will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events) based on BICR.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and **2.5%** alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median OS for placebo. **87 PFS events will be required at the final analyses.**

Patients are to be followed for the final analysis of OS (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6 month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

Assuming that the study accrual period will be approximately 15 months, **87** progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that **44** PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 death events will occur approximately 31 months after first patient in.

8.9.1 Interim analysis

A single interim PFS analysis for futility will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter. **Safety data including death rates will also be reviewed at this time.**

The futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the final number of PFS events (n=87) is reached (Lachin 2005). The determination of this probability will be conditional on the observed data at the time of the interim analysis and on the assumed hazard ratio for the alternative hypothesis (PFS HR=0.54). If the probability is less than 20%, the IDMC will consider the option of declaring futility.

The exact figure used for the futility boundary will be calculated by AZ and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time. As an example, if exactly 50% of the PFS events required for the primary PFS analysis have occurred at the time of the interim analysis (44 events), then the HR that corresponds to 20% conditional power for the interim analysis will be 1.02. Therefore, if the observed HR for PFS at the interim is more than 1.02, the IDMC will consider the option of declaring futility.

An interim analys**i**s of OS will be performed at the time of the **primary analysis** of PFS (**approximately 87** events), and **again** when approximately 106 OS events have occurred.

The futility analyses on PFS will be used to guide decisions on stopping the study for futility or continuing the study. Details will be documented in the IDMC charter.

9. STUDY AND DATA MANAGEMENT BY PAREXEL

9.1 Training of study site personnel

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

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

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

9.2 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 CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant

to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

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

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

9.2.1 Source data

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

9.2.2 Study agreements

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

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

9.2.3 Archiving of study documents

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

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2014 and to end by Q2 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.

9.4 Data management by PAREXEL

Data management will be performed by PAREXEL. .

The data collected through third party sources will be obtained and reconciled against study data.

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

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

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

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

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca. Data from external providers (eg 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, the results of any analyses will not be recorded in the database, but information relating to the processing of the sample, including 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.

Exploratory 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 analyse samples. The results from this exploratory genetic research will not be reported in the CSR.

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.

Site staff will enter PRO booklet data into Medidata Rave exactly as reported by the patient.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Patient data protection

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

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**.**

The exception to the above is the result of the Myriad *BRCA* test. This will be made available to the Investigator and patient.

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.

10.3 Ethics and regulatory review

An Institutional Review Board (IRB)/Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

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

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

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

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

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

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

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

The amendment is to be approved by the relevant Ethics Committee 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 Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

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

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

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

Alexandrov et al 2013
Alexandrov et al. Signatures of mutational processes in human cancer Nature 2013;500;7463;415-21

American Cancer Society 2013
American Cancer Society. Cancer Facts and Figures 2013. Atlanta, Georgia: American Cancer Society, 2013. http://www.cancer.org

Audeh et al 2010
Audeh, M.W., Carmichael, J, Penson R.T. et al., Oral poly(ADP-ribose) polymerase inhibitor Olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet, 2010. **376**(9737): p. 245-51.PMID: 20609468

Bang et al 2013
Bang et al. Olaparib plus paclitaxel in patients with recurrent or metastatic gastric cancer: A randomized, double-blind phase II study. J Clin Oncol 31, 2013 (suppl; abstr 4013)

Bergfeldt et al 1995
Bergfeldt K, Einhorn S, Rosendahl I & Hall P. Increased risk of second primary malignancies in patients with gynecological cancer. A Swedish record-linkage study. Acta Oncol. 1995;34(6):771-7.

Berry et al 1999
Berry G, Kitchin RM & Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-755

Bryant et al 2005
Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature, 2005. 434(7035): p. 913-7. PMID: 15829966

Chen and Sun 2011
Quantification of PFS Effect for Accelerated Approval of Oncology Drugs. Statistics in Biopharmaceutical Research 2011, Vol. 3, No. 3DOI: 10.1198/sbr.2011.09046

Cole and Strair 2010
Cole M, & Strair R. Acute myelogenous leukemia and myelodysplasia secondary to breast cancer treatment: case studies and literature review. Am J Med Sci 2010;339(1):36-40.

Conroy et al 2011
Conroy T. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer, 2011 NEngl J Med 364; 1817-25

Cowley et al 2013
Cowley et al Understanding pancreas cancer genomes. J Hepatobiliary Pancreat Sci (2013) 20:549–556

Fayers et al 1999
Fayers P, Aaronson N, Bjordal K & Sullivan M (1999). EORTC QLQC30, Scoring Manual. Belgium: EORTC Data Center.

Fayers et al 2001
Fayers et al. EORTC QLQ-C30 Scoring Manual (Third Edition). Belgium: EORTC Quality of Life Group, 2001.

Ferrone CR et al 2009
Ferrone CR. et al.BRCA Germline Mutations in Jewish Patients With Pancreatic Adenocarcinoma. Journal of Clinical Oncology, Vol 27, No 3 (January 20), 2009: pp. 433-438.

Fitzsimmons D et al 1999
Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. Eur. J. Cancer 35: 939-941, 1999.

Fong et al 2009
Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med. 2009;361(2):123-34.

Fowble et al 2001
Fowble B, Hanlon A, Freedman G, Nocolaou N, Anderson P. Second cancers after conservative surgery and radiation for stages I-II breast cancer : identifying a subset of women at increased risk. Int J Radiat Oncol, Biol, Phys. 2001; 51 (3);679-690.

Gaymes et al 2008
Gaymes TJ, Shall S, MacPherson LJ, Twine NA, Lea NC, Farzaneh F, and Mufti GJ. Inhibitors of poly ADP-ribose polymerase (PARP) induce apoptosis of myeloid leukemic cells: potential for therapy of myeloid leukemia and myelodysplastic syndromes. Haematologica 2009; 94:638-646. doi:10.3324/haematol.2008.00193

Ginsburg et al 2010
Ginsburg et al *BRCA1* and *BRCA2* families and the risk of skin cancer Springer Science+Business Media B.V. 2010

Goggins M. et al 1996
Germline M et al BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res. 1996 Dec 1;56(23):5360-4

Hay et al 2009
Hay T, Matthews JR, Pietzka L, Lau A, Cranston A, Nygren AO, et al. Poly(ADP-ribose) polymerase-1 inhibitor treatment regresses autochthonous Brca2/p53-mutant mammary tumors in vivo and delays tumor relapse in combination with carboplatin. Cancer Res. 2009;69(9):3850-5.

Hahn et al 2003
Hahn et al BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst. 2003 Feb 5;95(3):214-21.

Helleday 2011
Helleday T. The underlying mechanism for the PARP and *BRCA* synthetic lethality: Clearing up the misunderstandings. Molecular Oncology 2011; 5: 387-393.

Jemal A et al 2011
Jemal A et al. Global cancer statistics. CA Cancer J Clin. 2011 Mar-Apr;61(2):69-90

Kaufman B et al 2013
Kaufman B, Shapira-Frommer R Schmutzler RK, Audeh MW, et al. Olaparib monotherapy in patients with advanced cancer and a germline *BRCA1/2* mutation: An open label phase II study. J Clin Oncol 31, 2013 (suppl; abstr 11024)

Kim et al 2014
Kim et al. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poor prognosis. Clin Cancer Res Published Online First January 31, 2014

Lachin 2005
Lachin, J. M. A review of methods for futility stopping based on conditional power. Statist. Med. (2005) 24: 2747–2764.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70: 659-63.

Ledermann et al 2013
Ledermann, J Clin Oncol 31, 2013. Olaparib maintenance therapy in patients with platinum sensitive relapsed serous ovarian cancer (SOC) and a *BRCA* mutation (*BRCAm*)

Lowery M et al 2011
Lowery M et al.An Emerging Entity: Pancreatic Adenocarcinoma Associated with a Known BRCA Mutation: Clinical Descriptors, Treatment Implications, and Future Directions The Oncologist 2011, 16:1397-1402.

Murai et al 2012
Murai J, Huang SN, Das BB, Renaud A, Zhnag, Y, Doroshow, JH, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. AACR; 72(21); 5588–99.

Murphy KM et al 2002
Evaluation of Candidate Genes MAP2K4, MADH4, ACVR1B, and Mutations in 17% BRCA2 in Familial Pancreatic Cancer: Deleterious BRCA2. Cancer Res 2002;62:3789-3793.

Osoba D et al 1998
Osoba D, Rodrigues G, Myles J, Zee B and Pater J. Interpreting the significance of changes in health-related quality-of-life scores. JCO January 1998 vol. 16 no. 1 139-144

Ozcelik et al 1997
Ozcelik et al Germline *BRCA2* 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients Nature Genetics 16, 17 - 18 (1997)

Rahma et al 2013
Rahma et al Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. Annals of Oncology 2013 Aug;24(8):1972-9.

Robins et al 1991
Robins JM, Tsiatis AA. Correcting for noncompliance in randomized trials using rank preserving structural failure time models. Communications in Statistics - Theory and Methods 1991; 20:2609-2631.

Robins 1993
Robins J. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. Proceedings of the Biopharmaceutical Section, American Statistical Association 1993; 24-33.

Rottenberg et al 2008
Rottenberg S, Jaspers JE, Kersbergen A, van der Burg E, Nygren AO, Zander SA, et al. High sensitivity of *BRCA1*-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci. 2008;105(44):17079-84.

Roy et al 2012
Roy, R., J. Chun, and S.N. Powell, *BRCA1* and *BRCA2*: different roles in a common pathway of genome protection. Nat Rev Cancer, 2012. **12**(1): p. 68-78. PMID: 22193408

Sadler ZK. 2012
Sadler ZK. 2012. BRCA and Pancreatic Cancer: Selection of Chemotherapy Journal of the Pancreas JOP. J Pancreas (Online) 2012 Mar 10; 13(2):180-181

Sellke et al 1983
Sellke, T. and Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 70: 315-326, 1983

Stone 2010
Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. Pharm. Statistics 5 (2010) 151-161

Sun and Chen 2010
Sun X, Chen C: Comparison of Finkelstein's Method With the Conventional Approach for Interval-Censored Data Analysis. Stat Biopharm Research 2:97-108, 2010

The Breast Cancer Linkage Consortium 1999
The Breast Cancer Linkage Consortium: 1999 J Natl Cancer 91:1310-16

Tutt A et al 2010
Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel J et al,. Oral poly(ADP-ribose) polymerase inhibitor Olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010; 376: 235–44

Von Hoff et al 2013
Daniel D. Von Hoff, M.D. et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine N Engl J Med 2013; 369:1691-1703

Wesolowski et al 2007
Wesolowski R, Choueiri TK, Rybicki L, Shealy AG, Casey G, Weng D, et al. BRCA mutation status and risk of secondary malignancy following chemotherapy for breast cancer. J Clin

Oncol, 2007;ASCO Annual Meeting Proceedings Part I. Vol (25);No. 18S (June 20 Supplement):11017.

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Clinical Study Protocol Appendix B	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

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.

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Clinical Study Protocol Appendix C	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

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/dgr/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/dgr/Pages/infectious_substances.aspx)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	Olaparib
Study Code	D081FC00001
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Appendix D
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. Hy's Law 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 Product (IP).

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)

A Potential Hy's Law (PHL) case is defined as a study subject with an increase in serum Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN irrespective of serum Alkaline Phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law (HL)

A Hy's Law (HL) case is defined as a study subject with an increase in serum AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL to be met the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

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

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

- 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:

- 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 patient's 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 3 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 were 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 IP. 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 IP:

- 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 (including the 30-day follow-up period) 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 subsequent 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 such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. 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 (including the 30-day follow-up period) 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 subsequent 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, such as fatigue, vomiting, rash, right upper quadrant pain, jaundice, eosinophilia. 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

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Clinical Study Protocol Appendix E	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	31 March 2014

Appendix E
Acceptable Birth Control Methods

1. 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 in combination while they are receiving study treatment and for 3 months after last dose of study drug.

Acceptable Non-hormonal birth control methods include

- Total/True abstinence: when the subject refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the study treatment and for 3 months after the last dose of study drug. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner plus male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia
- Tubal occlusion plus male condom
- IUD plus male condom. Provided coils are copper-banded

Acceptable hormonal methods

- Etonogestrel implants (eg, Implanon, Norplan) + male condom
- Normal and low dose combined oral pills + male condom
- Norelgestromin / EE transdermal system + male condom
- Intravaginal device + male condom (eg, EE and etonogestrel)
- Cerazette (desogestrel) + male condom. 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
Guidelines for Evaluation of Objective Tumour Response Using Modified RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

1. INTRODUCTION

This appendix details the implementation of modified RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al 2009) for the study D081FC00001 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 measurable disease and/or non measurable disease or no evidence of disease assessed at baseline by CT (or MRI where CT is contraindicated) will be entered in this study. RECIST 1.1 has been modified to allow the assessment of progression due to new lesions in patients with no evidence of disease at base-line.

Measurable lesions

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

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)

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

- Previously irradiated lesions. Localised post-radiation changes which affect lesion size, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTLs at baseline and followed up as part of the NTL assessment

- Skin lesions assessed by clinical examination

- Brain metastasis

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 non-cystic lesions should be selected as target lesions (TLs).

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 TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

3. METHODS OF MEASUREMENT

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

The methods to be used for RECIST assessment are summarised in Table 1 and those excluded for tumour assessments in this study are discussed below, 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
	X-ray, Chest x-ray	X-ray, Chest x-ray, Clinical examination
	Clinical examination	Ultrasound
		Bone scan
		FDG-PET

3.1 CT and MRI

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

In study D081FC00001 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 contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

3.2 Clinical examination

In study D081FC00001 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-rays

3.3.1 Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

3.3.2 Plain X-ray

In study D081FC00001 plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

3.4 Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs 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

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

3.6 Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment 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 the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs 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 NTLs and followed by the same method as per baseline assessment.

In the D081FC00001 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 D081FC00001 study FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

4. TUMOUR RESPONSE EVALUATION

4.1 Schedule of evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed every 8 weeks (±1 week) for 40 weeks and then every 12 weeks ± 1 week relative to date of randomisation, until objective disease progression as defined by modified RECIST 1.1. See Table 1: Study Schedule from Study Protocol for further information. 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.

All patients will continue to be assessed for radiological tumour assessments according to the study schedule, until objective radiological disease progression, irrespective of reasons for discontinuation of treatment.

4.2 Target lesions

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 TLs 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 millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs 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 TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

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

4.2.2 Evaluation of target lesions

Table 2 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 2 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, 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 TLs, 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 TLs 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 (NE) as a TL response

4.3 Non-Target lesions

4.3.1 Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs 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 NTLs at the investigational site at each visit.

Table 3 Overall Visit Response for Non-Target Lesions

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

Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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

4.4 New Lesions

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

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

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

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

4.5 Symptomatic deterioration

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

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

4.6 Evaluation of Overall Visit Response and Best Overall 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
NA	NA	No	NED

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease
IR = incomplete response, NE = not evaluable, NED = no evidence of disease, NA = not applicable (relevant when no TLs/NTLs at baseline)

5. CENTRAL REVIEW

All CT/MRI scans will be sent to an AstraZeneca appointed Clinical Research Organisation (CRO) for blinded independent central review. After the final Progression Free Survival (PFS) analysis, central review of scans will no longer be required. Patients should continue to receive study treatment until objective radiological disease progression as per modified RECIST 1.1 as assessed by the investigator, and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria. The CRO appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

6. REFERENCES

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J.

New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer. 45 (2009) 228-247.

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Clinical Study Protocol Appendix G	
Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
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Appendix G
ECOG Performance Status

1. ECOG PERFORMANCE STATUS

1.1 Example of Performance Status (ECOG SCALE)

DESCRIPTION	ECOG GRADE
Fully active, able to carry on all pre-disease performance without restriction.	0
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
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

Clinical Study Protocol Appendix H	
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Appendix H
CYP3A4/5 Restrictions

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GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS

NB. While this is not an exhaustive list, it covers the known potent inhibitors and inducers, which have most often previously been reported to be associated with clinically significant drug interactions. Please contact the Medical Monitor or AstraZeneca physician if further clarification is required.

1. POTENT INHIBITORS OF CYP3A4/5

In vitro data has shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4/5 and consequently, to ensure patient safety, **the following inhibitors of CYP3A4/5 must not be used during this study.**

Table 1 Competitive inhibitors of CYP3A4/5

Drug	Minimum washout period prior to starting olaparib
Ketoconazole	1 Week
Itraconazole	
Indinavir	
Saquinavir	
Telithromycin	
Nelfinavir	

Table 2 Time dependent inhibitors of CYP3A4/5

Drug	Minimum washout period prior to starting olaparib
Clarithromycin	1 Week
Ritonavir	

2. INDUCERS OF CYP

In addition, to avoid potential reductions in exposure due to drug interactions, **the following CYP3 inducers should be avoided:**

Table 3 Inducers of CYP

Drug	Minimum washout period prior to starting olaparib
Carbamazepine	3 Weeks

Table 3 Inducers of CYP

Drug	Minimum washout period prior to starting olaparib
Modafinil	
Nevirapine	
Phenytoin	
Rifabutin	
Rifampicin	
Rifapentin	
St John's Wort (Hypericum perforatum)	
Phenobarbitone	5 Weeks

After randomisation if the use of any potent CYP inducers or inhibitors of CYP3A4/5 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.

3. NATURAL / HERBAL PRODUCTS

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

4. INTERACTIONS WITH P450

Olaparib is an investigational drug for which no data on in vivo interactions is currently available. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity.

Clinical Study Protocol Appendix I	
Drug Substance	Olaparib
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Appendix I
Patient Reported Outcomes EORTC QLQ-C30, QLQ-PAN26, EQ-5D-5L

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

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 - PAN26

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 abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

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

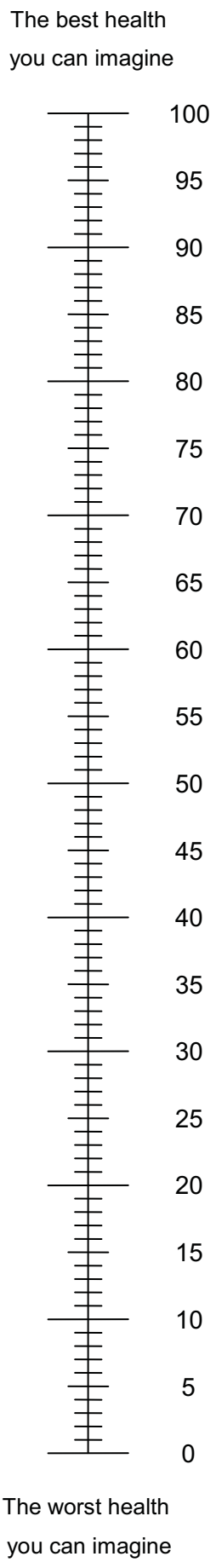
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 = ☐



AstraZeneca

Independent Data Monitoring Committee Guidelines

Drug Substance	Olaparib (AZD2281)
Project Code	D081FC00001
Edition No.	1
Date	13th November 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this guideline.

Abbreviation or special term	Explanation
AE	Adverse Event
AZ	AstraZeneca
BICR	Blinded Independent Central Review
COI	Conflicts of Interest
CTC	Common Toxicity Criteria
DBL	Database Lock
DCO	Data Cut-Off
eCRF	Electronic Case Report Form
gBRCA	Germline Breast Cancer susceptibility gene
GSP	Global Safety Physician
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
MSD	Medical Science Director
OS	Overall Survival
PFS	Progression Free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Steering Committee
SDAC	Statistical Data Analysis Centre

1. INTRODUCTION

This document defines the primary responsibilities of the Independent Data Monitoring Committee (IDMC) for this olaparib phase III study, the purpose and timings of the meetings, and the relationship of the IDMC with the study Steering Committee (SC). This document also defines the procedures for ensuring confidentiality, proper analysis, communication of interim data and a summary of the content of the Open and Closed Reports that will be provided to the IDMC.

1.1 Description of Study

This is a phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic cancer patients with gBRCA mutations (documented mutation in gBRCA1 or gBRCA2) that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16 weeks of first line platinum based chemotherapy.

The study will be conducted in USA, UK, Canada, Korea, Israel, Netherlands, Belgium, Australia, Spain, France and Germany.

1.2 Study Organisation

In the execution of the study, AstraZeneca (as the sponsor) will take responsibility for logistics, including site monitoring, provision of study medication, data management, statistical analysis and financial support.

The study execution is outsourced to PAREXEL under a Project Agreement between AstraZeneca and PAREXEL.

Changes to the study protocol have to be agreed upon by AstraZeneca in writing before being submitted, as per local requirements, and implemented. All contacts with regulatory authorities relating to the study should be channelled through AstraZeneca, unless specifically agreed and documented in writing between involved parties.

1.3 Study Timings

It is anticipated that the first patient to be recruited will be in Q4 2014, and the last patient to be recruited will be in Q4 2015. A single interim efficacy analysis for superiority and futility will be performed when approximately **45 progression free survival (PFS) events** have occurred. The interim analysis is expected to occur approximately 13-14 months after the first patient is recruited and is therefore anticipated to be in Q1 2016. AstraZeneca will inform the IDMC membership, in writing, of any changes in time schedule required for the services.

1.4 AstraZeneca Responsibilities to the IDMC:

AstraZeneca will have the following responsibilities;

- Overall responsibility for the operational work.
- Overall responsibility for data collection and data management.
- To provide reports on the progress of the olaparib study.
- To organise the IDMC meetings (face-to-face, telephone or video conferences).
- Making resources available to the IDMC as is required to carry out its designated functions.
- Making resources available for creating and maintaining an independent Statistical Data Analysis Centre (SDAC) to receive data from the Data Management Centre at AstraZeneca. The SDAC will then prepare reports for the IDMC.
- Responsibility for generating randomisation schemes and providing these to the SDAC as required. This will be done by AstraZeneca personnel who are completely independent of the D081FC00001 study team, ensuring that the AstraZeneca study team remain blinded until the primary analysis of the trial.
- For communicating the recommendations of the IDMC to the Regulatory Authorities as required.

1.5 Reporting and Publications

1.5.1 Reporting policy

In accordance with ICH-GCP, AstraZeneca is obliged to analyse and report all study data as described in the Clinical Study Protocol. On the basis of the data, AstraZeneca personnel, in co-operation with the SC, will write a Clinical Study Report intended for submission to Regulatory Authorities.

1.5.2 Publication policy

Principles

AstraZeneca is committed to full publication of its clinical research and to ensure that the data are reported in a responsible and coherent manner. AstraZeneca will manage the publication of the study results in partnership with the authors; the principal author will take a leading role in this process. AstraZeneca will propose suitable journals and/or meetings and timelines for publication production for agreement with the authors.

The results of the study will be submitted for publication in major scientific journals, once the final analyses have been performed and the manuscript authorised by AstraZeneca. AstraZeneca must approve the selection of journals prior to submission of the manuscript.

2. IDMC ROLE, REMIT AND COMPOSITION

2.1 Role and Remit

The IDMC is responsible for safeguarding the interests of study participants via review of accumulating safety and efficacy data. The IDMC will provide the AstraZeneca Medical Science Director (MSD) or delegate with recommendations for action with respect to study conduct and the management of patients treated under the auspices of the study protocols.

Additionally, the IDMC will be responsible for reviewing the results of the interim analyses, the results of which will not be revealed to any AstraZeneca personnel. The IDMC will make a recommendation whether the study should be continued, amended or terminated. Once the IDMC has reached its recommendation, notification will be provided to the SC. This report will state only the recommendation of the IDMC on whether the study should be continued, amended or terminated (if the study may continue subject to a protocol amendment, the details of the proposed amendment may also be included).

2.2 Composition

The IDMC consists of 3 members. Members have been restricted to individuals free of any personal or financial interest in the outcome of trial D081FC00001.

The members consist of 2 independent Medical Oncologists:

And 1 independent biostatistician

•

These members are all voting members.

The IDMC biostatistician will be supported by an independent statistician from the SDAC, who will not be a voting member. Please see Section 3.1 for further details.

IDMC membership is to be for the remaining duration of the study. If any member/s leave the IDMC during the course of the study, the sponsor, in consultation with the IDMC chair, will appoint their replacements.

2.3 Tasks and Responsibilities

Each voting member of the IDMC will be responsible for the following (in addition to other responsibilities contained herein):

- To read and understand the clinical study protocols, all administrative changes/amendments and other study requirements communicated and/or provided by AstraZeneca.

- To adhere to the guidelines contained herein, applicable for the full execution of the services.

2.4 Conflicts of Interest

Membership is restricted to individuals free of interest: the IDMC members are, therefore, neither study investigators, nor individuals who might have regulatory responsibilities for the study products.

Any potential candidate for the IDMC needs to declare any potential conflict of interest that, according to regulatory requirements, may influence the decision-making process in olaparib study D081FC00001. The Certification / Disclosure Form provided by AstraZeneca should be completed, signed and returned to AstraZeneca. Conflicts of interest (COI) will be an agenda item for the start of each meeting and any relevant change in circumstances of any of the voting members should be raised and discussed. The IDMC members will take the decision whether any COI precludes a member from continuing to form part of the IDMC.

2.5 Meeting Attendance

Safety review meetings: It is anticipated that there will be two safety review meetings and that these meetings will be conducted as teleconferences, when 50 patients are randomised and have received 3 months of treatment [expected Q3 2015] and at the time of the interim analysis.

Interim efficacy analysis review meeting: This study incorporates a single interim analysis of efficacy to be conducted when 50% of the final number of progression events have been reached (approximately 45 PFS events based on blinded independent central review [BICR]), expected Q3 2015. It is anticipated that the results of the interim analysis will be reviewed at a face-to-face meeting of the IDMC.

All 3 voting members must be present in order for the committee to be considered quorate.

3. STATISTICAL CONSIDERATIONS

3.1 The Role of the Independent Biostatistician

The independent SDAC biostatistician will be responsible for producing unblinded summaries of safety data for IDMC review. In addition, for the interim efficacy analysis, the independent SDAC biostatistician will also be responsible for producing unblinded efficacy analysis outputs for IDMC review and for providing statistical expertise in the interpretation of these outputs. The independent SDAC biostatistician will therefore be provided with the trial database, randomisation scheme and Statistical Analysis Plan (SAP). The SDAC will author the programs required for the safety review meetings but will be provided with the programs required for the interim efficacy analysis.

If additional analyses are deemed to be required beyond the scope of the SAP, the nature of these analyses will be discussed with the MSD/SC.

Unblinded interim data will be provided exclusively to the IDMC members. The AstraZeneca independent randomiser will provide the random scheme to the SDAC biostatistician. Apart from the IDMC biostatistician and the SDAC biostatistician(s) only the independent randomiser will have access to the randomisation schedule until the time of the final analysis.

3.2 The Statistical Data Analysis Centre

The SDAC is responsible for the overall data analysis preparation for review by the IDMC.

The SDAC prepares reports for review by the IDMC based on data generated by the Data Management Centre at AstraZeneca.

During the study, no unblinded analyses will be done by the SDAC on behalf of the SC or any investigator unless agreed to by the IDMC and AstraZeneca.

AstraZeneca will (in close cooperation with the SDAC and SC) decide on the statistical methods and guidelines for interim analyses, which will be finalised and documented before database lock (DBL) for the interim analysis as specified in the SAP.

4. RELATIONSHIP TO STEERING COMMITTEE

The study SC comprises of study investigators and members of the AstraZeneca project team, who jointly have responsibility for the design, conduct and final analysis of the clinical study.

The SC and the IDMC are responsible for safeguarding the interests of the participating patients and for the conduct of the study. AstraZeneca, however, retains final accountability and may go beyond the recommendations made by the IDMC, to ensure patient safety.

In order to execute their roles as described above, the SC will consider the recommendations made by the IDMC and act upon these recommendations as necessary, and help identify and address operational issues relating to study progress and conduct as they arise, referring issues related to patient safety to the IDMC as necessary.

4.1 Communication between IDMC and SC

The AstraZeneca MSD, Global Safety Physician (GSP) and Global Statistician, or their delegates, will act as liaison between the IDMC and the SC (see Appendix B Figure 1). The AstraZeneca MSD or Global Statistician will communicate the recommendations of the IDMC to the SC. However, the option of direct communication between the chair of the IDMC and the chair of the respective SC may be used if required. Ultimately it is the prerogative of AstraZeneca and the SC to act as appropriate upon IDMC recommendations concerning safety or study conduct. The IDMC will be informed by AstraZeneca in a timely manner of protocol amendments or other events, which impact on the conduct of the study (see Appendix B for a diagrammatic representation of the relationship between the IDMC and the SC).

5. PURPOSE OF THE IDMC MEETINGS

5.1 Interim Efficacy Analysis

The final analysis of the study will occur when approximately 89 PFS events have occurred. A single interim PFS analysis for superiority and futility will be performed when 50% of the final number of PFS events have been reached (approximately 45 PFS events).

The timing and scope of the interim analysis may be modified and/or additional safety analyses added based on recommendation by the IDMC, SC, or AstraZeneca.

The questions to be addressed by the IDMC following the interim efficacy and safety analyses are:

1. Do the results of the interim analysis of efficacy and safety if appropriate raise any concerns with respect to the ongoing conduct of this study?

2. Considering the response to question 1, should the study

   i) continue as planned

   ii) continue as planned with modification

   iii) early submission recommended (not applicable for safety IDMC review meeting)

   iv) terminate whole study for futility (not applicable for safety IDMC review meeting)

   v) terminate whole study for safety reasons

5.1.1 Superiority interim analysis

A multiple testing strategy will be employed for the analysis of PFS. The test mass alpha for PFS (one-sided 2.5%) will be split between the final and the interim analysis using a bespoke spending function where a fixed significance level of 0.5% one-sided alpha will be assigned at the interim analysis and the remaining significance level assigned to the final analysis, taking account of correlation (Stone 2010). Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$.

The IDMC may recommend early termination due to overwhelming efficacy if the stopping boundary is crossed for PFS; i.e. 1-sided p-value is less than the nominal significance level of 0.005. As an example, if exactly 45 PFS events have occurred at the time of the interim analysis, a significant result would equate to a hazard ratio (HR) < 0.46.

However, magnitude of PFS benefit, observed overall survival (OS) and safety data will form part of the superiority decision and the IDMC may make the decision to continue the study as planned for follow up on safety and secondary efficacy endpoints even if the statistical hurdle for superiority has been crossed.

If an early submission is recommended due to superiority, then analyses of all other endpoints would be performed and the results of these analyses will form the basis for submissions for regulatory approval. A further interim and final OS analysis is planned and irrespective of the PFS interim superiority outcome, patients would continue to be followed for survival until 106 patients have died where an updated analysis would be performed based on more mature survival data.

5.1.2 Futility interim analysis

At the same time as the superiority analysis, consideration will also be given to stop the study early for futility, guided by calculation of conditional power. The futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the final number of PFS events (n=89) is reached (Lachin 2005). The determination of this probability will be conditional on the observed data at the time of the interim analysis for superiority and on the assumed hazard ratio for the alternative hypothesis (PFS HR=0.54). If the probability is less than 20%, the IDMC will consider the option of declaring futility.

The exact figure used for the futility boundary will be calculated by AZ and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time. As an example, if exactly 50% of the final number of events have occurred at the time of the interim analysis (45 events), then the HR that corresponds to 20% conditional power for the interim analysis will be 1.00.

If and only if the PFS results lead to a decision to stop for futility, then the patients will be unblinded and given the option to discontinue treatment.

5.2 Review of Safety Data

The reviews will take place when 50 patients are randomised and have received 3 months of treatment [expected Q3 2015] and at the time of the interim analysis [expected Q1 2016]. They will involve review of baseline information and safety data including, all adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to death, exposure and laboratory data. The date of the data cut-off (DCO) for the review of safety data should be no more than six weeks prior to the date of the corresponding meeting of the IDMC. Data will be cleaned in an ongoing manner as part of the overall data cleaning and validation process for each study. However it should be recognised that the data supplied for use by the IDMC may not be fully cleaned or validated. Any fatal SAEs or SAEs of special interest that have been obtained between the DCO and up to one week before the safety review meeting will be collated and presented to the IDMC.

The questions to be addressed by the IDMC following the safety data review are:

1. Do the results of the safety data raise any concerns with respect to the ongoing conduct of this study?

2. Considering the response to question 1, should the study

i) continue as planned

ii) continue as planned with modification

iii) terminate whole study for safety reasons

6. CONDUCT OF IDMC DATA REVIEW MEETINGS

IDMC meetings will be conducted in open and closed sessions.

6.1 Open Sessions

In order to allow the IDMC to have adequate access to further relevant information SC members, and/or their delegates, may (with the majority consent of the voting members) attend open sessions, during which fully blinded data may be discussed. Open session discussion of administrative/operational issues; e.g. updated information on enrolment and eligibility, will precede the closed session.

Open session activities may include, but are not limited to the following:

- Representatives of the AstraZeneca team present a summary of the program status, study enrolment and key safety findings
- Communication of recommendations
- Discussion of administrative/operational issues including requirements for additional data for future meetings

6.2 Closed Sessions

Attendance will be limited to the IDMC members, allowing discussion of confidential data from the study, including the safety and relative efficacy of interventions. In order to ensure that the IDMC will be fully informed in its primary objective of safeguarding the interest of participating patients, the IDMC will be unblinded in its assessment of safety and efficacy data.

Following such meetings the IDMC will formulate a list of recommendations regarding further conduct of the study.

6.3 Meeting Minutes

Two sets will be prepared: the Open and Closed minutes. An AstraZeneca member of the SC will be responsible for preparing the Open Minutes, and the IDMC chair will be responsible for preparing the Closed Minutes.

The Open Minutes will describe the proceedings in the open session of the IDMC meeting, and will summarise all recommendations by the IDMC. Since these minutes will be circulated

immediately to the SC, it is important that they do not unblind the efficacy and safety data if the IDMC is not recommending early termination.

The Closed Minutes will describe the proceedings from all sessions of the IDMC meeting, including the list of recommendations by the Committee. As it is likely that these minutes will contain unblinded information, it is important that they are not made available to anyone outside the IDMC. Copies will therefore be retained by the IDMC chair and by the IDMC biostatistician preparing the interim reports, for distribution to the sponsor at the time of study closure. The recommendation from each closed session will be shared with AstraZeneca verbally shortly after the closed session has finished. Formal written recommendation and minutes will be provided to the SC and AstraZeneca within seven calendar days.

The AstraZeneca MSD, GSP and Global Statistician, or their delegates, will facilitate IDMC meetings and act as liaison between the IDMC and SC.

If a joint meeting of the IDMC and SC is required, this will be conducted as per an open session data review.

6.4 Open and Closed Reports

Open reports/presentations, available to all who attend the IDMC meeting, will include data on general study progress such as recruitment updates and any issues with the study. A representative from the AstraZeneca study team will prepare these open reports.

Closed reports, available only to those attending the Closed Sessions of the IDMC meeting, will include unblinded data. The independent biostatistician will prepare these Closed Reports. The identity of study treatments will be fully visible, with no 'masking' of treatment identities, such as Treatment A, Treatment B.

The Open and Closed Reports should provide information that is accurate with follow-up that is complete to a date no more than six weeks prior to the IDMC meeting. The Reports should be provided to IDMC members approximately seven calendar days prior to the date of the meeting.

6.5 Open Reports: An Outline

The following information will be provided at each IDMC meeting in the form of an Open Report. The summary data will be based on the overall population and will not be separated by treatment group.

- General study progress including status of the development program
- Actions taken as minuted in previous meetings where applicable
- Patients screened and randomised according to country
- Current patient accrual
- Protocol amendments

- Issues and any major protocol deviations

6.6 Closed Statistical Reports: An Outline

6.6.1 Data to be provided to the IDMC for safety review and interim analysis

The following outputs are proposed to be provided for the safety review and the interim analysis. The IDMC will decide if they agree on the proposal or they may revise the proposal to add/delete the data to be provided prior to the data review. Only datasets which support these outputs will be provided to the IDMC.

Demography

- Summary of analysis sets
- Summary of demographic characteristics (age, sex, race)
- Summary of patient recruitment by country and centre
- Summary of extent of disease
- Summary of previous disease-related treatment modalities (including previous anti-cancer chemotherapy, surgical history)
- Summary of disease characteristics (including, but not limited to, history of pancreatectomy, tumour measurability, ECOG performance status, histology type, number and site of metastatic sites at baseline, biomarker status)
- Summary of primary disease location on diagnosis (head, body, tail)
- Summary of patient disposition

Exposure

- Summary of duration of exposure – olaparib/placebo
- Summary of number of dose interruptions and reductions – olaparib/placebo

Safety data

Presented by treatment received:

- Summary of AEs in any category - patient level
- Summary of AEs by system organ class, preferred term and maximum reported CTC grade
- Summary of AEs by system organ class, preferred term and maximum reported CTC grade, causally related to olaparib/placebo
- Summary of AEs >= CTC grade 3

- Summary of AEs >= CTC grade 3 by system organ class, preferred term, causally related to olaparib/placebo
- Summary of AEs leading to discontinuation, by system organ class and preferred term
- Summary of AEs leading to discontinuation, by system organ class and preferred term, causally related to olaparib/placebo
- Summary of AEs leading to death
- Summary of AEs leading to death, causally related to olaparib/placebo
- Summary of SAEs
- Summary of SAEs, causally related to olaparib/placebo
- Summary of clinically important changes in laboratory parameters identified by IDMC prior to the data review
- Listing of SAEs (detailed case reports to be made available upon request)
- Listing of SAEs leading to death (detailed case reports to be made available upon request)
- Death rates (from the survival status eCRF)
- Reasons for subject discontinuation of study therapy (including details of non-compliance and loss to follow-up)
- Patients receiving anti-cancer therapy following discontinuation of study therapy

6.6.2 Additional data to be provided to the IDMC for interim analysis

In addition to the outputs listed in Section 6.6.1, the following efficacy outputs will be provided to the IDMC for the interim analysis. Results from the analysis of the secondary endpoint, OS, will be provided. However, the option of early termination of the study due to overwhelming efficacy may only be considered if the stopping boundary for superiority of the primary endpoint, PFS, has been crossed.

Efficacy

- Summary of progression status
- Summary of primary analysis of PFS
- Summary of median overall PFS

- Summary of patients censored for PFS at more than 14 weeks before the DCO
- Kaplan Meier plot of PFS
- Summary of secondary analysis of OS
- Summary of median OS
- Kaplan Meier plot of OS

6.6.3 Scheduled final analysis of the data

After DBL and clean file has been declared, AstraZeneca will be responsible for providing the results of the final analysis. The results of this analysis will be shared with the IDMC in a timely manner.

7. REFERENCES

Lachin 2005
Lachin, J. M. A review of methods for futility stopping based on conditional power. Statist. Med. (2005) 24: 2747–2764.
Stone 2010
Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. Pharm. Statistics (2010) 5: 151-161.

APPENDICES

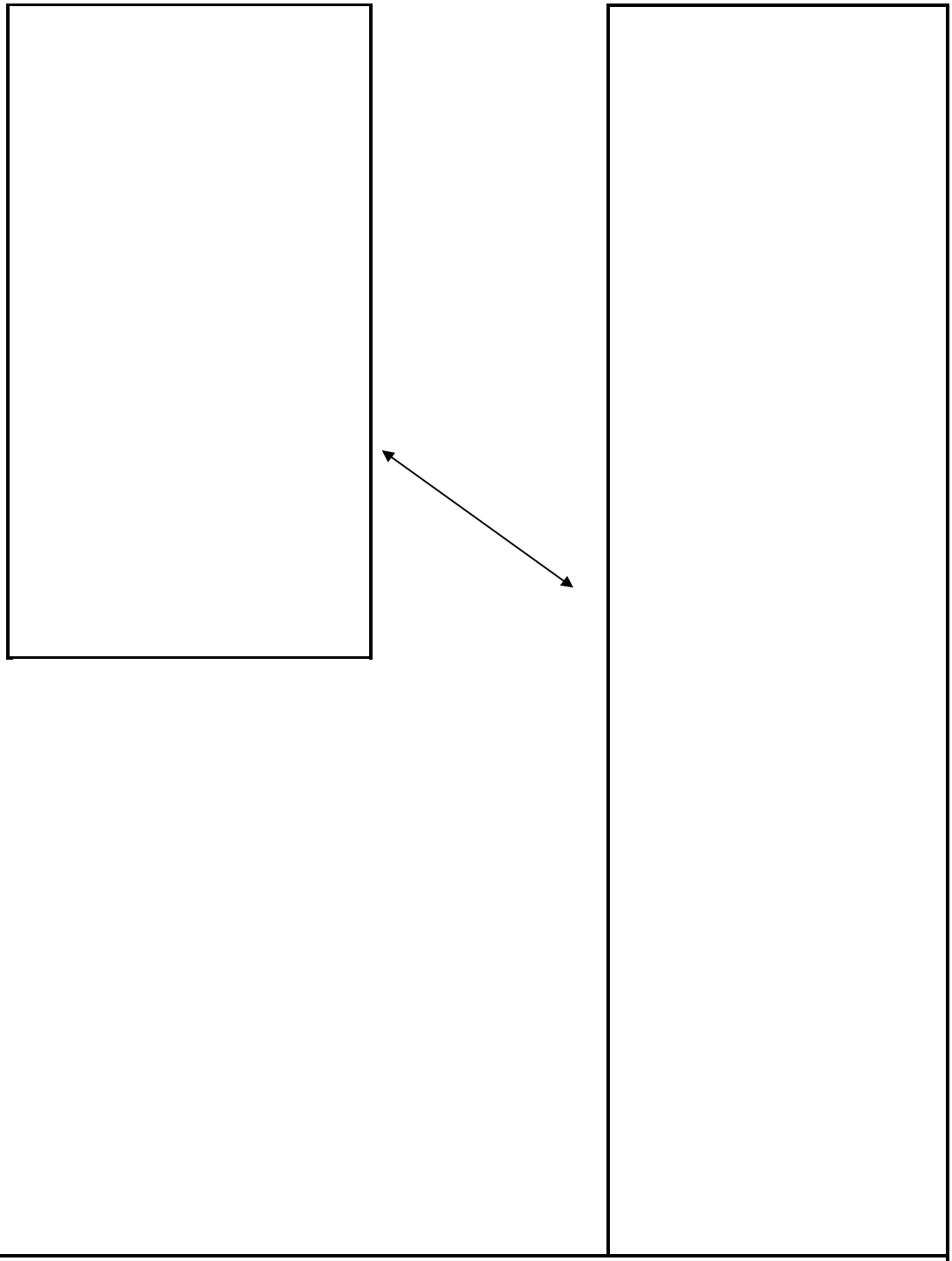
Appendix A: IDMC Voting Members Signature Pages

IDMC Member A

IDMC Member B

IDMC Member C

Appendix B: IDMC & Steering Committee Members and Roles



Data Reviewed	Patient safety & efficacy data by unblinded treatment	Patient accruals and blinded baseline data

Appendix C: Communication from IDMC to Olaparib Project Team following Interim Analysis

The following form will be completed by the IDMC to provide the olaparib team with a summary of their recommendations following the interim analysis meeting.

Recommendation of IDMC to Olaparib Project Team

Meeting: Study D081FC00001 Interim analysis, IDMC meeting

Meeting date: ……..

Following review of the interim analysis data, the IDMC has the following recommendation for the olaparib project team regarding Study D081FC00001:

Study should continue unchanged	☐
Study should continue as planned with modification	☐
Early submission recommended	☐
Terminate whole study for futility	☐
Terminate whole study for safety reasons	☐

Specify further details (if necessary):

Completed by: …….

Date: …….

Appendix D: Communication from IDMC to Olaparib Project Team following Safety Analysis

The following form will be completed by the IDMC to provide the olaparib team with a summary of their recommendations following each safety analysis meeting.

Recommendation of IDMC to Olaparib Project Team

Meeting: Study D081FC00001 Safety analysis, IDMC meeting

Meeting date: ……..

Following review of the safety data, the IDMC has the following recommendation for the olaparib project team regarding Study D081FC00001:

Study should continue unchanged ☐

Study should continue as planned with modification ☐

Terminate whole study for safety reasons ☐

Specify further details (if necessary):

Completed by: …….

Date: …….

Appendix E: Documentation of Unblinded Personnel

The following form will be completed to document exactly who had access to unblinded data for the interim analysis.

Documentation of Unblinded Personnel

Study D081FC00001 Interim analysis

Date study was unblinded: ……..

The following people had access to unblinded data at the Study D081FC00001 interim analysis:

Role	**Name**	**Affiliation**	**Any other relevant information?**
IDMC members			
Additional unblinded personnel			
Independent IDDI statistician and programmer(s)		IDDI	

Signed: ……..… …….

Date:

Clinical Study Protocol Amendment	
Amendment Number	1
Drug Substance	Olaparib
Study Code	D081FC00001
Date	14 October 2014
Protocol Dated	31 March 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

Affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

1.4.1.1 Myelodysplastic syndrome/acute myeloid leukaemia

Previous text:

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every 3 weeks during the rest of the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

Revised text:

To ensure robust safety monitoring, patients in this clinical trial will have weekly safety assessments during the first cycle and then safety assessments every **4** weeks during the rest of

the treatment period. Clinical guideline of managing bone marrow toxicity and use of G-CSF is implemented as the safety management plan.

Section of protocol affected:

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

Previous text:

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-u

	Screen PART 1 (Patients with unknown *BRCA* status only)	**Screen PART 2** (All patients)	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Haematology/clinical chemistry		**X**	**X** l				**X**	**X**	**X**	**X**	

l Haematology and clinical chemistry should be performed at screening and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

Revised text:

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

	Screen PART 1 (Patients with unknown *BRCA* status only)	**Screen PART 2** (All patients)	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up** [v]
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Haematology/clinical chemistry		**X**	**X** [l]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	

l Haematology and clinical chemistry should be performed at screening, **cycle 1 day 1, 8, 15, 22 and** day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly

Section of protocol affected:

4.2 Treatment period

Previous text:

Haematology and clinical chemistry: Day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study treatment and which must have been 3 weeks after last dose of chemotherapy based therapy, unless the investigator believes that it is likely to have changed significantly.

Revised text:

Haematology and clinical chemistry: **cycle 1 day 1, 8, 15, 22 and d**ay 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if there have been separate assessments within 7 days before starting study treatment and which must have been 3 weeks after last dose of chemotherapy based therapy, unless the investigator believes that it is likely to have changed significantly

Reason for Amendment:

To ensure protocol consistency and correct typo.

Persons who initiated the Amendment:

Clinical Study Protocol Amendment No 1
Appendix A

Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1
Date	14 October 2014
Protocol Dated	31 March 2014

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

10 / 11 / 2014
Date
(Day Month Year)

Jane Robertson
Medical Science Director
AstraZeneca
Alderley Park
Macclesfield
Cheshire SK10 4TG, UK

ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

10-November-2014

Date
(Day Month Year)

May Lien
Study Leader
AstraZeneca China Hub
Building 7, Lane 898 HaLei Road
Zhangjiang Hi-tech Park
Shanghai 201203 China

ASTRAZENECA SIGNATURE(S)

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

03/11/2014
Date
(Day Month Year)

Helen Mann
Global Product Statistician
AstraZeneca
90T 169-3 East Wing, Parklands
Alderly Park, Macclesfield
Cheshire SK10 4TG, UK

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

Centre No.:

Signature:

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

This Clinical Study Protocol and all Amendments to the CSP have been subjected to an internal AstraZeneca peer review.

I agree to the terms of this study protocol/amendment.

Signature:

ISRAEL

Clinical Study Protocol Global Amendment

Amendment Number	2
Drug Substance	Olaparib
Study Code	D081FC00001
Date	28 February 2015
Protocol Dated	31 March 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients with *gBRCA* Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden

Centres affected by the Amendment:

Affects all centres in the study.

The protocol for the study is to be amended as follows:

Section of protocol affected:

Synopsis, Statistical methods

Previous text:

Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately 89 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for superiority and futility will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events). The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and 2.26% alpha (1-sided) (accounting for a single interim PFS analysis), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo. At the interim analyses, 0.5% of alpha (1-sided) will be spent, and controlling the type I error across the two time points, 89 PFS events will be required at the final analyses.

Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. Assuming 45 PFS events at the interim, a HR $\leqslant$ 0.46 would equate to a 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26% (Stone 2010). Assuming 89 PFS events, a HR $\leq$ 0.65 would equate to a 1-sided p-value <0.0226.

Assuming that the study accrual period will be approximately 15 months, 89 progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that 45 PFS events will occur approximately 13 to 14 months after the first patient enters the trial.

Revised text:

Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately **87** PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for futility will be performed when 50% of the final number of progression **event**s needed for the **primary PFS analysis** has been reached (approximately **44** PFS events). The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and **2.5%** alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo.

Assuming that the study accrual period will be approximately 15 months, **87** progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that **44** PFS events will occur approximately 13 to 14 months after the first patient enters the trial.

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

Synopsis, Statistical methods

Previous text:

OS analyses will be performed at the same time as the interim (if PFS null hypothesis rejected) and final analysis of PFS and will use the same methodology and model as PFS. A final analysis of OS will be performed when approximately 106 death events have occurred and a multiplicity adjustment will be made to account for the different analyses. At the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data.

…

PFS2 analyses will be performed at the same time as the interim and final analyses of PFS, and at the time of the final analysis of OS. PFS2 will be analysed using the same methodology and model as PFS.

Revised text:

OS analyses will be performed at the same time as the **primary** analysis of PFS and will use the same methodology and model as PFS. A final analysis of OS will be performed when approximately 106 death events have occurred and a multiplicity adjustment will be made to account for the different analyses. At the time of the PFS analysis, a predicted treatment effect for OS at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using PFS data.

…

PFS2 analyses will be performed at the same time as the **primary** analysis of PFS, and at the time of the final analysis of OS. PFS2 will be analysed using the same methodology and model as PFS.

Reason for Amendment:

Removal of the superiority analysis at the time of the interim analysis as per FDA recommendation, therefore OS and PFS2 will not be analysed at this time.

Section of protocol affected:

Synopsis, Patient Reported Outcomes

Previous text:

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales. Time to global QoL and pancreatic pain scale deterioration will be analysed using the same methodology and model as described for the primary analysis of PFS. Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model.

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

As supportive analyses, change from baseline in global QoL and pancreatic pain scale scores will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit.

Revised text:

The impact of olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC QLQ-C30 global quality of life **(QoL)** and **QLQ-**PAN26 pancreatic pain scales. **Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. As a supportive analysis,** global QoL improvement rate will be analysed using a logistic regression model.

An exploratory analysis will examine adjusted mean change from baseline on EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, social) and on EORTC QLQ-C30 and QLQ-PAN26 symptom scales/items (including pancreatic pain, fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice).

EORTC QLQ-C30 and **QLQ-**PAN26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Reason for Amendment:

To change the type of analysis used for EORTC QLQ-C30 global QoL score to MMRM analysis of adjusted mean change from baseline, which is independent of minimal important differences (MID) values that are not well-defined, and is suitable for analysing continuous responses measured repeatedly over time. The MMRM statistical analysis will be based on

actual scores, rather than pre-selected MIDs, and will analyse data from all time points. A supportive analysis of global HRQoL improvement rate will be conducted using the 'generic' cut off of 10% change from baseline as suggested in Osoba et al 2005. An exploratory analysis will be performed to examine adjusted mean change from baseline on EORTC QLQ-C30 and QLQ-PAN26 functioning domains and symptom scales/items.

Section of protocol affected:

Section 1.4 Benefit risk and ethical assessment

Previous text:

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumours are estimated to have received treatment with Olaparib across the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of Olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to date. Approximately 304 patients have received comparator or placebo across the Olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given Olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to Olaparib capsule for ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term Olaparib (capsule) monotherapy exposure.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

Revised text:

As of 2 October 2013, an estimated 2103 patients with ovarian, breast, gastric, pancreas, and a variety of other solid tumours are estimated to have received treatment with Olaparib across the dose range 10 mg qd to 600 mg bid in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies. Olaparib has been given as either monotherapy (18 studies, an estimated 1214 patients) or in combination with other chemotherapy/anticancer agents (25 studies, an estimated 889 patients). Many of these combinations studies are ongoing. The majority of patients to date have received the capsule formulation of Olaparib (an estimated 1635 patients). Approximately 468 patients have received the tablet formulation to

date. Approximately 304 patients have received comparator or placebo across the Olaparib development programme.

An analysis of monotherapy data across 12 AstraZeneca sponsored monotherapy studies in 975 patients who have been given Olaparib capsule estimated that 16.1% (157/975) of patients had been exposed to Olaparib capsule for ≥12 months at the time of database closure for the 12 studies. Furthermore, 41/ 975 patients received treatment for >24 months (longest duration was 44 months). From the available data to date, there is no evidence of any unexpected toxicity following long-term Olaparib (capsule) monotherapy exposure.

Additionally statistical analysis of the pooled QT/QTc data from 2 studies in a total of 109 patients for the primary multiple dose analysis and 119 patients for the supportive single dose analysis showed that following multiple dosing of olaparib (300 mg bd), the upper confidence limit of the 2-sided 90% confidence interval (CI) around the mean treatment effect for QT Fridericia Correction Formula (QTcF) was <10 ms at all time points. Furthermore, the supportive analysis showed that following a single dose of olaparib, of either 100mg or 300mg the upper confidence limit of the 2-sided 90%CI around the mean treatment effect for QTcF was also <10 ms at all time points.

In conclusion, there was no indication of a clinically relevant effect of olaparib on cardiac repolarisation (as determined by prolongation of QTcF) following multiple dosing (300 mg bd) or following single dosing.

As a further supporting analysis, concentration-effect modelling of the pooled QT/QTc data from the same patients was conducted. Predictions, from the concentration-effect relationship obtained of the likely magnitude of effect of olaparib on ΔQTcF, showed that at the range of plasma concentrations achieved following the 300 mg bd tablet dose, olaparib would not be expected to cause prolongation of QTc interval of a magnitude that would be of clinical concern or which would cross the threshold for regulatory concern as described in ICH E14.

Olaparib as monotherapy at doses up to 400 mg bid capsule is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, anaemia mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity. In addition, in a small number of patients MDS/AML or pneumonitis have been observed and identified as important risks.

Reason for Amendment:

To provide additional data on the QT study that has been conducted.

Section of protocol affected:

1.5 Study Design

Previous text:

The primary analysis of the study will occur when approximately 89 progression events have occurred, although an interim analysis for superiority will be done when 50% of the planned PFS events have occurred (see statistical Section 8).

Revised text:

The primary analysis of the study will occur when approximately **87** progression events have occurred, although an interim analysis for futility will be done when 50% of the planned PFS events have occurred (see statistical Section 8).

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

Table 1 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

Previous text:

i ECG assessments to be completed within **7** days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

Revised text:

i ECG assessments to be completed within **14** days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

Reason for Amendment:

To ensure that the patient can start treatment within 8 weeks of their last chemotherapy dose. Due to the screening period, the original text meant that patients would have had to start treatment within 7 weeks of their last chemotherapy dose, this was not the intention. Extending this window by 7 days makes it clearer for the investigators and reduces the risk of protocol deviations.

Section of protocol affected:

Table 2 Study Schedule – Screening, On Study Treatment, Discontinuation and Follow-up

Previous text:

r. Adverse events must be captured from time of consent. However, in Screening PART 1 of the study only SAEs related to study procedures will be collected.

Revised text:

r. Adverse events must be captured from time of consent. **Only SAE's related to blood sampling for the Myriad gBRCA test will be collected at this visit.**

Reason for Amendment:

To clarify the SAE reporting requirements in the screening PART 1 phase

Section of protocol affected:

3.2 Exclusion criteria 9

Previous text:

Resting ECG with QTC > 470msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTC >470 msec, patient will only be eligible if repeat ECG demonstrates QTC ≤470 msec.

Revised text:

Resting ECG with QTC **≥450** msec detected on 2 or more time points within a 24 hour period or family history of long QT syndrome. If ECG demonstrates QTC **≥450** msec, patient will only be eligible if repeat ECG demonstrates QTC ≤ **450** msec.

Reason for Amendment:

To be consistent with the ICH E14 guideline as requested by the German Ethics committee. Of note the additional data added to section 1.4 of the protocol as part of this amendment summarises the clinical data on ECG and concludes that Olaparib does not affect QT interval.

Section of protocol affected:

4.1 Enrolment/screening period

Previous text:

- ECG (within **7** days prior to the start of the study treatment)

Revised text:

- ECG (within **14** days prior to the start of the study treatment)

Reason for Amendment:

To ensure that the patient can start treatment within 8 weeks of their last chemotherapy dose. Due to the screening period, the original text meant that patients would have had to start treatment within 7 weeks of their last chemotherapy dose, this was not the intention. Extending this window by 7 days makes it clearer for the investigators and reduces the risk of protocol deviations.

Section of protocol affected:

4.3.7 Subsequent Treatment

Previous text:

The data cut-off date for the final statistical analysis for the primary objective of the study will be established when approximately 89 confirmed progression events are expected to have occurred.

Revised text:

The data cut-off date for the final statistical analysis for the primary objective of the study will be established when approximately **87** confirmed progression events are expected to have occurred.

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

5.2.4 ECG

5.2.4.1 Resting 12-lead ECG

Previous text:

ECGs are required during screening within **7** days prior to starting study treatment and when clinically indicated afterwards.

Revised text:

ECGs are required during screening within **14** days prior to starting study treatment and when clinically indicated afterwards.

Reason for Amendment:

To ensure that the patient can start treatment within 8 weeks of their last chemotherapy dose. Due to the screening period, the original text meant that patients would have had to start treatment within 7 weeks of their last chemotherapy dose, this was not the intention. Extending this window by 7 days makes it clearer for the investigators and reduces the risk of protocol deviations.

Section of protocol affected:

5.6.3 Handling, storage and destruction of biological samples

Previous text:

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

Biological samples for future research will be retained at AstraZeneca or a 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.

Revised text:

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

Biological samples for future research will be retained at AstraZeneca or a 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.

Reason for Amendment:

Deleted duplicate statements.

Section of protocol affected:

5.6.4Labelling and shipment of biohazard samples

Previous text:

5.6.4Labelling and shipment of biohazard samples

Revised text:

5.6.3Labelling and shipment of biohazard samples

Reason for Amendment:

Changed the title number to ensure protocol consistency.

Section of protocol affected:

5.6.5Chain of custody of biological samples

Previous text:

5.6.5 Chain of custody of biological samples

Revised text:

5.6.4 Chain of custody of biological samples

Reason for Amendment:

Changed the title number to ensure protocol consistency.

Section of protocol affected:

5.6.6 Withdrawal of informed consent for donated biological samples

Previous text:

5.6.6 Withdrawal of informed consent for donated biological samples

Revised text:

5.6.5 Withdrawal of informed consent for donated biological samples

Reason for Amendment:

Change the title number to ensure protocol consistency.

Section of protocol affected:

Section 6.7.1 Management of haematological toxicity Olaparib

Previous text:

6.7.1 Management of haematological toxicity Olaparib

Table 3 Management of Haematological Toxicity Olaparib

Toxicity	Study treatment dose adjustment
CTCAEa gr 1-2	Dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation
Repeat CTCAE gr 1-2	Dose interruption until recovery to CTCAE gr 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for max of 4 weeks and dose reduction to 200 mg bid
Repeat CTCAE gr 3-4	Discontinue study treatment

[a] CTCAE Version 4

6.7.1.1 Management of anaemia

Adverse events 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 (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment 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 study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

Revised text:

Table 6 Management of Haematological Toxicity Olaparib

Toxicity	Study treatment dose adjustment
CTCAE gr 1-2	Dose interruption as judged by the investigator; appropriate supportive treatment and causality investigation

Toxicity	Study treatment dose adjustment
Repeat CTCAE gr 1-2	Dose interruption until recovery to CTCAE gr 1 and dose reduction to 250 mg bid as first step and 200 mg bid as second step
CTCAE gr 3-4	Dose interruption until recovered to CTCAE gr 1 for max of 4 weeks and dose reduction to **250 mg bid as first step and 200 mg bid as second step**
Repeat CTCAE gr 3-4	Discontinue study treatment **if 2 dose reductions are not able to manage the anaemia.**

[a] CTCAE Version 4

6.7.1.1 Management of anaemia

Patients can enter the study with a haemoglobin value of > 9g/dl, this should be taken into account when considering the management of anaemia. Adverse events 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 (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. However, if a patient develops anaemia CTCAE grade 3 (Hb < 8g/dl) or worse, study treatment should be interrupted for up to maximum of 4 weeks. Study treatment can be restarted a**t a reduced dose (see Table 4)** if Hb has recovered to > 9 g/dl. Any subsequently required **a further** anaemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose **reduction** to 200 mg bid..

If a patient has been treated for anaemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependant as judged by investigator, study treatment should be interrupted for up to a maximum of 4 weeks to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose **if bone marrow recovers.**

Reason for Amendment:

The management of haematological toxicity has been made clearer and this is reflected in the revised text. The text and table are better aligned and an additional dose reduction increment has been added.

Section of protocol affected:

6.8.1 Data Monitoring Committee

Previous text:

This study will use an external independent data monitoring committee (IDMC) to perform interim reviews of accumulating study safety data and the interim analyses for superiority and futility based on PFS.

Revised text:

This study will use an external independent data monitoring committee (IDMC) to perform interim reviews of accumulating study safety data and the interim analyses for futility based on PFS.

Reason for Amendment:

Removal of the interim superiority analysis as per FDA recommendation.

Section of protocol affected:

8.2.3 PRO analysis set

Previous text:

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

Revised text:

The analysis population for PRO data will be the subset of the FAS (ITT) population; **who** have **evaluable** baseline **EORTC QLQ-C30 and QLQ-PAN26 forms.**

Reason for Amendment:

To clarify the definition of the PRO analysis set.

Section of protocol affected:

Table 7 Summary of Outcome Variables and Analysis Populations

Previous text:

Table 4 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	FAS (ITT), Myriad confirmed *BRCAm* subgroup

Outcome Variable	Populations
- Secondary endpoints to be analysed: OS, PFS2, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to treatment discontinuation (TDT), time to deterioration and improvement rate of Global QoL and PAN-26 pain scale	FAS (ITT), Myriad confirmed *BRCAm* subgroup
- Secondary endpoints to be summarised: objective response rate, disease control rate	FAS (ITT), Myriad confirmed *BRCAm* subgroup
Demography	FAS (ITT)
Safety Data	
- Exposure	Safety
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

Revised text:

Table 5 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	FAS (ITT), Myriad confirmed *BRCAm* subgroup
- Secondary endpoints to be analysed: OS, PFS2, time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), time to treatment discontinuation (TDT)	FAS (ITT), Myriad confirmed *BRCAm* subgroup
-Adjusted mean change from baseline in EORTC QLQ-C30 global QoL score	**PRO (subset of the FAS (ITT) who have evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms)**
-Secondary endpoints to be summarised:	
-Objective response rate.	FAS (ITT) **(patients with measurable disease at baseline only)**, Myriad confirmed *BRCAm* subgroup
-Disease control rate	**FAS (ITT), Myriad confirmed *BRCAm* subgroup**
Demography	FAS (ITT)

Outcome Variable	Populations
Safety Data	
- Exposure	Safety
- Adverse Events	Safety
- Lab measurements	Safety
- Vital Signs	Safety

Reason for Amendment:

To change the health-related quality of life secondary endpoint from time to deterioration as assessed by the EORTC QLQ-C30 global QoL score to adjusted mean change from baseline in EORTC QLQ-C30 global QoL score.

To clarify the analysis sets used for the analysis of objective response rate, disease control rate and QoL endpoints.

Section of protocol affected:

8.3.1 Primary endpoint (PFS)

Previous text:

As a supportive summary to PFS, time to start of first subsequent chemotherapy or death will be assessed (see section 8.8.3). Time to first subsequent chemotherapy or death is defined as the time from the date of randomisation to the earlier of first subsequent chemotherapy start date, or death date. Any patient not known to have had a further subsequent therapy or death will be censored at the last known time to have not received subsequent chemotherapy.

Revised text:

Deleted the text.

Reason for Amendment:

To remove repeated text detailing the time to first subsequent therapy endpoint. This is a secondary endpoint detailed in Section 8.3.2.4.

Section of protocol affected:

8.3.2.2 Best overall RECIST response (BoR)

Previous text:

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix F. 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.

…

Best overall response will be determined programmatically based on the RECIST criteria using BICR data.

Revised text:

Best overall RECIST response (BoR) is calculated based on the overall visit responses from each RECIST assessment, described in Appendix F. It is the best response a patient has had **after randomisation but prior to starting any subsequent cancer therapy and prior to** RECIST progression or the last evaluable assessment in the absence of RECIST progression.

…

Best overall response will be determined programmatically based on the RECIST criteria using BICR data. **In addition, this will also be reported using investigator-recorded assessment.**

Reason for Amendment:

To bring text in line with current AstraZeneca oncology statistical guidance which states that objective response rate should only be calculated using data up to the point of any subsequent therapies being used.

Section of protocol affected:

8.3.2.4 Time to first subsequent therapy or death (TFST)

Previous text:

Time to start of first subsequent therapy or death (TFST) will be assessed. TFST is defined as the time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death. Subsequent therapies will be reviewed to assess which represent clinically important treatments intended to control ovarian cancer.

Revised text:

Time to start of first subsequent therapy or death (TFST) will be assessed. TFST is defined as the time from randomisation to the earlier of first subsequent **cancer** therapy start date following study treatment discontinuation, or death.

Reason for amendment:

To specify that TFST is the time to first subsequent cancer therapy and to remove text copied from the ovarian cancer study which is not relevant to this study.

Section of protocol affected:

8.3.2.5 Time to second subsequent therapy or death (TSST)

Previous text:

Time to start of second subsequent therapy or death (TSST) will be assessed. TSST is defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death.

Revised text:

Time to start of second subsequent therapy or death (TSST) will be assessed. TSST is defined as the time from randomisation to the earlier of the second subsequent **cancer** therapy start date following study treatment discontinuation, or death.

Reason for amendment:

To specify that TSST is the time to second subsequent cancer therapy.

Section of protocol affected:

8.5 Calculation or derivation of patient reported outcome variables

Previous text:

EORTC-QLQC30 and QLQ-PAN26

The EORTC QLQ-C30 will be scored according to the EORTC scoring manual (Fayers et al 1999). Each scale will be transformed to a 100-point scale as per the manual.

Mean change from baseline in health related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30 global QoL scale which includes two items from the QLQ-C30: “How would you rate your overall health during the past week?” (Item 29) and “How would you rate your overall quality of life during the past week?” (Item 30)

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life (two items: “How would you rate your overall health during the past week?” (Item 29) and “How would you rate your overall quality

of life during the past week?" (Item 30)) and PAN-26 pancreatic pain (items 31, 33, 34, 35) scales . Time to global QoL and pancreatic pain scale worsening will be analysed using the same methodology and model as described for the primary analysis of PFS. However sensitivity analyses will not be performed (with the exception of attrition bias).

Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model and using the same covariates as used in the PFS analyses. If the overall response rate is < 5%, no analysis will be performed. (Note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed.) If the expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Revised text:

EORTC QLQ-C30 and QLQ-PAN26

The EORTC QLQ-C30 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.

Reason for Amendment:

To remove analysis details that are repeated in Section 8.8.4.6 Analysis of PRO endpoints.

Section of protocol affected:

8.5 Calculation or derivation of patient reported outcome variables

Previous text:

Higher scores represent more symptoms, except for health care satisfaction scale and sexuality scale where higher scores represent greater satisfaction and sexuality. For change scores, a score of +5 is considered deterioration (except for the two scales mentioned above) and a score of -5 is considered as improvement.

Revised text:

Higher scores represent more symptoms, except for health care satisfaction scale and sexuality scale where higher scores represent greater satisfaction and sexuality.

The threshold for a clinically important deterioration is outlined below (Table 8):

Table 8 Visit Response in EORTC QLQ-C30 Global QoL Score

Score	Change from baseline	Visit response
EORTC QLQ-C30 global QoL score	≥ +10	Improved
	≤ -10 or patient too ill to complete measure	Deterioration
	Otherwise	No change

Further detail will be provided in the SAP.

Best overall QoL response

A patient's best overall QoL response will be derived as the best QoL response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. The criteria in Table 9 will be used to assign a best QoL response for HRQoL based on the 2-item global QoL score. Improvement rate will be defined as the proportion of patients whose best overall QoL response was "Improved".

Table 9 Best QoL Response in EORTC QLQ-C30 Global QoL Score

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 qualify for overall score response of "improved". A visit response of "deterioration" without response of "improved" or "no change" within 21 days.
Other	Does not qualify for one of the above.

Compliance

Summary measures of overall compliance and compliance over time will be derived for the EORTC QLQ-C30 and QLQ-PAN26 questionnaires. These will be based upon:

- **Received forms = number of EORTC QLQ-C30 / QLQ-PAN26 questionnaire forms received back plus the number not received back where the reason was 'Subject too affected by symptoms of disease under investigation'.**

- **Expected forms = number of patients still under QoL follow-up at the specified assessment time excluding patients in countries with no available translation.**

- **Evaluable forms = subset of expected EORTC QLQ-C30 / QLQ-PAN26 questionnaire forms with at least one subscale that can be determined; or where the reason questionnaire not completed is ticked as 'Subject too affected by symptoms of disease under investigation'.**

Thus the compliance rate for QLQ-C30 and for QLQ-PAN26 is defined as the number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline EORTC QLQ-C30 / QLQ-PAN26 questionnaire form. In addition, an overall compliance rate defined as number of patients with an evaluable baseline and at least one evaluable follow-up, divided by the number of patients expected to have completed at least a baseline for both, the EORTC QLQ-C30 AND QLQ-PAN26 questionnaire form, will be calculated.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

Reason for Amendment:

To provide additional detail of the derivation of best overall QoL response, improvement rate and compliance.

Section of protocol affected:

8.8 Methods for statistical analysis

Previous text:

A single interim PFS analysis for futility and superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events). The interim analysis will be performed by an Independent Data Monitoring Committee (IDMC) and full details will be provided in the IDMC charter. A final PFS analysis will be performed when approximately 89 progression events have occurred (~60% maturity). No further analyses of PFS are planned beyond this point unless requested by health authorities.

Timing of the statistical analyses are given in Section of protocol affected:

Table 8 Timing of statistical analyses

Previous text:

Table 6.

Revised text:

A single interim PFS analysis for futility-will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events). The interim analysis will be performed by an Independent Data Monitoring Committee (IDMC) and full details will be provided in the IDMC charter. A final PFS analysis will be performed when approximately **87** progression events have occurred (**60%** maturity). No further analyses of PFS are planned beyond this point unless requested by health authorities.

Timing of the statistical analyses are given in Table **10**.

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

Table 8 Timing of statistical analyses

Previous text:

Table 6 Timing of statistical analyses

7 Timing of analyses	8 Outcome Variable
	Efficacy Data
Interim PFS analyses (~ 45 PFS events)	- PFS
Final PFS (~ 89 PFS events)	- PFS, PFS2, TDT, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pain scale
Final OS analyses (~ 106 OS events)	- PFS2, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pain scale

** Only if superiority is met for PFS at the PFS interim analyses, will analyses of the following endpoints be performed: PFS2, TDT, TFST, TSST, OS, time to deterioration of Global QoL and PAN-26 pancreatic pain scale.

Revised text:

Table 10 Timing of Statistical Analyses

Timing of analyses	**Outcome Variable**
	Efficacy Data
Interim PFS analyses (~ 4**4** PFS events)	- PFS
Final PFS (~ 8**7** PFS events)	- PFS, PFS2, TDT, TFST, TSST, OS, **adjusted mean change from baseline in** global QoL **score**
Final OS analyses (~ 106 OS events)	- PFS2, TFST, TSST, OS, **adjusted mean change from baseline in** global QoL **score**

Reason for Amendment:

To change the health-related quality of life secondary endpoint from time to deterioration as assessed by the EORTC QLQ-C30 global QoL score to adjusted mean change from baseline in EORTC QLQ-C30 global QoL score.

Removal of the superiority analysis at the time of the interim analysis as per FDA recommendation.

Section of protocol affected:

Table 9 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Previous text:

Table 9 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	**Notes**
PFS (Time from randomisation to first progression or death)	Primary analysis: log-rank test using BICR data Key sensitivity analysis[a]: log rank test using BICR data in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS) Additional sensitivity analyses: 1) Evaluation time bias analysis; log-rank test using BICR data

Endpoints Analysed	Notes
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data
	4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
Overall Survival (Time from randomisation to death due to any cause)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
	Supportive analysis: KM plot of time to censoring for OS
Second Progression Free Survival (PFS2)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to treatment discontinuation (TDT)	Primary analysis: Stratified log rank test of time from randomisation to treatment discontinuation
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to first subsequent therapy (TFST)	Primary analysis: Stratified log rank test of time from randomisation to first subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to second subsequent therapy (TSST)	Primary analysis: Stratified log rank test of time from randomisation to second subsequent therapy or death

Endpoints Analysed	Notes
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to deterioration in global QoL (as measured by the global QOL score from the EORTC-QLQ-C30 questionnaire)	Primary analysis: Stratified log rank test of time from randomisation to deterioration in global QOL

[a] See Section 8.8.3 for further details

Revised text:

Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS (Time from randomisation to first progression or death)	Primary analysis: log-rank test using BICR data
	Key sensitivity analysis[a]: log rank test using BICR data in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
	Additional sensitivity analyses:
	1) Evaluation time bias analysis; log-rank test using BICR data
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data
	4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
Overall Survival (Time from randomisation to death due to any cause)	Primary analysis: log-rank test
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
	Supportive analysis: KM plot of time to censoring for OS
Second Progression Free Survival (PFS2)	Primary analysis: log-rank test

Endpoints Analysed	Notes
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to treatment discontinuation (TDT)	Primary analysis: log rank test of time from randomisation to treatment discontinuation
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to first subsequent therapy (TFST)	Primary analysis: log rank test of time from randomisation to first subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Time to second subsequent therapy (TSST)	Primary analysis: log rank test of time from randomisation to second subsequent therapy or death
	Key sensitivity analysis: log rank test using in randomised patients confirmed as *gBRCA* mutation positive by central Myriad test (if subset of FAS)
Adjusted mean change from baseline in global QoL score from the EORTC QLQ-C30 questionnaire	**Primary analysis: mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit**
	Supportive analysis: logistic regression on global QoL score improvement rate.

[a] See Section 8.8.3 for further details

Reason for Amendment:

To change the health-related quality of life secondary endpoint from time to deterioration as assessed by the EORTC QLQ-C30 global QoL score to adjusted mean change from baseline in EORTC QLQ-C30 global QoL score.

Correction to change ‘stratified log-rank test’ to ‘log-rank test’ as there is no stratification in this study.

Section of protocol affected:

8.8.1 Multiplicity strategy for primary and key secondary endpoints

Previous text:

At the interim analyses for PFS, 1% of alpha will be spent; statistical significance will be declared at the interim analysis if the 1-sided p<0.005. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26%. (Stone 2010). If PFS is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. Two interim analyses for OS will be performed; the first at the time of the interim PFS analysis (approximately 45 PFS events) and the second at the time of the final PFS analysis (approximately 89 PFS events). A final analysis of OS will be performed when approximate 106 death events have occurred. Statistical significance for OS will be declared the first at interim analyses for OS if the null hypothesis for PFS is rejected and the observed p-value for OS is p<0.005. If the null hypothesis for OS is not rejected at this time, then statistical significance for OS will be declared at the next interim analyses (final analysis of PFS) if the null hypothesis for PFS has been rejected and the observed 1-sided p-value for OS is < 0.01499. The final significance level will be determined accounting for the actual correlation between the interim and final OS analyses. To ensure that the type I error will be controlled at the 2.5% 1-sided level, if the interim analyses occur at exactly 30% and 57% of events respectively and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final analysis would be 1.53%

Revised text:

OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. **One** interim analys**i**s for OS will be performed; the time of the final PFS analysis (approximately **87** PFS events). A final analysis of OS will be performed when appr**oximately 106 death** events have occurred. **The Lan and DeMets approach that approximates the O'Brien & Fleming spending function will be employed to preserve the overall 1-sided type I error rate of 2.5% (Lan and DeMets 1983). If the interim analysis for OS occurs at exactly 57% of the 106 OS events,** statistical significance for OS will be declared if the null hypothesis for PFS is rejected and the observed p-value for OS is p<0.00**3, which equates to a HR ≤ 0.49. The significance level at the final analysis will be determined based on the exact number of events at the time of the interim and final analyses.** If the interim analys**is for OS** occur**s** at exactly 57% of events and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final

analysis **will** be **2.4**%. **Statistical significance for OS will be declared if the observed p-value for OS is p<0.024, which equates to a HR ≤ 0.68.**

Reason for Amendment:

Removal of the interim superiority analysis as per FDA recommendation. OS will be tested at the time of the primary PFS analysis and again after approximately 106 death events. To ensure that the type I error is controlled at the 2.5% 1-sided level overall for OS, the significance level will be allocated between the two analyses based on the O'Brien & Fleming spending function.

Section of protocol affected:

8.8.2 Analysis of the primary variable (s)

Previous text:

A single interim PFS analysis for superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on the BICR. A final PFS analysis will be performed when approximately 89 progression events have occurred (~60% maturity) based on the BICR. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

Revised text:

The primary PFS analysis will be performed when approximately **87** progression events have occurred (**60%** maturity) based on the BICR. No further analyses of PFS are planned beyond this point unless requested by Health Authorities.

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

8.8.2 Analysis of the primary variable(s)

Previous text:

As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, the HR and associated

confidence interval calculated from a Cox Proportional Hazards model containing treatment and these additional demographic variables, may be reported.

Revised text:

Deleted the text.

Reason for Amendment:

To remove statistical assessment of balance at baseline. If anything appeared quite strongly not to be balanced, this will be commented in the CSR and additional analysis requested to be produced.

Section of protocol affected:

8.8.2 Analysis of the primary variable(s)

Previous text:

The following subgroups of the full analysis set will be analysed for PFS:

- Type of chemotherapy (doublets vs triplets)
- Time on first line treatment till randomisation (⩽6 months vs >6 months)
- Best response on first line treatment (SD vs PR/CR)
- Measurable versus non measurable disease /no evidence of disease at baseline
- *BRCA* mutation type, eg *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation (>=65 vs. <65)
- Race
- Sex

Revised text:

The following subgroups of the full analysis set will be analysed for PFS:

- **Previous chemotherapy (FOLFIRINOX variants vs gemcitabine/cisplatin)**
- **Presence or absence of biliary stent**
- Type of **previous** chemotherapy (doublets vs triplets)

- Time on first line treatment till randomisation (⩽6 months vs >6 months)
- Best response on first line treatment (SD vs PR/CR)
- Measurable versus non measurable disease /no evidence of disease at baseline
- *BRCA* mutation type, eg *BRCA1, BRCA2* or *BRCA1/2* (both)
- Age at randomisation (>=65 vs. <65)
- Race
- Sex

Reason for Amendment:

To include additional subgroup analyses of PFS; previous chemotherapy (FOLFIRINOX variants versus gemcitabine/cisplatin),-and presence/absence of biliary stent will be analysed in Cox proportional hazards models.

Section of protocol affected:

8.8.3.2 Attrition bias

Previous text:

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

Revised text:

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

Reason for amendment:

To clarify censoring rules for the attrition bias sensitivity analysis.

Section of protocol affected:

8.8.4.1 Analysis of OS endpoint

Previous text:

OS data will be analysed at the time of the interim (if PFS null hypothesis rejected) and final analyses of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

Revised text:

OS data will be analysed at the time of the final analyses of PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

Reason for Amendment:

Removal of the superiority analysis at the time of the interim analysis as per FDA recommendation, therefore OS will not be analysed at this time.

Section of protocol affected:

8.8.4.6 Analysis of PRO endpoints

Previous text:

The analysis population for PRO data will be the subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

The impact of Olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales.

Time to global QoL and pancreatic pain scale deterioration will be analysed using the same methodology and model as described for the primary analysis of PFS. However sensitivity analyses will not be performed (with the exception of attrition bias).

Global QoL and PAN-26 pain scale improvement rate will be analysed using a logistic regression model. If the overall response rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but $\geqslant$ 5% in the other treatment group then the analysis will still be performed). If the overall expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile

likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC-QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Supportive analyses (of time to deterioration and improvement rates) will be performed for the individual QLQC30 domains (physical, role, cognitive, emotional, social). Treatment estimates and 95% CI for each domain will be presented on forest plots (one for Time to deterioration and one for improvement rate). P-values will not be calculated for these supportive analyses. These additional sub-scales are considered exploratory to support the primary QLQC30 global QoL and will be used to assess whether any observed differences in the global measure are driven by particular domains of functioning, symptoms or group of symptoms.

Descriptive statistics and graphs will be reported for the Global QoL item and the pancreatic pain scale by visits as well as change in these scores from baseline. Summary tables of QLQC30 best change rates will be provided (improvement, worsening, no change).

As supportive analyses, change from baseline in global QoL and pancreatic pain scale scores will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, pooled centre, visit and treatment by visit interaction as explanatory variables and the baseline score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; centre will be a random effect. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive. If there are still issues with the fit of the model or estimation of the treatment effects, CENTRE will be treated as a fixed effect.

The adjusted mean estimates and corresponding 95% confidence intervals will be presented by visit for each treatment group.

No formal testing will be done on the global QoL and pancreatic pain scale data. Data will be descriptive and plots will be used to visualise the adjusted mean global QoL score across time for each treatment arm.

Compliance

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 QoL score, divided by the number of patients randomised. Compliance over time is calculated separately for each visit, including baseline, as the number of patients providing an evaluable assessment for the global QoL score at that visit divided by the number of patients expected to have provided an assessment.

QLQC30 and PAN-26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Revised text:

The analysis population for PRO data will be the **PRO analysis set including patients with evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms**.

The impact of olaparib on health related quality of life and pain will be assessed through an analysis of the EORTC-QLQC30 global quality of life and PAN-26 pancreatic pain scales.

Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, and autoregressive.

The adjusted mean change from baseline estimates and corresponding 95% CIs will be presented by visit for each treatment group and corresponding plots over time will be presented.

As a supportive analysis, EORTC QLQ-C30 global QoL **score** improvement rate will be analysed using a logistic regression model. If the overall response rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall expected response rate is low (< 20%) a Fisher's exact test will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together

with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

EORTC QLQ-C30 (overall compliance and by visit compliance) will be summarised for each treatment group.

Descriptive statistics and graphs will be reported for the global QoL **score** by visits as well as **unadjusted** change in these scores from baseline. Summary tables of **EORTC** QLQ-C30 best **overall QoL response as defined in Table 9** will be provided (improvement, **deterioratio**, no change).

An exploratory analysis will examine adjusted mean change from baseline on QLQ-PAN26 symptom scales/items (including pancreatic pain). This is detailed in Section 8.8.5.1.

Reason for Amendment:

To change the health-related quality of life secondary endpoint from time to deterioration as assessed by the EORTC QLQ-C30 global QoL score to adjusted mean change from baseline in EORTC QLQ-C30 global QoL score, to be analysed in an MMRM model.

Section of protocol affected:

8.8.5.1 Exploratory analysis of PRO endpoints (PAN-26 symptom scales and items)

Previous text:

8.8.5.1 Exploratory analysis of PRO endpoints (PAN-26 symptom scales and items)

Exploratory analyses, examining improvement rates and time to worsening, will be performed for the individual PAN-26 symptom scales and items (with a particular focus on fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice), and presented on forest plots (showing treatment estimates and 95% CI for each domain). P-values will not be calculated for these exploratory analyses.

Descriptive statistics and graphs will be reported for the symptom scales and items (specifically fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite and jaundice). Summary tables of PAN26 best change rates will be provided (improvement, worsening, no change).

Change from baseline in QLQC30 functioning domain scores and PAN-26 scales and items may be analysed using the same MMRM model described in Section 8.8.4.6 for Global QoL score and the pancreatic pain score.

Descriptive summaries for individual symptom items within the PAN-26 will also be provided.

Revised text:

8.8.5.1 Exploratory analysis of PRO endpoints (**QLQ-**PAN26 symptom scales and items)

Exploratory analyses examining **adjusted mean change from baseline** will be performed **for EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional, social) and** for the individual **EORTC QLQ-C30 and QLQ-PAN26** symptom scales/items (with a particular focus on **pancreatic pain,** fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite), jaundice), **using the same MMRM model described in Section 8.8.4.6 for the global QoL score.**

Descriptive statistics and graphs will be reported for the **EORTC QLQ-C30 functioning domains and EORTC QLQ-C30 and QLQ-PAN26** symptom scales/items (specifically **pancreatic pain,** fatigue, nausea, weight loss (difficulty gaining weight/loss of appetite) and jaundice).

EORTC QLQ- PAN26 compliance (overall compliance and by visit compliance) will be summarised for each treatment group.

Reason for Amendment:

To change the exploratory analysis to MMRM to examine adjusted mean change from baseline on EORTC QLQ-C30 and QLQ-PAN26 functioning domains and symptom scales.

Section of protocol affected:

8.9 Sample Size Determination

Previous text:

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately 89 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on BICR.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and 2.26% alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median OS for placebo. At the interim analyses, 0.5% of alpha (1-sided) will be spent, and controlling the type I error across the two time points, 89 PFS events will be required at the final analyses.

Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. Assuming 45 PFS events at the interim, a $HR \leq 0.46$ would equate to a 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level

will be determined accounting for the actual correlation between the interim and final PFS analyses. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 50% of events and the number of PFS events at the final analysis is as expected then the 1-sided significance level to be applied for the final analysis would be 2.26%. (Stone 2010). Assuming 89 PFS events, a HR $\leq$ 0.65 would equate to a 1-sided p-value <0.0226.

…

Assuming that the study accrual period will be approximately 15 months, 89 progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that 45 PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 death events will occur approximately 31 months after first patient in.

Revised text:

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of Olaparib:placebo) and the primary PFS analysis will occur once approximately **87** PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for **futility** will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events) based on BICR.

The study is sized assuming a true treatment effect is a PFS Hazard Ratio (HR) of 0.54, assuming 80% power and **2.5%** alpha (1-sided), with 3:2 randomisation (Olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median OS for placebo. **87** PFS events will be required at the final analyses.

…

Assuming that the study accrual period will be approximately 15 months, **87** progression events are anticipated to be observed approximately 18-19 months after the first patient is randomised in the study. It is estimated that **44** PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 death events will occur approximately 31 months after first patient in.

Reason for Amendment:

The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced.

Section of protocol affected:

8.9.1 Interim analysis

Previous text:

A single interim PFS analysis for superiority and futility will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

Section 8.8.1 details the spending function used to account for multiplicity introduced by including interim analyses for superiority.

Interim analyses of OS will be performed at the time of the interim analyses of PFS (~89 PFS events),and again at the final analyses at the final analyses of PFS (~89 events), and when approximately 106 OS events have occurred.

If the interim PFS results indicate superiority, then analyses of all other endpoints would be performed and the results of these analyses will form the basis for submissions for regulatory approval. Patients would continue to be followed for PFS and survival until ~89 PFS events had occurred, and then followed for survival until 106 patients had died.

Revised text:

A single interim PFS analysis for futility will be performed when 50% of the final number of progression **events required for the primary PFS analysis** has been reached (approximately **44** PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter. **Safety data including death rates will also be reviewed at this time.**

The futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the final number of PFS events (n=87) is reached (Lachin 2005). The determination of this probability will be conditional on the observed data at the time of the interim analysis and on the assumed hazard ratio for the alternative hypothesis (PFS HR=0.54). If the probability is less than 20%, the IDMC will consider the option of declaring futility.

The exact figure used for the futility boundary will be calculated by AZ and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time. As an example, if exactly 50% of the PFS events required for the primary PFS analysis have occurred at the time of the interim analysis (44 events), then the HR that corresponds to 20% conditional power for the interim analysis will be 1.02. Therefore, if the observed HR for PFS at the interim is more than 1.02, the IDMC will consider the option of declaring futility.

An interim analys**i**s of OS will be performed at the time of the **primary analysis** of PFS (**approximately 87** events), and **again** when approximately 106 OS events have occurred.

Reason for Amendment:

To include additional details of the interim futility analysis.

Section of protocol affected:

11 LIST OF REFERENCES

Previous text:

Cowley et al 2013

Cowley et al Understanding pancreas cancer genomes. J Hepatobiliary Pancreat Sci (2013) 20:549–556

Fayers et al 1999

Fayers P, Aaronson N, Bjordal K & Sullivan M (1999). EORTC QLQC30, Scoring Manual. Belgium: EORTC Data Center.

Ferrone CR et al 2009

Ferrone CR. et al.BRCA Germline Mutations in Jewish Patients With Pancreatic Adenocarcinoma. Journal of Clinical Oncology, Vol 27, No 3 (January 20), 2009: pp. 433-438

Kim et al 2014

Kim et al. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poor prognosis. Clin Cancer Res Published Online First January 31, 2014

Ledermann et al 2013

Ledermann, J Clin Oncol 31, 2013. Olaparib maintenance therapy in patients with platinum sensitive relapsed serous ovarian cancer (SOC) and a *BRCA* mutation (*BRCAm*)

Revised text:

Cowley et al 2013

Cowley et al Understanding pancreas cancer genomes. J Hepatobiliary Pancreat Sci (2013) 20:549–556

Fayers et al 2001

Fayers et al. EORTC QLQ-C30 Scoring Manual (Third Edition). Belgium: EORTC Quality of Life Group, 2001.

Ferrone CR et al 2009

Ferrone CR. et al.BRCA Germline Mutations in Jewish Patients With Pancreatic Adenocarcinoma. Journal of Clinical Oncology, Vol 27, No 3 (January 20), 2009: pp. 433-438

Kim et al 2014

Kim et al. Having pancreatic cancer with tumoral loss of ATM and normal TP53 protein expression is associated with a poor prognosis. Clin Cancer Res Published Online First January 31, 2014

Lachin 2005

Lachin, J. M. A review of methods for futility stopping based on conditional power. Statist. Med. (2005) 24: 2747–2764.

Lan and DeMets 1983

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70: 659-63.

Ledermann et al 2013

Ledermann, J Clin Oncol 31, 2013. Olaparib maintenance therapy in patients with platinum sensitive relapsed serous ovarian cancer (SOC) and a *BRCA* mutation (*BRCAm*)

Reason for Amendment:

To include updated reference to the EORTC QLQ-C30 scoring manual.

To include two new references to detail the approach for the alpha spending function and the futility analysis.

AstraZeneca

Clinical Study Protocol Global amendment-Appendix A

Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	2
Date	28 February 2015
Protocol Dated	31 March 2014

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A randomized phase III, multicentre, efficacy and safety study of Olaparib compared to physician's choice of chemotherapy in the treatment of metastatic pancreas cancer patients with germline *BRCA1/2* mutations after previous treatment for advanced disease

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

I agree to the terms of this study protocol/amendment.

AstraZeneca Research and Development site representative

7/4/2015

Jane Robertson
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AstraZeneca
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Date
(Day Month Year)

ASTRAZENECA SIGNATURE(S)

A randomized phase III, multicentre, efficacy and safety study of Olaparib compared to physician's choice of chemotherapy in the treatment of metastatic pancreas cancer patients with germline *BRCA1/2* mutations after previous treatment for advanced disease

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AstraZeneca Research and Development site representative

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08-Apr-2015
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(Day Month Year)

ASTRAZENECA SIGNATURE(S)

A randomized phase III, multicentre, efficacy and safety study of Olaparib compared to physician's choice of chemotherapy in the treatment of metastatic pancreas cancer patients with germline *BRCA1/2* mutations after previous treatment for advanced disease

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

I agree to the terms of this study protocol/amendment

AstraZeneca Research and Development site representative

4/7/2015

Date
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SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomized phase III, multicentre, efficacy and safety study of Olaparib compared to physician's choice of chemotherapy in the treatment of metastatic pancreas cancer patients with germline *BRCA1/2* mutations after previous treatment for advanced disease

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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice and local regulations, and I ensure that all relevant site staff follows the instructions given in the latest version of the Laboratory Manual for Investigators.

Signature:

USA

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A randomized phase III, multicentre, efficacy and safety study of Olaparib compared to physician's choice of chemotherapy in the treatment of metastatic pancreas cancer patients with germline *BRCA1/2* mutations after previous treatment for advanced disease

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Signature:

ISRAEL

AstraZeneca

Statistical Analysis Plan

Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	1.0
Date	22 September 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Statistical Analysis Plan
Drug Substance Olaparib
Study Code D081FC00001
Edition Number 1.0
Date 22 September 2014

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

PAREXEL Study Statistician

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

AstraZeneca Study Statistician

Wendy Bannister

02 OCT 2014

Date

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Astra Zeneca Global Product Statistician

Helen Mann _____ 02/10/2014
Date

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study Statistical Analysis Plan.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to first dosing with study treatment
BDRM	Blind data review meeting
bid	Bis in die (Latin for 'twice a day')
BICR	Blinded independent central review
BMI	Body mass index
BoR	Best overall RECIST response
BRCA	Breast cancer susceptibility gene
BRCA mutation or BRCAm	Breast cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
CI	Confidence interval
CIF	Cumulative incidence function
CR	Complete response
CRF / eCRF	Case Report Form (electronic)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation of investigational product due to adverse event
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient’s disease is progressing.

Abbreviation or special term	Explanation
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
FAS	Full Analysis Set
gBRCA	Germline BRCA
gBRCA mutation or gBRCAm	The term "gBRCA mutation" is used to refer to a germline BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants.
HR	Hazard ratio
HRQoL	Health-related quality of life
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
ITT	Intention to treat
KM	Kaplan-Meier
LD	Longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesions
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall Survival
PARP	Polyadenosine 5’diphosphoribose [poly (ADP ribose)] polymerisation
p.o.	Per os (by mouth, orally)
PD	Progressive disease
PFS	Progression-free survival
PFS2	Time from randomisation to second progression

Abbreviation or special term	Explanation
PID	Percentage intended dose
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1.
REML	Restricted maximum likelihood
RS	Raw Score
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SOC	System organ class
Study treatment	Olaparib or matching placebo
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
VAS	Visual analogue scale

1 STUDY DETAILS

As described in the protocol.

1.1 Study Objectives

Study objectives will be addressed in patients with deleterious or suspected deleterious germline mutation in breast cancer susceptibility gene 1 and/or 2 (*BRCA1* and/or *BRCA2*) and metastatic pancreas cancer who have achieved disease control (absence of objective progression) after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy.

Primary:

To determine the efficacy of olaparib maintenance monotherapy compared to placebo by progression-free survival (PFS), using blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; in the following referred to as RECIST.

Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of

- Overall Survival (OS).
- Time from randomisation to second progression (PFS2).
- Time from randomisation to first subsequent therapy or death (TFST).
- Time from randomisation to second subsequent therapy or death (TSST).
- Time from randomisation to study treatment (olaparib or matching placebo) discontinuation or death (TDT).
- Objective response rate by BICR using modified RECIST criteria.
- Disease control rate (DCR) at week 16 by BICR using modified RECIST criteria.

2. To compare the effects of olaparib maintenance monotherapy compared to placebo on the health-related quality of life (HRQoL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 global quality of life (QoL) scale.

Safety:

To assess the safety and tolerability of olaparib maintenance monotherapy by assessment of adverse events (AEs), physical examination, vital signs including blood pressure, pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.

Exploratory:

1. To explore the effect of olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional and social).

2. To explore the effect of olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales.

3. To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), and jaundice.

4. To assess the change in performance status as measured by the Eastern Cooperative Oncology Group (ECOG) performance status scale.

5. To investigate the health economic impact of treatment and the disease on hospital-related resource use and health state utility.

6. To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.

7. To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.

8. To identify tumour tissue-based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRRCA methylation and/or other homologous recombination repair deficiencies biomarkers) that could be used to guide future patient segmentation approaches for development.

9. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.

Parts of the exploratory analyses may not be part of the analysis described in this statistical analysis plan (SAP) and as such, may not be reported in the Clinical Study Report (CSR). If not, they will be reported separately by AstraZeneca.

1.2 Study Design

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic cancer patients with germline BRCA (gBRCA) mutations (documented mutation in gBRCA1 or gBRCA2) that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16-weeks of first-line platinum-based chemotherapy.

Approximately 145 patients will be randomised (using an Interactive Voice Response System / Interactive Web Response System) in a 3:2 ratio to the treatments as specified below:

- olaparib tablets per os (p.o.) 300 mg twice daily.
- placebo tablets p.o. twice daily.

Eligible patients will be those patients with pancreas cancer previously treated for metastatic disease gBRCA mutated, who have not progressed following completion of at least 16 weeks of first-line platinum-based chemotherapy before randomisation. All patients must have a known deleterious or suspected deleterious germline BRCA mutation to be randomised. Determination of gBRCA mutation will be done before enrolment to the study at Myriad laboratories.

Patients with known gBRCA mutation prior to randomisation will enter the study based on these results (by considering all other eligibility criteria as well), but undergo a confirmatory gBRCA test post-randomisation, while patients with unknown gBRCA mutation will enter the study after confirmation of gBRCA mutation.

Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of last treatment) and study treatment will start as soon as possible but no less than 4 and no more than 8 weeks after the last chemotherapy dose. At the time of starting study treatment, all previous chemotherapy treatment should be discontinued.

Following randomisation, patients will attend clinic visits weekly for the first 4 weeks of treatment (days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment and will continue treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once a patient has discontinued study treatment, clinic visits will be reduced to every 8 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator. It is anticipated (but not required) that patients will be re-treated with their previous platinum-based regimen. Details of any further systemic anti-cancer treatment will be collected until death, loss to follow-up, or withdrawal of consent. In addition to their regular 8 weekly contacts, patients will be contacted in the 7 days following a specified day (data cut-off date [DCO]) to capture survival status.

Patients will have tumour assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to modified RECIST criteria. RECIST will be modified to assess patients with clinical CR at entry who will be assessed as having no evidence of disease (NED) until they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue to undergo scheduled objective tumour assessments according to the study plan in order to assess objective radiological progression of disease. Failure to do so may result in bias in the study results. Once a patient has progressed, the patient will be followed for second progression every 8 weeks and then survival until the final analysis. Patients will be contacted in the week following last patient last visit for each analysis of survival.

The final PFS analysis of the study will occur when approximately 89 PFS events have occurred, although an interim PFS analysis for superiority and futility will be performed when 50% of the PFS events required for the final PFS analysis have occurred. Both interim and final PFS analyses will be based on BICR of disease progression by modified RECIST version 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

The study flow chart is in Appendix A while the study schedule is in Appendix B.

1.3 Number of Patients

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of olaparib:placebo) and the final PFS analysis will occur once approximately 89 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for superiority and futility will be performed when 50% of the PFS events required for the final analysis (approximately 45 PFS events) based on BICR have occurred.

The study is sized assuming a true treatment effect that is a PFS Hazard Ratio (HR) of 0.54 at the final analysis, assuming 80% power and 2.26% alpha (1-sided), with 3:2 randomisation (olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4-month improvement in median PFS over an assumed 4-month median PFS for placebo. At the interim PFS analysis, 0.5% alpha (1-sided) will be spent, and controlling the type I error across the two time points, 89 PFS events will be required for the final PFS analysis.

Statistical significance will be declared for PFS at the interim analysis if the 1-sided $p<0.005$. Assuming 45 PFS events at the interim, a HR ≤ 0.46 would equate to a 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analysis time point then PFS will be tested again when approximately 89 PFS events have occurred. The final significance level will be determined accounting for the actual correlation between the interim and final PFS analyses. In order to ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 45 PFS events and the number of PFS events at the final analysis is

as planned (89 PFS events), the 1-sided significance level to be applied for the final analysis would be 2.26% (Stone 2010). Assuming 89 PFS events, a HR ≤ 0.65 would equate to a 1-sided p-value<0.0226.

Patients are to be followed for the final analysis of OS and PFS2 (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6-month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

Assuming that the study accrual period will be approximately 15 months, 89 PFS events are anticipated to be observed approximately 18 to 19 months after the first patient is randomised in the study. It is estimated that 45 PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 deaths will have occurred approximately 31 months after first patient in.

2 ANALYSIS SETS

2.1 Definition of Analysis Sets

Full Analysis Set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or discrepancy between local and Myriad gBRCA results. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy endpoints will be summarised and analysed using the FAS on an ITT basis.

In addition, key sensitivity analysis of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a gBRCA mutation confirmed by the Myriad test.

Safety Analysis Set

All patients who received at least one dose of randomised investigational product, olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, all patients who received at least one dose of olaparib will be accounted for in the olaparib treatment group. Erroneously treated placebo patients (those randomised to placebo but actually received at least one dose of olaparib) will be accounted for in the olaparib treatment group. Any mis-randomisations will be discussed on an individual basis and decisions will be documented at the blind data review meeting (BDRM).

Patient Reported Outcome Analysis Set

The analysis population for patient reported outcome (PRO) data will be a subset of the FAS (ITT) population; patients must have a baseline score to be included in the analysis of PRO data.

Table 1 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
- Primary: PFS	FAS (ITT), Myriad confirmed Breast cancer susceptibility gene mutation (BRCAm) subgroup
- Secondary analysis: OS, PFS2, TFST, TSST, TDT	
- Secondary summary: objective response rate (ORR), disease control rate (DCR)	
PRO Data	
- Time to deterioration and improvement rate of global QoL and pancreatic cancer symptom scale	PRO
Demography	FAS (ITT)
Safety Data	
- Exposure, AEs, Laboratory measurements; ECGs, Vital signs, ECOG, Physical examinations	Safety

2.2 Violations and Deviations

The important protocol deviations will be listed and summarised by randomised treatment group. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1. A per-protocol analysis excluding patients with significant protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis will be performed excluding patients with deviations that may affect the efficacy of the trial therapy if > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock or data freeze for interim and final analysis and will be documented prior to the analysis being conducted.

The following general categories will be considered important deviations and be listed and discussed in the CSR as appropriate for study.

- Patients randomised but who did not receive olaparib/matching placebo.
- Patients who deviate from key entry criteria (to be determined at the BDRM), which will be documented ahead of database lock.

- Baseline RECIST scan > 28 days before start of study treatment.

- Baseline RECIST scan after randomisation.

The categorisation of these as important deviations is not automatic and will depend on duration and the perceived effect on efficacy.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post-entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified.

Mis-randomisations in terms of errors in treatment dispensing, will also be summarised and listed separately to the important protocol deviations. A mis-randomisation is when a patient is not randomised or treated according to the randomisation schedule. It is envisaged that there will be 2 subcategories of this:

(a) Patients who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where patients may stop taking drug.

(b) The patient receives a treatment pack with a different code from their randomisation code. However, the actual treatment may still match the randomised treatment. For example, a patient is given randomisation code 0001, which according to the randomisation schedule is olaparib. However, at the randomisation visit they are given treatment pack 0003, but this still contains olaparib.

The summary will include all patients with a dispensing error but will also include information on how many of those patients received at least one dose of the wrong treatment (olaparib/placebo) at any time.

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle mis-randomisations will be made on an individual basis with written instruction from the study team leader and/or statistician.

The final classification of deviations will be made at the BDRM prior to database lock or data freeze and all decisions will be made whilst blinded to study treatment allocation. For example, details of disallowed concomitant medication use will be reviewed by a physician using blinded data and may be determined as key. Decisions made at the BDRM will be documented and approved by AstraZeneca prior to analysis and unblinding.

3 PRIMARY AND SECONDARY VARIABLES

At each visit patients will be assigned a RECIST visit response of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE) or NED depending on the status of their disease compared to baseline and previous assessments, based on the BICR. This will be repeated using the Investigator assessed RECIST data.

3.1 Derivation of RECIST Visit Responses

Patients with measurable or non-measurable disease or NED assessed at baseline by computed tomography (CT) / magnetic resonance imaging (MRI) will be entered in this study. RECIST has been modified to allow the assessment of progression due to new lesions in patients with NED at baseline (inclusion criteria #4).

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to modified RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best overall response.

Baseline radiological tumour assessments are to be performed no more than 28 days before start of study treatment and as close as possible to randomisation. Tumour assessments are then performed every 8 weeks (±1 week) up to 40 weeks and then every 12 weeks (±1 week) following randomisation until disease progression.

If an unscheduled assessment was performed and the patient had 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.

At each visit, an overall visit response will be provided by the BICR and separately by the investigator - using the information from target lesions (TL), non-target lesions (NTL) and new lesions.

3.1.1 Target lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest to randomisation will be used to define the baseline sum of TLs. 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.

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

Note: For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTLs assessment and the absence/presence of new lesions (see Section 3.1.3 of the Clinical Study Protocol (CSP) for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

For patients with NED at baseline (ie, no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be NED.

Table 2 TL Visit Responses

Visit Responses	Description
CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, 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 indicate an absolute increase of at least 5 mm.
NE	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
NA	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm from nadir, even assuming the non-recorded TLs have disappeared. Note: the nadir can only be taken from assessments where all the TLs had a longest diameter (LD) recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm, then although the sum may be > 0 mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met ie, if a lymph node LD increases by 20% but remains < 10 mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes), then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.
- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD, then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined, the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure, this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (ie, lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having had intervention for the remainder of the study, noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and scale up as described below as long as there remain ≤ 1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

  Scaling will be based on the sizes at the nadir visit, to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-intervention lesions to the nadir sum of diameters excluding the lesions with interventions.

Table 3 Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5

Table 3 Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 has had an intervention at the follow-up visit.

The sum of lesions 1 to 4 at the follow-up is 26 cm. The sum of the corresponding lesions at baseline visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

- Step 3: If after both steps PD has not been assigned, then if appropriate, a scaled sum of diameters will be calculated, treating the lesion with intervention as missing, and PR or SD, then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or < 10 mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0 recorded. If scaling-up is not appropriate due to too few non-missing sizes then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up where appropriate (as per step 2 above).

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

Change in method of assessment of TLs

Computed tomography and MRI are the only methods of assessment that can be used within the trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (eg, CT changes to clinical examination), any affected lesions should be treated as missing.

3.1.2 NTLs and new lesions

At each visit an overall assessment of the NTL response should be recorded. This section provides the definitions of the criteria used to determine and record overall response for NTL at each visit.

The NTL response will be derived based on the overall assessment of NTLs as follows:

Table 4 NTL Visit Responses

Visit Responses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
NE	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
NA	Only relevant if there are no NTLs at baseline.

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

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

New lesions will be identified on the electronic case report form (eCRF). The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

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

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.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

'Symptomatic deterioration' is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs. 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.

3.1.3 Overall visit response

Table 5 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 5 Overall Visit Responses

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

NA is only relevant if there were no TL/NTL at baseline.

3.1.4 Independent review

The BICR data will be used for the analysis of PFS.

The independent review charter contains the details of the independent central review conducted by the AstraZeneca-appointed central Core Imaging Laboratory and will be developed in advance of the start of the study. The independent data review will provide RECIST measurements for each visit for each patient at the time of DCO for the interim and final analyses of PFS. After the final PFS analysis, BICR of scans will no longer be required. On an ongoing basis, patients who are determined to have progressed according to modified RECIST 1.1 criteria by the investigator will have scans centrally reviewed for confirmation of

objective disease progression. If disease progression is not confirmed at BICR, an additional RECIST assessment will be requested at the next scheduled RECIST visit.

For each patient, the independent reviewer will provide at each time point, TL and NTL responses with supporting dates, measurements and assessments, location of new lesions and comments (if applicable), overall visit responses and the relevant scan dates. The overall visit response data as determined by the BICR will be used to derive PFS and best overall RECIST response (BoR) for the primary and secondary analyses.

3.2 Outcome Variables

At each visit patients will be assigned a RECIST visit response of CR, PR, SD, PD, NED, NE depending on the status of their disease compared to baseline and previous assessments, using the time point responses and relevant dates from the BICR. Separately, the investigator will assign a RECIST visit response of CR, PR, SD, PD, NED, NE depending on the status of their disease compared to baseline and previous assessments.

Where applicable, outcome variables, eg, PFS, OS, PFS2 etc., will be derived using time point responses and relevant dates from the BICR, unless otherwise stated.

3.2.1 Progression-Free Survival

Progression-free survival is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease 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 (prior to the missing visits). 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 an extra two weeks for early and late visits. After 40 weeks, two missing visits will equate to more than 26 weeks. If two missed visits occur over the period when the scheduled frequency of RECIST assessments changes (ie, from every 8 weeks to every 12 weeks), this will equate to more than 22 weeks (allowing for an early assessment at Week 32 and a late assessment at Week 52).

The baseline RECIST assessment should be performed prior to randomisation but if an evaluable RECIST assessment occurs after randomisation but before treatment then this assessment will be used as the baseline assessment. 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 tumour assessment visits of randomisation (16 weeks plus 1 week allowing for a late assessment within the visit window).

If a patient has two missing visits between two evaluable RECIST assessments with outcome not equal to progression at the second evaluable RECIST assessment, but then subsequently progresses, the patient will not be censored when analysing for PFS. For example, if RECIST

assessments were performed at week 8 with outcome SD, week 32 with outcome SD and week 40 with a progression event (weeks 16 and 24 were missed), the patient will be analysed from time of randomisation until progression event at week 40 without considering the interruptions.

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

The 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 by the investigator and BICR 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 TLs (compared to previous minimum sum) and an absolute increase of > 5 mm, or an overall NTLs assessment of progression or a new lesion.

The primary analysis will be based on the programmatically derived PFS based on the BICR of the radiological scans, and using all scans regardless of whether they were scheduled or not. A sensitivity analysis based on the derived PFS based on investigator-recorded assessments will be carried out.

3.2.2 Overall Survival

Overall Survival is defined as the time from the date of randomisation 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 DCO for the analysis, and if patients are confirmed to be alive or if the death date is not available these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

3.2.3 Time from randomisation to second progression

The PFS2 is defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of objective radiological or symptomatic progression or death. The RECIST assessments will not be collected for assessment of PFS2.

The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

Second progression status will be reviewed every 8 weeks following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

3.2.4 Time to first subsequent therapy or death

As a supportive summary to PFS, TFST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks, in line with survival follow-up visits. The TFST is defined as the time from randomisation to the earlier of first subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

3.2.5 Time to second subsequent therapy or death

As a supportive summary to PFS2, TSST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks, in line with survival follow-up visits. The TSST is defined as the time from randomisation to the earlier of the second subsequent therapy start date following study treatment discontinuation, or death. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received second subsequent therapy, ie, the last follow-up visit where this was confirmed.

3.2.6 Time to study treatment discontinuation or death

The TDT is defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive.

3.2.7 Best overall RECIST response

Best overall RECIST response is calculated based on the overall visit responses from each RECIST assessment (Table 5). It is the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on the RECIST criteria using the following order of response categories: CR, PR, SD, NED (applies only to those patients entering the study with no disease at baseline), PD and NE.

BoR will be determined programmatically from the overall visit response using BICR data.

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 7 weeks (ie, 8 weeks minus 1 week to allow for an early assessment within 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 ≤ 17 weeks (ie, 16 weeks +1 week to allow for a late assessment within the assessment window) after randomisation then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurred > 17 weeks (ie, 16 weeks +1 week) after randomisation then BoR will be assigned to the NE category.

Progression events that have been censored due to them being more than two missed visits 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 following randomisation, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.8 Objective response rate

For each treatment group, the ORR is the number of CR and PR divided by the number of patients in the treatment group with measurable disease at baseline. Only patients with PR and measurable disease at baseline can achieve an objective response of CR or PR.

3.2.9 Disease control rate

The DCR is defined as the percentage of patients who have at least one confirmed visit response of CR or PR or have demonstrated SD or NED for at least 15 weeks (ie, 16 weeks minus 1 week to allow for an early assessment within assessment window) prior to any evidence of progression. In the case of SD and NED, follow-up assessments must have met the SD or NED criteria for a minimum interval of 15 weeks following randomisation.

3.3 Patient Reported Outcome Variables

Patient reported disease related symptoms and HRQOL will be evaluated using the validated EORTC QLQ-C30 and the EORTC QLQ-PAN26 questionnaire. The EORTC QLQ-C30 was developed to assess HRQoL and functioning while the EORTC QLQ-PAN26 was developed specifically for patients with pancreas cancer.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following scales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social)
- 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
- A 2-item global health status / QoL scale
- 5 single items assessing the following common cancer symptoms:
  - dyspnoea
  - loss of appetite
  - insomnia
  - constipation
  - diarrhoea
- 1 item on the financial impact of the disease.

The pancreas cancer module, PAN26, is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation, or palliative chemotherapy. The module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreas cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).

All the EORTC scales range from 0 to 100 (through transformation of scores as detailed below). The EORTC QLQ-C30 scales can be interpreted as following: 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. The interpretation of the EORTC QLQ-PAN26 depends on the symptoms or problems. For digestive symptoms, altered bowel habit, hepatic, sexuality and body image, a higher score represents worse QoL, while a lower score represents a good outcome. For the health care satisfaction scale (items 53 and 54), a higher score represents good outcome while a less score represents worsening.

Transformation of scores

The EORTC QLQ-C30 / QLQ-PAN26 will be scored according to the EORTC scoring manual (Fayers et al 1999). Each scale will be transformed to a 100-point scale as following:

For all scales, the Raw Score (RS) is the mean of the component items:

$$RS = (I_1 + I_2 + \cdots + I_n)/n$$

To obtain the score S, the following linear transformation will be applied:

Table 6 Linear Transformation of EORTC Scales

Scale	Item number QLQ-C30	Item number QLQ-PAN26*	Calculation of score
Functional scale	1-7, 20-27	NA	$S = \left\{1 - \frac{RS-1}{range}\right\} * 100$
Symptom scales	8-19, 28	31, 33-37, 44-49	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Global Health Status / QoL	29, 30	NA	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Health care satisfaction scale	NA	53, 54	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Sexuality	NA	55, 56	$S = \left\{1 - \frac{RS-1}{range}\right\} * 100$

Range is the difference between the maximum possible value of RS and the minimum possible value.
*A few items of the QLQ-PAN26 questionnaire are not part of the table as they are not part of a multi-item scale (ie, item number 32, 38, 39-43, 50-52). Nevertheless, they need to be transformed in the same way as for symptom scales.

The QLQ-C30 / PAN26 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6.

HRQoL visit responses

A change of at least 10 points in the global QoL score will be considered as a clinically relevant or a minimally important difference (Osoba D et al 1998). A change of at least 10 points in the pancreas cancer module will be considered as a clinically relevant or a minimally important difference, too (Serrano et al 2014).

Table 7 Mean Change and Visit Response in Health-Related QoL

Score	Change from baseline	Visit response
EORTC QLQ-C30 symptom scales	≥ +10 or patient too ill to complete measure	Deterioration
	≤ -10	Improved
	Otherwise	No change
EORTC QLQ-C30 Global QoL score and functional scales: physical, role, emotional, cognitive and social	≥ +10	Improved
	≤ -10 or patient too ill to complete measure	Deterioration
	Otherwise	No change

Table 7 Mean Change and Visit Response in Health-Related QoL

Score	Change from baseline	Visit response
EORTC QLQ-PAN26 scales*: pancreatic pain, digestive symptoms, altered bowel habit, hepatic, sexuality and body image multi item scales and single item measures	≥ +10 or patient too ill to complete measure	Deterioration
	≤ -10	Improved
	Otherwise	No change
EORTC QLQ-PAN26 scales*: Satisfaction with health care	≥ +10	Improved
	≤ -10 or patient too ill to complete measure	Deterioration
	Otherwise	No change

*The change from baseline of 10 points for detecting a deterioration or improvement in the pancreas cancer module is based on recent investigations by Serrano et al 2014.

Note for some patients it will not be immediately possible to obtain a visit response for a particular subscale, for example:

- Patients with no baseline score for a particular subscale, or no baseline data at all
- Patients whose baseline subscale score is too close to the maximum or minimum possible score to allow an increase or decrease of the specific size to be observed.
  - For patients whose baseline score is greater than the maximum possible score for that subscale minus the score needed to satisfy improvement, the best visit response possible will be "No Change".
  - For patients whose baseline score is less than the threshold needed for worsening all post-baseline visit responses will be considered not-calculable.

Time to deterioration of HRQoL

Time to deterioration of HRQoL, as measured by the EORTC QLQ-C30 (global QoL) and EORTC QLQ-PAN26 (pancreas cancer symptom) scores, will be defined as the time from date of randomisation to the date of a clinically important deterioration in the EORTC QLQ-C30 / PAN26 score (Table 7) or death (by any cause) in the absence of a clinically important deterioration, provided death occurs within two HRQoL assessment visits of the last evaluable assessment, and regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to deterioration. "Subject Too Affected by Symptoms of Disease Under Investigation" answered as the reason for not completing HRQoL at a post-baseline visit will also signify a clinically important deterioration in HRQoL.

Patients whose HRQoL has not shown a clinically important deterioration and who are alive at the time of the analysis will be censored at the time of their last evaluable HRQoL assessment.

Also, if HRQoL deteriorates after two or more missed HRQoL assessment visits or the patient dies after two or more missed HRQoL assessment visits, the patient will be censored at the time of the last evaluable HRQoL assessment.

A patient's best overall QoL response will be derived as the best QoL response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy, date of HRQoL deterioration or death. The criteria in Table 8 will be used to assign a best QoL response for HRQoL based on the 2-item global QoL score. Improvement rate will be defined as the proportion of patients whose best overall QoL response was "Improved".

Table 8 Best Response in EORTC QLQ-C30 Scores

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 qualify for overall score response of "improved". A visit response of "deterioration" without response of "improved" or "no change" within 21 days.
Other	Does not qualify for one of the above.

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. 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 items 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.

3.3.1 Compliance

Summary measures of overall compliance and compliance over time will be derived for the global QoL score. These will be based upon:

- Received forms = number of EORTC QLQ-C30 / EORTC QLQ-PAN26 questionnaire forms received back plus the number not received back where the reason was 'Subject too affected by symptoms of disease under investigation'.

- Expected forms = number of patients still under QoL follow-up at the specified assessment time excluding patients in countries with no available translation.

- Evaluable forms = subset of expected EORTC QLQ-C30 / EORTC QLQ-PAN26 questionnaire forms with at least one subscale that can be determined; or where the reason questionnaire not completed is ticked as 'Subject too affected by symptoms of disease under investigation'.

Thus the compliance rate for QLQ-C30 and for QLQ-PAN26 is defined as number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline EORTC QLQ-C30 / EORTC QLQ-PAN26 questionnaire form. In addition, an overall compliance rate defined as number of patients with an evaluable baseline and at least one evaluable follow-up, divided by the number of patients expected to have completed at least a baseline for both, the EORTC QLQ-C30 **AND** EORTC QLQ-PAN26 questionnaire form, will be calculated.

Compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

3.4 Safety

Safety and tolerability will be assessed in terms of AEs (including serious AEs [SAEs]), deaths, laboratory data, vital signs, ECGs, physical examination, ECOG performance status, and exposure. These will be collected for all patients.

3.4.1 Adverse events

Adverse events and SAEs will be collected throughout the study, from informed consent until 30 days after the last dose of olaparib/placebo. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Other significant adverse events

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 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

3.4.2 Treatment exposure

Exposure will be defined as follows:

Total (or intended) exposure of olaparib/placebo:

- Total (or intended) exposure in days = last dose date - first dose date + 1

Actual exposure of olaparib/placebo:

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above. Dose interruptions are any periods when the patient does not take any treatment.

To calculate actual exposure, dose interruptions will include those where a patient forgot to take a dose.

Number of days on 300 mg olaparib/placebo bis in die (bid)

- Number of days on 300 mg olaparib/placebo bd = actual exposure for the dose assigned. Any days with changes in doses will not be counted.

Compliance will be assessed by calculating the actual administration days (total planned days - days of interruption) divided by the total planned administration days (last dose date - first dose date + 1) in percent. In addition, patient's individual drug accountability will be listed.

3.4.3 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression. Both will be derived using study treatment data up to the date of objective disease progression as defined by RECIST using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this will not be included in the derivation of dose intensity.

RDI and PID will be defined as follows:

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

- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended (or planned) cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

3.4.4 Laboratory data

Laboratory data will be collected throughout the study, from screening to 30-day follow-up visit as described in Appendix B. Blood and urine samples for determination of pregnancy, haematology, clinical chemistry, and urinalysis will be collected as described in Section 5.2.1 of the CSP. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.5 Electrocardiograms

Electrocardiogram data will be collected during screening within 7 days prior to starting study treatment and when clinically indicated afterwards. For derivation of post baseline visit values considering visit window and how to handle multiple records present in any visit window, derivation rules as described in Section 3.4.9 below will be used.

3.4.6 Vital signs

Vital signs data including body temperature, height, weight, pulse and blood pressure will be collected as described in Appendix B. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.7 Physical examination

Physical examination data including 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 will be collected as described in Appendix B.

3.4.8 ECOG performance status

ECOG data will be collected as described in Appendix B. For derivation of post baseline visit values considering visit window, derivation rules as described in Section 3.4.9 below will be used.

3.4.9 General consideration for safety assessments

Time windows will need defining for any presentations that summarise values by visit. The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit

of the first post-baseline visit will be Day 2). The equation to be used to calculate the time windows for each post-baseline visit is:

Lower limit of interval=Upper limit of previous visit's time window +1

Upper limit of interval=Nominal day at visit + ([nominal day at $visit_{i+1}$ - nominal day at $visit_i$]/2), where i = 3, 4, 5, 5.1, 5.2..., etc.

If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

For example, the visit windows for vital signs data with 28 days between scheduled assessments are:

- Day 29, visit window 2 – 42
- Day 57, visit window 43 – 70
- Day 85, visit window 71 – 98
- Day 113, visit window 99 – 126
- ...

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit-based summaries:
  - If there is more than one value per patient within a time window, then the closest value should be summarised, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group visit data should only be summarised if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed. For example, if 150 patients were dosed in the study (1/3*150 = 50), data at a particular visit would be summarised if the number of observations is greater than min (20, 50). This would be in each treatment group. Eg, if olaparib arm at Visit 6 has > 20 observations and placebo arm has < 20 observations, the visit data will be summarised for the olaparib arm but not the placebo arm. If both had < 20 patients, the data for that visit will be presented as 'NC' (Not Calculated).

- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.

- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment (olaparib or placebo). For laboratory data and vital signs data, any assessments made on day 1 will be considered pre-dose. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment (olaparib or placebo).

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (ie, below the lower limit of quantification) or "> x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

3.5 Resource Use

Resource use outcome variables include the following:

- Total number of hospitalisations
- Length of hospital stay
- Reasons for hospitalisation
- Total number of ICU admissions
- Length of any time spent in an intensive care unit (ICU)
- Reasons for ICU admission

The length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date when occurred during hospital stay) and the start date of hospitalisation or start of study drug if the start of study drug is after start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). Patients with missing discharge dates will be calculated as the difference between the last day with available data (if possible, the very first confirmed date outside hospital will be used as discharge date) and the start date of hospitalisation.

Sum of total duration of hospital stay will be considered for analysis if patient was admitted to hospital more than one time during study period.

Hospital and ICU admissions will be counted as a single event if a patient is re-admitted within 24 hours.

The length of ICU stay will be calculated using the same method as detailed above for the length of hospital stay.

4 ANALYSIS METHODS

4.1 General Principles

Efficacy data will be summarised and analysed using the FAS on an ITT basis while HRQoL data will be analysed using the PRO analysis set (see Section 2.1). In addition, as sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless specified otherwise.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set. The safety data will be summarised descriptively and will not be formally analysed.

4.1.1 Presentation of results in summary tables

If not stated otherwise, tabulations will be presented by treatment group as follows:

- Olaparib 300 mg bd
- Placebo bd
- Total

Data listings will include at least the following details:

- Patient identifier
- Centre identifier
- Actual / randomised treatment group

Data listings will be sorted by actual treatment group and patient ID, if not stated otherwise.

4.2 Analysis Methods

A single interim PFS analysis for futility and superiority will be performed when 50% of the final number of progressions has been reached (approximately 45 PFS events). A final PFS analysis will be performed when approximately 89 progression events have occurred (~60% maturity). No further analyses of PFS are planned beyond this point.

Two interim analyses for OS will be performed; the first at the time of the interim PFS analysis (approximately 45 PFS events) and the second at the time of the final PFS analysis (approximately 89 PFS events). A final analysis of OS will be performed when approximate 106 death events have occurred.

Individual efficacy response data will be listed in a by-patient listing.

Timing of the statistical analysis is given in Table 9.

Table 9 Timing of Statistical Analyses

Timing of analysis	Outcome Variable
Interim PFS when ~45 PFS events reported	PFS PFS2, TDT, TFST, TSST, OS, and time to deterioration and improvement rate of global health status / QoL and pancreatic cancer symptom scale.
Final PFS when ~89 PFS events reported	PFS, PFS2, TDT, TFST, TSST, OS, and time to deterioration and improvement rate of global health status / QoL and pancreatic cancer symptom scale.
Final OS when ~106 OS events reported	PFS2, TFST, TSST, OS, and - time to deterioration and improvement rate of global health status / QoL and pancreatic cancer symptom scale.

Safety variables will be analysed at each analysis time point.

The treatment comparison is olaparib 300 mg bid versus placebo.

The following table details which efficacy endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 10 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS	**Primary analysis**: log-rank test using BICR data
	Key sensitivity analyses: log-rank test using BICR data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
	Additional sensitivity analyses:
	1) Evaluation time bias analysis; log-rank test using BICR data
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data
	4) Deviation bias analysis; log-rank test using BICR data
OS	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)

Table 10 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
	Supportive analysis: Kaplan-Meier (KM) plot of time to censoring for OS
PFS2	**Primary analysis**: log-rank test using investigator assessment of second progression
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TDT	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TFST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TSST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
Time to deterioration in global QoL (as measured by the global QoL score from the EORTC QLQ-C30 questionnaire) and in pancreatic symptoms (EORTC QLQ-PAN26	**Primary analysis**: log-rank test
	Sensitivity analysis: Attrition bias analysis (using alternative censoring rules); log rank test
Improvement rate in global QoL and in pancreatic symptoms (EORTC QLQ-PAN26	**Primary analysis:** Logistic regression model

4.2.1 Multiplicity

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS and OS will be tested at a 1-sided significance level of 2.5%.

In addition to these planned analyses, which will be performed and reported in the CSR, in order to strongly control the type I error at 2.5% 1-sided for key label claims, a multiple testing procedure (MTP) will be employed across the primary endpoint (PFS) and key secondary endpoint (OS).

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha 2.5% 1-sided) and key secondary endpoints of OS will then be tested using a MTP with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 1).

The MTP is detailed below.

Figure 1 Multiple Testing Procedure

One interim efficacy analysis for PFS is planned at the time when approximately 45 PFS events (50% of the total 89 PFS events required for the final analysis) have occurred. The test mass alpha for PFS (1-sided 2.5%) will be split between the final and interim analysis using a bespoke spending function where a fixed significance level of 0.5% 1-sided alpha will be assigned at the interim and the remaining significance level assigned to the final analysis, taking into account of correlation (Stone 2010). Statistical significance will be declared at the interim analysis if the 1-sided $p<0.005$. If the null hypothesis for PFS is not rejected at the interim analyses time point then PFS will be tested again when approximately 89 PFS events have occurred. To ensure that the type I error will be controlled at 2.5% 1-sided level, if the interim occurs at exactly 45 PFS events and the final analysis at 89 PFS events accounting for the actual correlation between the interim and final PFS analyses, then the 1-sided significance level to be applied for the final analysis would be 2.26% (Stone 2010). If PFS is significant at either the interim or final analyses, the full test mass (alpha) will be carried forward to OS.

The OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. Two interim analyses for OS will be performed; the first at the time of the interim PFS analysis (approximately 45 PFS events) and the second at the time of the final PFS analysis (approximately 89 PFS events). A final analysis of OS will be performed when approximately

106 death events have occurred. Statistical significance for OS will be declared at the first interim analysis for OS if the null hypothesis for PFS is rejected and the observed p-value for OS is $p<0.00005$. If the null hypothesis for OS is not rejected at this first interim analysis, then statistical significance for OS will be declared at the next interim analysis (final analysis of PFS) if the null hypothesis for PFS has been rejected and the observed 1-sided p-value for OS is <0.01499. The final significance level will be determined accounting for the actual correlation between the interim and final OS analyses. For example, to ensure that the type I error will be controlled at the 2.5% 1-sided level, if the interim analyses occur at exactly 30% and 57% of events respectively and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final analysis would be 1.53%.

Table 11 shows the expected nominal p-values required to produce a significant result at each of the planned analyses. Note that the actual nominal significance level at final analysis will depend on the exact number of patients analysed (information fraction).

Table 11 1-Sided Significance Levels and Critical Values for PFS and OS to Control Type-I Error at 2.5% Across Multiple Time Points

kth-Stage	PFS			OS		
	1-sided significance level	Expected events	Critical HR	1-sided significance level	Expected events	Critical HR
1	0.005	~45	0.46	0.00005	~32	0.22
2	0.0226	~89	0.65	0.01499	~60	0.56
3	---			0.0153	~106	0.65

Assumes: 50% of final PFS events at k=1 for PFS; 30% and 57% of final OS events at k=1 and 2 for OS. Note, the null hypothesis for OS could not be rejected if PFS hurdle is not met. The significance levels at k=2 for PFS and k=3 for OS will be adjusted to account for the correlation between final and interim analysis while the significance levels at k=1 for PFS and k=1, 2 for OS will be fixed and does not account for patient accrual.

Summary tables of hierarchical testing after approximately 50% progression events and 57% death events will be provided.

4.2.2 Primary variable - progression free survival

A summary of PFS will be prepared to present the number of patients with progression and no progression. Tabulation will detail the total number of progressions and no progressions, the number of patients with progression identified by RECIST (separately for TLs, NTLs, and new lesions) and death as well as details about non-progressed patients including the number of patients progression-free at time of DCO, lost to follow-up, withdrawn consent, and prematurely censored (RECIST or death) if they did not progress and if the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date. The summary will be presented by treatment group.

The PFS as defined in Section 3.2.1 will be analysed using a log-rank test for generation of the p-value and using the Breslow approach for handling ties in the following manner:

```
PROC LIFETEST DATA=...;
  TIME pfsTime*censor(1);
  TEST trtn;
RUN;
```

By using the TEST-Statement within LIFETEST procedure the test statistics U and the covariance matrix will be averaged over the possible orderings of the tied failure times (SAS Lifetest 2008).

The HR and its CI will be estimated from the log-rank (U and V statistics) follows directly from the LIFETEST model as used above for calculation of p-values (Berry et al 1999 and Sellke et al 1983)

$$HR = EXP\left(\frac{U}{V}\right)$$

$$95\%\ CI = \left[EXP\left(\frac{U}{V} \pm \frac{1.96}{\sqrt{V}}\right)\right]$$

Where $U = \sum_i (d_{1j} - e_{1j})$ is the log-rank test statistic (with d_{1j} and e_{1j} the observed and expected events in group 1); and V the variance of the log-rank test statistic. U and V will be obtained directly from LIFETEST procedure; U will be taken from the table "*Rank Statistics*" while V will be taken from the table "*Covariance Matrix for the Log-Rank Statistics*".

The log-rank test statistic, the HR (olaparib vs. placebo) together with its corresponding 95% CI and p-value will be presented (a HR less than 1 will favour olaparib).

The median and 95%-CI of PFS and the proportion of patients progression-free at 6 months, 12 months will be summarised and presented by treatment group.

In addition, duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to be non-progressor) in censored (not progressed) patients only, presented by treatment group.

The following KM plots of PFS will be presented by treatment group. The KM plot will be prepared using LIFETEST procedure and selecting ODS graphics. The plot will identify censored patients using a different symbol and include patients at risk at specific time points:

- PFS
- PFS with censoring and event flags reversed

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 producing 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 complementary log-log plot will be directly produced in SAS LIFETEST procedure using ODS graphics option PLOTS=(LLS) in the PROC-Statement. The graph will be assessed visually. Two parallel lines favour the proportionality assumption. To support the proportionality assessment a Cox proportional hazard's model will be constructed containing the interaction of treatment and the logarithm of PFS (treatment*log(PFS)). The p-value obtained from the Wald Chi-squared test for the time dependent covariate will be presented. The following SAS-code may be used:

```
PROC PHREG DATA=...;
  CLASS trtn (REF='placebo') / PARAM=REFERENCE;
  MODEL pfs*censor(1)=trtn timeDependent / TIES=EFRON;
  timeDependent = trtn*LOG(pfs);
  proportionality_test: TEST timeDependent;
RUN;
```

A further analysis of PFS (using investigator assessed RECIST) may be performed at the time of the final OS analyses, if requested by health authorities. A final decision will be made at the BDRM for the final OS analysis.

4.2.2.1 Progression-free survival sensitivity analyses

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test. The same methodology and model will be used as for the primary analysis and the HR and associated 95% CI will be reported. A KM plot of PFS in this subset of patients will be presented by treatment group.

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) 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 their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

A KM plot of the time to censoring where the censoring indicator of the primary PFS analysis is reversed will be produced (called median time to follow-up where events will be censored and previously censored patients will be treated as events).

A by-patient listing will be produced similar to the PFS listing but including only patients who progressed but were censored for the primary analysis due to missing of two, or more, non-evaluable tumour assessments. The actual PFS times will be reported.

(b) Evaluation-time bias

A sensitivity analysis 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 log-rank test, as described for the primary analysis of PFS, will be repeated using the midpoint between the time of progression and the previous evaluable RECIST assessment to derive PFS time for patients with RECIST progression events. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Chen and Sun 2010). This approach will use the BICR RECIST assessments.

To support this analysis, the individual mean time difference between RECIST assessments (patient inter-assessment times) will be calculated and summarised using descriptive statistics.

(c) Ascertainment bias

The primary analysis of PFS (log-rank test) will be repeated using investigator assessed RECIST data. The HR and 95% CI will be presented.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the investigator review as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the investigator review as a proportion of all discrepancies.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using investigator assessments, the proportion of patients with site but no central confirmation of progression will be summarised by treatment group and the primary analysis will be repeated for this subset of patients. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists. Discrepancy between the primary analysis using BICR assessments and investigator assessments of progression will be discussed at the BDRM. The study team will decide whether the discrepancy between assessments is of importance and whether or not additional analyses are required.

A by-patient listing will be produced to present patients where at least one assessment differs between investigator and central reviews of RECIST progression.

(d) Deviation bias

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with "important" deviations that may affect the efficacy of the trial therapy will be performed if the following deviations were reported for > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A log-rank test will be repeated using the BICR RECIST data, using the same method as described for the primary analysis of PFS. The HR and 95% CI will be presented.

The treatment status at progression by patients who have progressed / censored including the number of patients and percentage of on-treatment or discontinued will be tabulated. The number of days from treatment discontinuation to progression for patients who have discontinued treatment will be summarised descriptively. Data will be presented by treatment group.

Patients censored for progression at more than 14 weeks before the DCO ('censored > 14 weeks before DCO', 'censored <= 14 weeks before DCO') will be tabulated and presented by treatment group.

A by-patient listing will be produced including patients with an important deviation only.

4.2.2.2 Progression-free survival subgroup analyses

Subgroup analyses will be conducted comparing PFS between treatments. 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 PFS will not be formally analysed. In this case, only descriptive summaries will be provided.

The following subgroups will be analysed for PFS:

- Type of previous chemotherapy (doublets vs. triplets); Reference=doublets
- Time on first-line treatment till randomisation (≤ 6 months vs > 6 months); Reference=≤6 months
- Best response on first-line treatment (SD vs PR/CR); Reference=SD

These will be determined from the "Previous Cancer Therapy" (CAPRX) module of the eCRF at screening.

- Measurable versus non measurable disease / NED at baseline; Reference=non measurable disease / NED at baseline

This will be determined from the "Tumour Evaluation Target Lesions RECIST1.1 - Baseline" (RECIST11) module of the eCRF at screening.

- BRCA mutation type, eg, BRCA1, BRCA2 or BRCA1/2 (both); Reference=BRCA1

This will be determined from the Myriad central laboratory test data transfer. If there are less than 20 events in the "BRCA1/2 both" category, these patients will be excluded from this analysis.

- Age at randomisation (>= 65 vs. < 65); Reference=< 65
- Race; Reference=White
- Sex; Reference=Male

These will be determined from the "Demography" (DEM) module of the eCRF at screening.

Other baseline variables may also be assessed if there is clinical justification. A final decision will be made at the BDRM.

For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (TIES = Efron) that contains the treatment group, factor (subgroup) and treatment-by-factor interaction term. Reference cell coding will be used introduced by the PARAM=REFERENCE option in the CLASS-Statement. Individual reference levels will be defined using the REF= option within the CLASS-Statement for each subgroup. The treatment effect HRs for each treatment comparison along with their CIs will be obtained for each level of the subgroup from this single model. Analysis will be carried out using PHREG procedure in SAS in the following manner:

```
PROC PHREG DATA=...;
  CLASS trtn (REF='placebo') chemoType (REF='doublets')
    / PARAM=REFERENCE;
  MODEL pfs*censor(1)=trtn chemoType trtn*chemoType
    / TIES=EFRON;
RUN;
```

The HRs and 95% CIs will be presented in an overview table as well as on a forest plot including the HR and 95% CI from the overall population (using the HR and 95% CIs from the primary analysis).

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 PFS.

A by-patient listing will be produced for presenting individual PFS data.

4.2.3 Overall Survival

A summary of survival status at the time of analysis will be produced. This will summarise the number of patients who have died, who are still in survival follow-up, who are lost to follow-up or who have withdrawn consent. Results will be presented by treatment group.

Overall Survival as defined in Section 3.2.2 will be analysed at the time of the interim and final analysis for PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 20 deaths], if not descriptive summaries only will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

Median Overall Survival will be summarised including the number of deaths, and survival at month 6 and 12. Results will be presented by treatment group.

The sensitivity analyses outlined for PFS in Section 4.2.2 will not be repeated for OS with the exception of a KM plot. Two KM plots will be produced. The first KM plot will show time to censoring of OS and the second KM plot will show will show time to censoring where the censoring indicator is reversed (median time to follow-up where events will be censored and previously censored patients will be treated as events).

Overall Survival data will be listed in a by-patient listing.

Overall Survival effect at the final analysis

A predicted treatment effect for OS at the final OS analysis will be calculated in a supportive analysis to assist in quantifying the treatment effect for PFS in terms of a clinical benefit at the time of the PFS analysis (interim and final) when the OS analysis would still be underpowered. This predicted OS effect, $\hat{\Delta}_I$,will be derived using a weighted sum of the observed OS effect and an estimate of the OS effect using observed PFS data at the time of the PFS analyses (interim and final) in the following way (see Chen and Sun 2011):

$$\hat{\Delta}_I = w\Delta_{OS} + (1-w)\Delta_p \quad (1)$$

with

$$\Delta_p = \rho\Delta_{PFS} \quad (2)$$

$$w = \frac{Var(\hat{\Delta}_P)}{Var(\hat{\Delta}_P)+\hat{\sigma}^2_{OS}} \quad (3)$$

$$Var(\hat{\Delta}_P) = \hat{\rho}^2\hat{\sigma}^2_{PFS} + \hat{\Delta}^2_{PFS}\hat{\sigma}^2_{\hat{\gamma}} + \hat{\sigma}^2_{\hat{\gamma}}\hat{\sigma}^2_{PFS} \quad (4)$$

where

- $\hat{\Delta}_J$ is the predicted OS treatment effect at the final analysis. This will be referred to as the predicted OS effect (average weighting).
- w is the weight, based on the inverse of the variance (ie, those studies included in the assessment of the relationship between PFS and OS based on historical data with more uncertainty will be given less weight).
- $\hat{\Delta}_{OS}$ is the observed treatment effect (ln HR) for OS (see Section 4.2.3).
- $\hat{\Delta}_P$ is the natural estimate of the OS effect (ln HR) based on the historical relationship in effect size.
- $\hat{\rho}$ represents the estimated slope relating PFS to OS from historical data (ratio of OS effect to PFS effect on natural log scale), and $\hat{\sigma}^2_{\hat{\gamma}}$ (> 0) is the corresponding standard error.

Historical data from Phase III studies and large Phase II studies (>40 patients per arm) comparing treatments for metastatic pancreatic cancer will be included. A simple linear regression model weighted by the size of the trial (where size = number of OS events [Sabin et al 2014]) will be constructed with the intercept assumed to be zero to obtain estimates of the slope and standard error. Full details including a list of studies to be included and all relevant model specifications and derivations will be described in a separate plan, which will include the details of the correlation between PFS and OS in historical advanced pancreatic cancer data under the responsibility of AstraZeneca.

- $\hat{\Delta}_{PFS}$ is the observed treatment effect (ln HR) for PFS (see Section 4.2.3).
- $\hat{\sigma}^2_{OS}$ is the variance estimate for observed OS treatment effect (on natural log scale).
- $\hat{\sigma}^2_{PFS}$ is the variance estimate for observed PFS treatment effect (on natural log scale).

In addition, a predicted OS effect using a more conservative weighting which will take into account any residual variability from the linear regression model on historical data, will also be calculated. The variance of $\hat{\Delta}_P$ will include a term, $\hat{\sigma}^2_{res}$, to incorporate this:

$$Var(\hat{\Delta}_p) = \rho^2\theta_{PFS}^2 + \hat{\Delta}_{PFS}^2\theta_\gamma^2 + \theta_\gamma^2\theta_{PFS}^2 + \theta_{res}^2 \quad (4')$$

The predicted OS effect based on a more conservative weighting using the variance (4') will be referred to as the predicted OS effect (*alternative weighting*).

Assume asymptotic normality for the test-statistic $\hat{Z}_J$, each predicted OS effect, $\hat{\Delta}_J$, will be considered statistically significant at the 2.5% (one-sided) level if

$$\hat{Z}_J = \frac{\hat{\Delta}_J}{\sqrt{Var(\hat{\Delta}_J)}} < Z_{0.025} = 1.96$$

with

$$Var(\hat{\Delta}_J) = w^2\theta_{OS}^2 + (1-w)^2 Var(\hat{\Delta}_p) + 2w(1-w)\,\rho\rho\theta_{OS}\theta_{PFS} \quad (5)$$

where ρ is an estimate of the correlation between θ_{OS}^2 and θ_{PFS}^2 (the observed treatment effects for OS and PFS) and will be estimated via a bootstrapping method performed on the observed data. Datasets with the same number of patients as the overall study will be created from sampling pairs of PFS and OS data. For each dataset, the PFS and OS treatment effects (ln HRs) will be calculated. This will be repeated 10,000 times and a linear regression analysis performed to estimate the correlation between PFS and OS, ie, ρ.

The estimates of both the predicted OS effect (*average weighting*) and the predicted OS effect (*alternative weighting*), together with 95% CIs and p-values will be presented.

4.2.4 Time from randomisation to second progression

The status of PFS2 as defined in Section 3.2.3 will be summarised by the number and percentage of patients experiencing a PFS2 event and the type of progression (objective progression by RECIST, symptomatic progression or death). Results will be presented by treatment group.

The analysis of PFS2 will use the same methodology and model as the primary analysis of PFS. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

A KM plot of PFS2 will be provided by treatment group. A KM plot of the time to censoring where the censoring indicator of the PFS2 analysis is reversed will be produced (called median time to follow-up where events will be censored and previously censored patients will be treated as events).

As a key sensitivity, the analysis of PFS2 will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

The median and 95%-CI of time to PFS2 and the proportion of patients progression-free at 6 months, 12 months will be summarised and presented by treatment group.

Median time and 95% CI from PFS2 to previous investigator assessment will be summarised by treatment group.

A by-patient listing will be produced including details about time of second progression.

4.2.5 Time to first subsequent therapy or death

The TFST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group.

As a key sensitivity, the analyses of TFST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. A KM plot of TFST in this subset of patients will be presented by treatment group.

The time between progression and starting subsequent therapy will be summarised.

In addition, best overall RECIST response to first subsequent therapy by treatment group will be provided.

Individual TFST will be presented in a by-patient listing.

4.2.6 Time to second subsequent therapy or death

The TSST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group.

As a key sensitivity, the analyses of TSST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. KM plots of TSST in this subset of patients will be presented by treatment group.

In addition, best overall RECIST response to second subsequent therapy by treatment group will be provided.

Individual TSST will be presented in a by-patient listing.

4.2.7 Time to study treatment discontinuation or death

The TDT will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group.

As sensitivity, the analyses of TDT will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. A KM plot of TDT in this subset of patients will be presented by treatment group.

Individual TDT will be presented in a by-patient listing.

4.2.8 Best overall RECIST response and objective response rate

For each treatment group, BoR as defined in Section 3.2.7 will be summarised by n (%) for each category (CR, PR, SD, NED, PD, NE). No formal statistical analyses are planned.

The ORR as defined in Section 3.2.8 will be summarised and analysed (ie, number of patients [%]) by treatment group, in patients in the FAS (ITT population) with measurable disease at baseline. Any patients who experienced CR or PR which was first observed whilst receiving subsequent therapy after discontinuation of olaparib will be identified. The denominator for the response rate will be measurable disease at baseline as defined by the BICR data. The ORR will be analysed using a logistic regression model. The model will include a binary variable as response (response=1; no response =0) and treatment group as explanatory variable in the MODEL-Statement together with the option CLPARM=PL to compute profile likelihood CIs and p-values. Explanatory variables will be introduced using a reference cell coding (option PARAM=REFERENCE) while the option REF= will be used to identify the reference. The following provides sample SAS code for implementing the analysis:

```
PROC LOGISTIC DATA=… ALPHA=0.05;
   CLASS trt(REF='PLACEBO') / PARAM=REFERENCE;
   MODEL improvement (EVENT='1') = trt / CLPARM=PL;
   EXACT trt / ESTIMATE;
RUN;
```

If the overall response rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall response rate is low (< 20%) a Fisher's exact test (for an example SAS code see below) will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

```
PROC FREQ DATA=…;
   TABLE improvement * trt / FISHER;
   EXACT OR / ALPHA=0.05;
RUN;
```

In addition, the duration and onset of objective response in patients with objective response will be summarised by treatment group. Duration and onset of objective response is defined as time from the first documentation of CR/PR until the date of progression, or the last evaluable RECIST assessment for patients that do not progress.

BoR will be presented in a by-patient listing. In addition, a listing will be prepared including objective responders (confirmed CR or PR) only.

4.2.9 Disease control rate

The DCR as defined in Section 3.2.9 will be summarised (ie, n, %) by treatment group. The DCR will be presented based on the BICR data and also the investigator recorded data.

4.2.10 Target lesion summary and other efficacy

Target lesion size, and percentage change from baseline will be summarised by treatment group and time point using descriptive statistics. The best change in TL will be presented in a waterfall plot for each treatment group separately. The best change in TL size is the maximum reduction from baseline or the minimum increase from in the absence of a reduction. Lesion data will be listed in a by-patient listing.

Subsequent cancer therapy relative to progression will be summarised using frequency counts and percentages. The tabulation will detail any patients receiving any further therapy for cancer by time of therapy ('After progression', 'Before progression', 'No progression'). Tabulation will include the number of patients where no subsequent cancer therapy was recorded as well. Data will be presented by treatment group.

4.2.11 Patient reported outcomes

The analysis population for PRO data will be the PRO analysis set as defined in Section 2.1. Derivations and rules for transformation of PRO data are defined in Section 3.3.

Impact of olaparib on HRQOL

The impact of olaparib on HRQOL will be assessed through an analysis of the global health status / QoL gathered from items 29 and 30 of EORTC QLQ-C30 while pancreatic pain will be assessed through items 31, 33, 34, 35 of EORTC QLQ-PAN26.

Descriptive statistics including change from baseline score will be produced by time point for the EORTC QLQ-C30 global health status / QoL and EORTC QLQ-PAN26 pancreatic pain scores. Results will be presented by treatment group. Arithmetic mean (± standard deviation) plots of scores versus time point will be produced in linear scale.

Frequency tables will be prepared to present the number of patients (and percentages) with a deterioration and improvement in global health status / QoL and pancreatic cancer symptoms scores. Results will be presented by treatment group.

Time from randomisation to first global health status / QoL and pancreatic cancer symptoms scale deterioration will be analysed using the same methodology and model as described for the primary analysis of PFS including a KM-Plot. However, sensitivity analyses will not be performed (with the exception of attrition bias). Results will be presented by treatment group.

Global health status / QoL and pancreatic pain scores improvement rate will be analysed using a logistic regression model. The model includes a binary variable as response (improvement=1; no improvement=0) and treatment group as an explanatory variable in the MODEL-Statement together with the option CLPARM=PL to compute profile likelihood CIs and p-values. Explanatory variables will be introduced using a reference cell coding (option PARAM=REFERENCE) while the option REF= will be used to identify the reference. The following provides sample SAS code for implementing the analysis:

```
PROC LOGISTIC DATA=… ALPHA=0.05;
   CLASS trt(REF='PLACEBO') / PARAM=REFERENCE;
   MODEL improvement(EVENT='1') = trt / CLPARM=PL;
   EXACT trt / ESTIMATE;
RUN;
```

If the overall improvement rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall response rate is low (< 20%) a Fisher's exact test (for an example SAS code see below) will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

```
PROC FREQ DATA=…;
   TABLE improvement * trt / FISHER;
   EXACT OR / ALPHA=0.05;
RUN;
```

In addition, a summary table of global health status / QoL and pancreatic pain best change rates will be provided (improvement, worsening, no change).

As supportive analyses, change from baseline in global health status / QoL and pancreatic symptoms scale scores will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit. The study discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, centre, visit and treatment by visit interaction as explanatory variables and the baseline score as a covariate. Treatment, visit and treatment by visit interaction will be fixed effects in the model; centre will be a random effect. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-patient error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample SAS code for implementing the MMRM analysis:

```
PROC MIXED DATA=… METHOD=REML;
   CLASS trt centre visit patient;
   MODEL cfb = trt visit centre trt*visit base / S DDFM=KR;
   REPEATED visit / TYPE=UN SUBJECT=patient;
   RANDOM intercept / SUBJECT=centre;
   LSMEANS trt*visit / SLICE=visit PDIFF ALPHA=0.05 CL;
RUN;
```

where TRT is the treatment group, CENTRE is the centre, VISIT is the visit, CFB is the change from baseline in the global health status / QoL (separately the PAN26) score, and BASE is the baseline score.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, and autoregressive. If there are still issues with the fit of the model or estimation of the treatment effects, CENTRE will be treated as a fixed effect and the RANDOM-Statement removed.

The adjusted mean estimates (obtained from LSMEANS-Statement as the calculated least square means are adjusted for the random component of the model) and corresponding 95% CIs will be presented by visit for each treatment group.

A by-patient listing will be produced presenting the EORTC QLQ-C30 global health status / QoL scale. A separate by-patient listing will be produced for EORTC QLQ-PAN26 scales. Listings will include the items of interest and the transformed scales by time point.

Compliance

The EORTC QLQ-C30 and EORTC QLQ-PAN26 compliance (overall compliance and by visit compliance) will be summarised and presented by treatment group.

4.2.12 Exploratory analyses

EORTC QLQ-C30 functional and symptom scales and EORTC QLQ-PAN26 scales

The analysis as described above to assess the impact of olaparib on HRQoL will be repeated for EORTC QLQ-C30 functional and symptom scales as well as for EORTC QLQ-PAN26 scales. This involves the following analysis:

- Descriptive statistics including change from baseline
- Frequency table of deterioration and improvement
- Arithmetic mean (±standard deviation) plots of scores versus time point
- Analyses of time to deterioration
- Analyses of improvement rate

- Analyses of compliance

Supportive analyses (of time to first deterioration and improvement rates) will be performed for the individual EORTC QLQ-C30 functional scales (physical, role, cognitive, emotional, social). Treatment estimates and 95% CI for each domain will be presented on forest plots (one for HRs of time to deterioration and one for odds ratios of improvement rate). P-values will not be calculated for these supportive analyses. These additional sub-scales are considered exploratory to support the primary EORTC QLQ-C30 global QoL and will be used to assess whether any observed differences in the global measure are driven by particular domains of functioning, symptoms, or group of symptoms.

A by-patient listing will be produced presenting the EORTC QLQ-C30 functional and symptom scales. A separate by-patient listing will be produced for EORTC QLQ-PAN26 scales. Listings will include the items and the transformed scales by time point.

EuroQoL five dimensions, five level health state utility index

EuroQoL five dimensions, five level health state utility index (EQ-5D-5L) and visual analogue scale data will be analysed using the PRO analysis set.

Five level health state utility index will be tabulated by presenting the baseline and the worst status during treatment. Visual analogue scale (VAS) for health status will be summarised using descriptive statistics. The change from baseline and the percentage change from baseline will be calculated for each time point and presented by actual treatment group. The VAS will be presented graphically using arithmetic mean (±standard deviation) plot.

By-patient listings will be produced presenting the individual EQ-5D-5L raw scores and review assessments.

Resource use

Total length of hospital stay and total length of ICU stay (number of days) will be summarised by randomised treatment group. Total number of nights spent in hospital and in ICU, the number of hospitalisations and reasons for hospitalisation will also be summarised by randomised treatment group.

A by-patient listing will be produced presenting details of hospital and ICU stay.

ECOG

A by-patient listing will be produced presenting details of ECOG performance status.

Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analysis

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. Decision will be made at the BDRM.

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 patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the analyses. Further detail will be provided in the Payer Analysis Plan under the responsibility of AstraZeneca. These analyses are intended to support reimbursement appraisals.

Biomarkers

If available, individual biomarker will be listed in a by-patient listing.

4.2.13 Safety

Safety data will be summarised and listed only. No formal statistical analyses will be performed on the safety data. All safety data will be summarised by actual treatment group (olaparib or placebo). However, some listings such as AEs listings will display the actual dose the patient received at onset of an AE.

Adverse events

All AEs, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and Common Toxicity Criteria for Adverse Events (CTCAE) grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment group. MedDRA dictionary will be used for coding. Any AE occurring before olaparib/placebo treatment (ie, before Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined as 30 days following discontinuation of olaparib/placebo treatment. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment will also be included in the AE listings, but not in the summary tables.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each PT will be presented (ie, multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percent of patients by actual treatment) will be tabulated for:

- All AEs

- All AEs causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to study medication
- AEs with outcome of death
- AEs with outcome of death causally related to study medication
- All SAEs
- All SAEs causally related to study medication
- DAEs
- AEs leading to discontinuation of olaparib/placebo, causally related to study medication
- OAEs
- Other significant AEs causally related to study medication

An overall summary of the number and percentage of patients in each category will be presented, as will an overall summary of the number of episodes in each category.

In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarised by PT, by decreasing frequency. This cut-off may be modified after review of the data.

Each AE event rate (per 1000 patient years) will also be summarised by PT within each system organ class (SOC). The event rate will be calculated as the number of patients with that AE divided by the sum of the duration of therapy (for patients without the event) and the time to the AE (for patients with the event) in each group multiplied by 1000. The denominator defines the time at risk for an event with:

- Duration of therapy (days) calculated as:
  MINIMUM([date of last dose + 30-day safety follow-up period], OS date, DCO) – date of first dose + 1
- Time to the AE (days) calculated as date of first occurrence of the AE – date of first dose + 1 (in days)

$$eventRate_{PT} = \frac{\#patients_{PT}}{\sum durationTherapy_{\neq PT} + \sum timeToAE_{PT}} * 1000$$

PT =Patients with the event reported; eg, all patients with an AE where PT equals to 'Headache'.

$\neq PT$ =Patients without the event; eg, all patients who never experienced an AE where PT is equal to 'Headache'.

AEs will be assigned CTCAE grades (National Cancer Institute CTCAE version 4.0) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and actual treatment group. Tabulation will be repeated to present AEs with a CTCAE grade 3 or higher and separately those AEs, causally related to study treatment by SOC and PT. Fluctuations observed in CTCAE grades within the same PTs during study will be listed.

Tabulation of AEs causally related to study treatment will be summarised by SOC and PT and presented by treatment group.

Summaries of the number and percentage of patients with AEs leading to dose change of olaparib/placebo and also dose interruptions of olaparib/placebo will be presented by PT and treatment group.

A summary table will be prepared presenting AEs which started prior to first dose or > 30 days following date of last dose by SOC and PT. Data will be presented by treatment group.

Death

A summary of all AEs resulting in deaths will be provided with number and percentage of patients by actual treatment group, categorised as:

- Related to disease under investigation
- AE outcome=death
- Both related to disease under investigation and with AE outcome=death
- AE with outcome=death ≥30 days after last treatment dose
- Deaths ≥ 30 days after last treatment dose, unrelated to AE or disease under investigation
- Patients with unknown reason for death

In addition, AEs with outcome of death will be summarised. The following summary tables will be prepared and presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT

- Death will be listed as part of TLFs for part 11 of the CSR

Serious AEs

The following SAE summaries and listings will be prepared. Summaries will be presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT
- Listing of key information

Discontinuation

AEs leading to discontinuation of study treatment will be summarised by SOC and PT. In addition, AEs leading to discontinuation of study treatment, causally related to study treatment will be summarised by SOC and PT. Details of AEs leading to discontinuation will be presented in a by-patient table.

Listings

By-patient listings will be produced as following:

- A by-patient listing of AEs
- A by-patient listing of AEs causally related to olaparib
- A by-patient listing of SAEs
- A by-patient listing of AEs with CTCAE grade 3 or higher (separately for causally related to olaparib)
- A by-patient listing of AEs leading to dose reduction or dose interruption
- A by-patient listing of AEs presenting any events that occur prior to dosing or starting more than 30 days after discontinuing therapy

Summary of Long Term Tolerability

To assess long term tolerability, prevalence plots, life table plots and cumulative incidence plots will be presented for:

- Nausea
- Vomiting
- Any other events considered important after review of the safety data, provided there are ≥ 5% events overall.

Data for nausea and vomiting will be listed in a by-patient listing.

For each AE, median time from randomisation to first onset of the AE (in days) will be presented by treatment group. Calculation will be done using the KM-technique. Patients who did not experience the AE will be censored at the end of their safety follow-up or DCO. Summary tables of time to first onset for each AE will also be produced (eg, 1-28 days, 29-56 days, 57-84 days, 85-112 days, >112 days). Median duration of the AE where each patient is represented for the first occurrence of a PT only will be presented in patients who experienced each AE. The end date of an AE should be defined as: MINIMUM(AE end date, [date of last dose + 30-day safety follow-up period], OS date, DCO).

Prevalence Plot

A prevalence plot provides information on the extent to which the events may be an ongoing burden to patients. The prevalence at time *t* after first dose of study treatment is calculated as the number of patients experiencing the event divided by the number of patients receiving study treatment or in safety follow-up at time *t*; generally, *t* is categorised by each day after dosing (*t*=0 at Day 1, which is the day of first dosing). Presented as formula:

$$prevalence_{PT,t} = \frac{\#patients_{PT,t}}{\#patients_{SF,t}}, \qquad t \geq 0$$

PT =Patients with the event reported at time t; eg, all patients with an AE where PT equals to 'Headache' at study day 11 (study day is relative to first dosing).

SF =All patients receiving study treatment or are in safety follow-up at time t.

The prevalence is plotted over time (in months) split by treatment group. Multiple occurrences of the same event are considered for each patient but a patient is only counted once in the numerator whilst they are experiencing one of the occurrences of the event.

Life-Table Plot

A life table plot can be used to describe the time to onset of the event and specifically when patients are at most risk of first experiencing the event. The hazard, or in other words, the probability of having an AE in a specified time period (eg, 0-1 months, 1-3 months, 3-6 months, etc.) given that the patient reaches that time period without having an event is plotted for each time period split by treatment group. The event rate is derived as the number of patients who had a first occurrence in that time period divided by the total number of patients receiving study treatment or are in safety follow-up who were event free at that time point. Presented as formula:

$$eventRate_{PT,t} = \frac{\#patients_{PT,t}}{\#patients_{SF,t}}, \qquad t \in \{'0\text{-}1', '1\text{-}3', '3\text{-}6', \ldots\}$$

PT =Patients with the event reported at time t; eg, all patients with an AE where PT equals to 'Headache' with first occurrence in time category '3-6' months.

SF =All patients event-free and receiving study treatment or are in safety follow-up at time t.

Cumulative Incidence Plot

A cumulative incidence plot is a plot of the raw cumulative incidence and cumulative incidence function (CIF) over time. Treatment groups will be presented on separate plots. The raw cumulative incidence is the actual probability that a patient will have experienced their first occurrence of the event by a given time point. The cumulative incidence function estimates the raw cumulative incidence if the DCO had not been imposed and all patients had completed safety follow-up. The CIF represents the probability that an individual will experience an event of type *i* by time *t* and can be calculated as following: (Pintilie M. 2006).

$$\hat{F}_i(t) = \sum_{all\ j, t_j \le t} \frac{d_{ij}}{n_j} \hat{S}(t_{j-1}), \text{ with}$$

$\hat{F}_i(t)$ = to be the empirical estimate of the CIF for the event of type *i*

d_{ij} = to be the number of events of type *i* that occur at time t_j

n_j = to be the number at risk at time t_j

$\hat{S}(t)$ = to be the KM-estimator of the probability of being free of any event by time t

$\hat{S}(t)$ can be obtained using PROC LIFETEST in SAS®. d_{ij} and n_j are time *j* and event *i* specific and can be calculated directly in SAS®.

Laboratory assessments

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

Shift tables for laboratory values by worst common toxicity criteria (CTC) grade will be produced, and for electrolytes separate shift tables indicating hyper- and hypo- directionality of change will be produced.

For parameters with no CTCAE grading, shift tables from baseline to worst value on-treatment will be provided (ie, on-treatment is defined as data collected up until the last dose of olaparib/placebo).

Shift tables for urinalysis values by worst grade will be provided.

Box-plots of absolute values and change from baseline for continuous laboratory assessments will be presented.

A scatter plot of alanine aminotransferase (ALT) versus total bilirubin, both expressed as multiples of upper limit of normal (ULN) (calculated as ULN divided by maximum observed post-baseline result), will be produced in log-scale. The scatter plot will be repeated for Aspartate aminotransferase (AST) versus total bilirubin.

Liver biochemistry test results over time for patients with elevated ALT or aspartate aminotransferase (AST) (AST or ALT ≥3xULN), and elevated total bilirubin (at any time ≥ 2xULN) will be tabulated and plotted.

Clinically significant laboratory results will be flagged and listed. Reference ranges will also be listed. All laboratory summaries and listings will be presented by actual treatment group.

By-patient listings of laboratory assessments will be provided showing at least: laboratory parameters, scheduled time point, measurements/results, CTC grade (if available), and the change from baseline value (for continuous data) (if appropriate). In addition a flag will indicate if the value was out of normal range, if appropriate:

- Laboratory reference ranges
- Hematology
- Serum chemistry
- Urinalysis
- Individual patient data with elevated ALT or AST plus total bilirubin
- Pregnancy report data

Electrocardiagrams

If available, overall evaluation of ECG will be summarised by visit as normal, abnormal or borderline.

All ECG data will be listed by actual treatment group.

Vital signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, body temperature and weight) will be summarised by time point in terms of absolute values, changes from baseline and percentage changes from baseline at each scheduled measurement by actual treatment group. A shift table comparing baseline to maximum value on treatment will be summarised for each vital sign by actual treatment group.

Box plots for absolute values and change from baseline in SBP, DBP, pulse rate, body temperature, and weight will be presented.

Vital signs data will be listed.

Other

- Any concomitant procedures patients experiencing during the study will be listed in a by-patient listing
- Patients experiencing a Hy's Law incident will be tabulated and details will be included in by-patient listings. Hy's Law incidents are those cases where a patient shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN. Please refer to Appendix D of the CSP for further instructions.

4.2.14 Demographic and baseline characteristics data

The following will be listed and summarised by randomised treatment group using the FAS analysis set:

- Listing of patients receiving the various batches of investigational product
- Listing of randomisation scheme and codes
- Patient disposition (including screening failures and reason for screening failure, reasons for patients prematurely withdrawing from study, patients with a mis-randomisation [treatment dispensing error] and patients who were unblinded, discontinuation of study treatment)
- Important deviations including patients with a dispensing error and the number of patients received at least one dose of the wrong study treatment (see Section 2.2)
- Inclusion and exclusion from analysis populations; exclusions from full, safety and PRO analysis set
- Demographics (age in years, age group in years ('< 33', '>= 33 - < 50', '>= 50 - < 65', '>= 65 - < 88' and '> 88'), sex, race, and ethnicity)
- Patient characteristics (baseline height [cm], baseline weight [kg], baseline body mass index [BMI] [kg/m²], weight group [< 70 kg, 70 kg to 90 kg, > 90 kg], BMI group ['Normal (< 25)', 'Overweight (25 - 30)', 'Obesity (> 30)'])
- Patient recruitment by country and centre
- All (allowed) concomitant medications on entry and during the study
- Disallowed concomitant medications on entry and during the study (defined at the BDRM)

- Disease characteristics at baseline including BRCA testing (local and Myriad) and pathology at time of diagnosis
- Extent of disease
- Disease related medical history per CRF
- Relevant surgical history per CRF
- Pregnancy at baseline (entry)
- Physical examination at baseline (entry)
- Archival paraffin embedded tumour tissue or cytology sample
- Blood transfusion
- Previous radiotherapy and radiotherapy post randomisation
- Post-discontinuation cancer therapy, defined as any therapy received after discontinuation of study treatment
- Patients who subsequently received a PARP inhibitor or entered a PARP inhibitor trial will be summarised and listed by treatment group according to line of subsequent therapy, ie, immediately after olaparib or as a later line, in addition to patients in the placebo arm who subsequently received olaparib
- Previous disease-related treatment modalities (metastatic pancreas cancer therapy)
- Previous non-disease-related treatment modalities
- Initial vomiting and nausea data will be listed only

AstraZeneca drug dictionary will be used for concomitant medication coding.

Patients who were unblinded (a) prior to disease progression and (b) prior to or on the day of treatment discontinuation will be listed.

4.2.15 Treatment exposure

The following summaries related to study treatment will be produced for the Safety Analysis Set by actual treatment group:

- Total exposure of olaparib/placebo
- Actual exposure of olaparib/placebo

- Number of days on 300 mg olaparib/placebo bd = actual exposure for the dose assigned

- Reasons for dose reductions, dose interruptions, and dose modifications of olaparib/placebo. Dose reductions and dose interruptions will be based on investigator initiated dosing decisions. Dose interruptions/reductions due to "Subject Forgot to Take Dose" will be omitted from these summaries

- Number of dose reductions, dose interruptions, and dose modifications of olaparib/placebo that last for a period of three days or more

- PID and RDI of olaparib/placebo (entire intended treatment period)

For patients on study treatment at the time of the PFS analysis, the DCO date will be used to calculate exposure.

Treatment compliance will be summarised by treatment group using descriptive statistics. Tabulation will be presented by actual treatment group.

All treatment information data will be listed:

- Study treatment compliance

- Administration of investigational product

- Duration of exposure

- Overdose report

5 INTERIM ANALYSES

A single interim PFS analysis for superiority and futility will be performed when 50% of the PFS events required for the final analysis have occurred (approximately 45 PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter.

Section 4.2.1 details the spending function used to account for multiplicity introduced by including interim analyses for superiority.

Interim analyses of OS will be performed at the time of the interim analyses of PFS (~45 PFS events), and again at the final analyses of PFS (~89 PFS events). A final analysis of OS will be performed when approximately 106 OS events have occurred.

If the interim PFS results indicate superiority, then analyses of all other endpoints would be performed and the results of these analyses will form the basis for submissions for regulatory

approval. Patients would continue to be followed for PFS and survival until ~89 PFS events had occurred, and then followed for survival until 106 patients had died.

The futility analyses on PFS will be used to guide decisions on stopping the study for futility or continuing the study. Safety data will form part of this decision. The predictive power will be calculated and used to guide the decision on stopping for futility. A predictive power of 20% or higher is considered to be sufficiently high to warrant continuing the study. The predictive power is the probability of a statistically significant result at the final OS analysis, given the observed treatment effect at the interim analysis and using that as the best estimate of the true treatment effect in the remainder of the study. Details will be documented in the IDMC charter.

6 CHANGES OF ANALYSIS FROM PROTOCOL

- Section 8.2.1 of the CSP says: "[…] *Therefore, all efficacy and health-related QoL data will be summarised and analysed using the FAS on an intention-to-treat (ITT) basis.*".

  Efficacy data will be summarised and analysed using FAS on an ITT basis while HRQoL data will be summarised and analysed using the PRO analysis set.

- Page 102, last paragraph of the CSP states the following: "*As patients will be randomised, imbalances in demographic factors between the treatment groups are not anticipated. However if any imbalances should occur, the HR and associated confidence interval calculated from a Cox Proportional Hazards model containing treatment and these additional demographic variables, may be reported.*".

  AstraZeneca do not normally carry out statistical assessment of balance at baseline so do not suggest it for this study as well. If anything appeared quite strongly not to be balanced, this will be commented in the CSR and additional analysis requested to be produced.

- Section 8.8.1 of the CSP details for OS that the "[…] *Statistical significance for OS will be declared the first at interim analysis for OS if the null hypothesis for PFS is rejected and the observed p-value for OS is p>0.005.* […]".

  AstraZeneca corrected the typographic error of the significance level for OS. Statistical significance for OS will be declared the first at interim analysis for PFS, if the null hypothesis for PFS is rejected and the observed p-value for OS is **p>0.00005**.

- Section 8.2.1 of the CSP defines the Full Analysis Set as following: "*The primary statistical analysis of the efficacy of Olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received.*[…]"

Clarification for ITT population with respect to gBRCA testing added, resulting in the following definition for the full analysis population: "*The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received* ***or discrepancy between local and Myriad gBRCA results***."

- Section 8.5 of the CSP defines deterioration and improvement for pancreas cancer quality of life questionnaire as following: "[…] *For change scores, a score of +5 is considered deterioration (except for the two scales mentioned above) and a score of -5 is considered as improvement.* […]".

  When the protocol was written, minimal interpretive data was available for quality of life assessment in pancreas cancer. Serrano et al 2014 suggest using a change of 10 points for detecting a deterioration or improvement for investigation of pancreas cancer. This SAP defines a change of 10 points as a notable change instead of a change of 5 points as defined by the CSP to be in line with recent investigations.

7 REFERENCES

Berry et al 1999
Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-755.

Chen and Sun 2010
Sun X, Chen C. Comparison of Finkelstein's method with the conventional approach for interval-censored data analysis. Stat Biopharm Research 2010; 2(1):97-108.

Chen and Sun 2011
Chen C, Sun LZ. Quantification of PFS Effect for accelerated approval of oncology drugs. Stat Biopharm Research 2011; 3(3):434-444.

Fayers et al 1999
Fayers P, Aaronson N, Bjordal K, Sullivan M (1999). EORTC QLQC30, Scoring Manual. Belgium: EORTC Data Center.

Osoba D et al 1998
Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16(1):139-144.

Pintilie M. 2006
Pintilie M. Competing risks - a practical perspective. 1st ed. West Sussex (England) John Wiley & Sons; 2006.

Sabin et al 2014
Sabin T, Matcham J, Bray S, Copas A, Parmar MKB. A quantitative process for enhancing end of phase 2 decisions. Stat Biopharm Research 2014; 6(1):67-77.

SAS Lifetest 2008
SAS Institute Inc. 2008. SAS/STAT® 9.2 User's Guide. Cary, NC: SAS Institute Inc.

Sellke et al 1983
Sellke, T., Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 1983; 70:315-326.

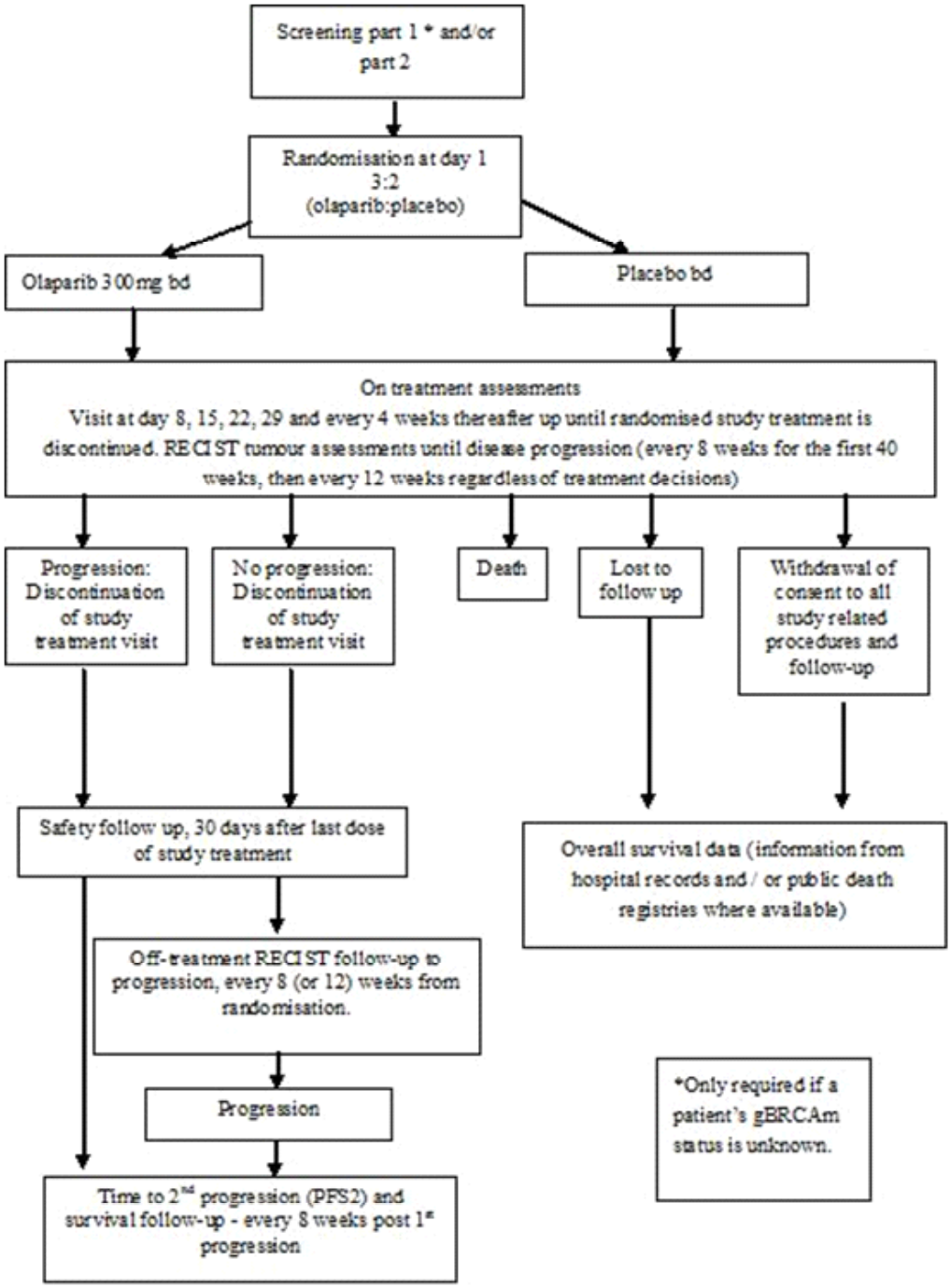
Stone 2010
Stone, A. The application of bespoke spending functions in group sequential designs and the effect of delayed treatment crossover in survival trials. Pharm Statistics 2010; 5:151-161.

Serrano et al 2014
Serrano PE, Herman JM, Griffith KA, et al. Quality of life in a prospective, multicenter phase 2 trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation in patients with resectable or borderline resectable pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys 2014; 90(2):270–277.

APPENDIX

Appendix A: Study Flow Chart

Figure 2 Study Flow Chart



Appendix B: Study Schedule

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up v**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Informed consent	X	X									
Randomisation f			X f								
Demographics	X	X									
Medical and surgical history, including blood transfusions a		X									
Prior cancer therapies including radiotherapy		X									
Inclusion/exclusion criteria	X (all * criteria) b	X									
Blood samples for gBRCA status c	X		X d								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up v**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Archival paraffin embedded tumour tissue or cytology sample e	X	X									
Concomitant medications		X	X	X	X	X	X	X	X	X	
ECOG performance status		X					X	X	X	X	
Vital signs		X g	X g				X	X	X	X	
Physical examination h		X					X	X	X	X	
ECG i		X	As clinically indicated								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up v**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Tumour assessment (modified RECIST) j		X (no more than 28 days before start of treatment) j	Every 8 weeks (± 1 week) until week 40 then every 12 weeks (±1 week), relative to the date of randomisation j						If patient does not have disease progression at the time of treatment discontinuation tumour assessments should be continued per the CSP schedule k		
Haematology/clinical chemistry		X	X l				X	X	X	X	
Coagulation m		X	As clinically indicated								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up v**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Urinalysis n		X	As clinically indicated								
Pregnancy test o	X	X	X								
Biomarker blood sample p			X					X (only at progression)			
EORTC QLQ-C30 q		X					X	X	X	X	
EORTC QLQ-PAN26 q		X		X	X	X	X	X	X	X	
Euro QoL EQ5D		X	X				X	X	X	X	
Hospital Resource Use			X	X	X	X	X	X	X	X	

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up v**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Adverse event r	SAEs related to study procedure s only	X	X	X	X	X	X	X	X	X	
Study drug dispensing s			X				X	X			
Study drug return							X	X	X	X	
Subsequent cancer treatment t										X	X
Second progression assessment u											X u
Survival status v											X v

a Include history of blood transfusion within previous 120 days from start of study treatment and the reasons eg, bleeding or myelosuppression.
b These screening assessments do not need capturing on the eCRF, but they must be recorded in the patient's notes.

c Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised to the study; this can be either a local lab result or a Myriad test result. Patients for whom their *gBRCA* status is already known, should be consented to the study within 28 days prior to day 1 of study treatment. Any patient who consents to study related Myriad *gBRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future diagnostic test(s) for g*BRCA* mutations.

d Samples to be taken on Day 1 only for patients with known *gBRCA* mutation who have not completed PART 1 Screening. The screening *gBRCA* test and method performed at site must be recorded in the eCRF.

e Collection of an archival tumour sample is requested, if available, for all patients. These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test.

f Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last treatment) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

g Vital signs performed on day 1 before every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

h Physical examination should be performed according to the schedule. After the baseline assessment it is not necessary to record the details on the eCRF, any clinically significant changes not unequivocally related to disease progression, should be reported as adverse events.

i ECG assessments to be completed within 7 days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

j Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment and as close as possible to randomisation. A randomisation must be within 6 weeks of last chemotherapy. Treatment should be started as soon as possible but no less than 4 weeks and no more than 8 weeks after their last dose of chemotherapy. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until disease progression assessed using modified RECIST criteria. 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. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit.

k For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST.).

l Haematology and clinical chemistry should be performed at screening and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

m Coagulation test should be performed at screening and if clinically indicated.

n Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

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

p Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

q Questionnaires to be completed prior to randomisation once eligibility has been confirmed and then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose. Questionnaires should be completed prior to dosing on all administrations.

r Adverse events must be captured from time of consent. However, in Screening PART 1 of the study only SAEs related to study procedures will be collected.

s Continuous Olaparib 300mg/ placebo twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

t All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

u Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Subsequent therapy will be collected for these patients from the time of treatment discontinuation.

v The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. 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 (see Section 3.10 of the CSP). In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for each survival analysis.

AstraZeneca

Statistical Analysis Plan

Drug Substance	Olaparib
Study Code	D081FC00001
Edition Number	5.0
Date	14 December 2018

A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients with gBRCA Mutated Metastatic Pancreatic Cancer whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

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PAREXEL Study Statistician		9 Jan 2019 Date

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AstraZeneca Study Statistician

David McGuinness Date

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Astra Zeneca Global Product Statistician

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08 JAN 2019

Date

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study Statistical Analysis Plan.

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
Baseline	Refers to the most recent assessment of any variable prior to first dosing with study treatment
BDRM	Blind data review meeting
bid	Bis in die (Latin for 'twice a day')
BICR	Blinded independent central review
BMI	Body mass index
BoR	Best overall RECIST response
BRCA	Breast cancer susceptibility gene
BRCA mutation	Breast cancer susceptibility gene mutation (see gBRCA mutation or gBRCAm)
CI	Confidence interval
CIF	Cumulative incidence function
CR	Complete response
CRF / eCRF	Case Report Form (electronic)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAE	Discontinuation of investigational product due to adverse event
DBP	Diastolic blood pressure
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
ECG	Electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group: A performance status using scales and criteria to assess how a patient's disease is progressing.
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL five dimensions, five level (EQ-5D-5L) health state utility index
FAS	Full Analysis Set
gBRCA	Germline BRCA
gBRCA mutation or gBRCAm	The term "gBRCA mutation" is used to refer to a germline BRCA1 or BRCA2 mutation classified as "deleterious" or "suspected deleterious" in accordance with the American College of Medical Genetics and Genomics recommendations for standards for interpretation and reporting of sequence variants.
HR	Hazard ratio
HRQoL	Health-related quality of life
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
ITT	Intention to treat
KM	Kaplan-Meier
LD	Longest diameter
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed model for repeated measures
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NA	Not applicable
NE	Not evaluable
NED	No evidence of disease
NTL	Non-target lesions
ORR	Objective response rate
OS	Overall Survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation
p.o.	Per os (by mouth, orally)
PD	Progressive disease

Abbreviation or special term	Explanation
PFS	Progression-free survival
PFS2	Time from randomisation to second progression
PID	Percentage intended dose
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
QoL	Quality of life
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours. This study will use modified RECIST version 1.1.
REML	Restricted maximum likelihood
RS	Raw Score
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SOC	System organ class
Study treatment	Olaparib or matching placebo
TCMD	Time to sustained clinically meaningful deterioration (in HRQoL)
TDT	Time from randomisation to study treatment discontinuation or death
TFST	Time from randomisation to first subsequent therapy or death
TL	Target lesions
TSST	Time from randomisation to second subsequent therapy or death
ULN	Upper limit of normal
VAS	Visual analogue scale

AMENDMENT HISTORY

Date	Brief description of change
14 Dec 2018	• Change in definition for best response in HRQoL. • Additional exposure calculation for mean total daily dose • Analysis population for EQ-5D-5L changed from Safety Set to Full Analysis Set • Additional statistics for treatment difference estimates in the change from baseline HRQoL analysis
02 Aug 2018	• Added analysis of time to sustained clinically meaningful deterioration in HRQoL.
06 Nov 2017	• Changes in line with changes and reductions to the TFL shells. • Update to the PRO analysis set definition. • Additional specification of important protocol deviations. • Logistic regression analysis for Objective Response Rate (ORR) added. • Remove selected OS analysis • Updated time to second progression (PFS2) analysis section to confirm that PFS2 is based on investigator assessment. Censoring rules in case of two or more missed visits also added.
29 May 2015	In line with the Clinical Study Protocol (CSP) Amendment: • Removal of the interim superiority analysis (change to futility only) as per Regulatory Agency recommendation. This included recalculation of the number of events needed for the primary PFS analysis. • Change to the method used for Type 1 error adjustment for the interim and final analyses of overall survival as per Regulatory Agency recommendation. • Inclusion of additional subgroup analyses as per Regulatory Agency recommendation. • Standardisation of the analysis of patient reported outcomes to be in line with other studies in the olaparib programme and to ensure consistency within the protocol. • Minor clarifications for the derivation of statistical endpoints in line with AZ oncology statistical guidance.

Date	Brief description of change
	Further updates: • Additional detail to clarify the independent central review process for tumour scans. • Clarification of programming of time-to-event endpoints in line with AZ oncology statistical guidance, i.e. to add one day to avoid issues with censoring at Day 1. • Clarification that best objective response, objective response rate and disease control rate will be repeated using investigator-recorded assessment as well as blinded independent central review data. • Additional detail to describe summaries of duration of response and time to onset of response. • Further detail on EQ-5D-5L questionnaire. • Further clarification of dose intensity calculations for olaparib. • Inclusion of interaction testing for progression-free survival. • Inclusion of overall survival subgroup analyses. • Correction of typographical errors and additional minor clarifications.

1. STUDY DETAILS

As described in the protocol.

1.1 Study Objectives

Study objectives will be addressed in patients with deleterious or suspected deleterious germline mutation in breast cancer susceptibility gene 1 and/or 2 (*BRCA1* and/or *BRCA2*) and metastatic pancreas cancer who have achieved disease control (absence of objective progression) after receiving a minimum of 16 weeks of first-line platinum-based chemotherapy.

Primary:

To determine the efficacy of olaparib maintenance monotherapy compared to placebo by progression-free survival (PFS), using blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; in the following referred to as RECIST.

Secondary:

1. To determine the efficacy of olaparib maintenance monotherapy compared to placebo by assessment of

- Overall survival (OS).
- Time from randomisation to second progression (PFS2).
- Time from randomisation to first subsequent therapy or death (TFST).
- Time from randomisation to second subsequent therapy or death (TSST).
- Time from randomisation to study treatment (olaparib or matching placebo) discontinuation or death (TDT).
- Objective response rate by BICR using modified RECIST criteria.
- Disease control rate (DCR) at week 16 by BICR using modified RECIST criteria.

2. To compare the effects of olaparib maintenance monotherapy compared to placebo on the health-related quality of life (HRQoL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 global quality of life (QoL) scale.

Safety:

To assess the safety and tolerability of olaparib maintenance monotherapy by assessment of adverse events (AEs), physical examination, vital signs including blood pressure, pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and haematology.

Exploratory:

1. To explore the effect of olaparib on functioning as measured by the EORTC QLQ-C30 functioning domains (physical, role, cognitive, emotional and social).

2. To explore the effect of olaparib on pancreas cancer symptoms as measured by the EORTC QLQ-PAN26 items and scales.

3. To assess clinically relevant symptoms as measured by the EORTC QLQ-C30 and PAN26, including pain, fatigue, nausea, weight loss (or difficulty gaining weight/loss of appetite), and jaundice.

4. To assess the change in performance status as measured by the Eastern Cooperative Oncology Group (ECOG) performance status scale.

5. To investigate the health economic impact of treatment and the disease on hospital-related resource use and health state utility.

6. To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent Polyadenosine 5'diphosphoribose (poly [ADP ribose]) polymerise (PARP) inhibitors or imbalances between the treatment arms for other potentially active agents.

7. To determine the frequency of and describe the nature of BRCA mutation/s in tumour samples and to compare this with germline BRCA mutation status.

8. To identify tumour tissue-based biomarkers (including but not limited to somatic BRCA1/2 mutations, BRRCA methylation and/or other homologous recombination repair deficiencies biomarkers) that could be used to guide future patient segmentation approaches for development.

9. Future exploratory research into factors that may influence development of cancer and/or response to treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumour samples (if available), blood samples at day 1 and on disease progression or on residual tissue material collected as part of the study.

Parts of the exploratory analyses may not be part of the analysis described in this statistical analysis plan (SAP) and as such, may not be reported in the Clinical Study Report (CSR). If not, they will be reported separately by AstraZeneca.

1.2 Study Design

This is a Phase III, randomised, double-blind, placebo-controlled, multi-centre study to assess the efficacy of olaparib maintenance monotherapy in metastatic pancreatic cancer patients with germline BRCA (gBRCA) mutations (documented mutation in gBRCA1 or gBRCA2) that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and whose tumours have not progressed on at least 16-weeks of first-line platinum-based chemotherapy.

Approximately 145 patients will be randomised (using an Interactive Voice Response System / Interactive Web Response System) in a 3:2 ratio to the treatments as specified below:

- olaparib tablets per os (p.o.) 300 mg twice daily.
- placebo tablets p.o. twice daily.

Eligible patients will be those patients with pancreas cancer previously treated for metastatic disease gBRCA mutated, who have not progressed following completion of at least 16 weeks of first-line platinum-based chemotherapy before randomisation. All patients must have a known deleterious or suspected deleterious germline BRCA mutation to be randomised. Determination of gBRCA mutation will be done before enrolment to the study at Myriad laboratories.

Patients with known gBRCA mutation prior to randomisation will enter the study based on these results (by considering all other eligibility criteria as well), but undergo a confirmatory gBRCA test post-randomisation, while patients with unknown gBRCA mutation will enter the study after confirmation of gBRCA mutation.

Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of last treatment) and study treatment will start as soon as possible but no less than 4 and no more than 8 weeks after the last chemotherapy dose. At the time of starting study treatment, all previous chemotherapy treatment should be discontinued.

Following randomisation, patients will attend clinic visits weekly for the first 4 weeks of treatment (days 8, 15, 22 and 29). Patients will then attend clinic visits every 4 weeks whilst on study treatment and will continue treatment until objective radiological disease progression as per RECIST as assessed by the investigator and as long as in the investigator's opinion they are benefiting from treatment and they do not meet any other discontinuation criteria.

Once a patient has discontinued study treatment, clinic visits will be reduced to every 8 weeks. Following discontinuation of study treatment, further treatment will be at the discretion of the investigator. It is anticipated (but not required) that patients will be re-treated with their previous platinum-based regimen. Details of any further systemic anti-cancer treatment will be collected until death, loss to follow-up, or withdrawal of consent. In addition to their regular 8 weekly contacts, patients will be contacted in the 7 days following a specified day (data cut-off date [DCO]) to capture survival status.

Patients will have tumour assessments according to RECIST at baseline and every 8 weeks (±1week) up to 40 weeks and then every 12 weeks (±1 week) relative to date of randomisation until objective radiological disease progression according to modified RECIST criteria. RECIST will be modified to assess patients with clinical complete response (CR) at entry who will be assessed as having no evidence of disease (NED) until they have progressed based on the appearance of new lesions.

Any patient who discontinues study treatment for reasons other than objective radiological progression should continue to undergo scheduled objective tumour assessments according to the study plan in order to assess objective radiological progression of disease. Failure to do so may result in bias in the study results. Once a patient has progressed, the patient will be followed for second progression every 8 weeks and then survival until the final analysis. Patients will be contacted in the week following DCO for each analysis of survival.

The final PFS analysis of the study will occur when approximately 87 PFS events have occurred, although an interim PFS analysis for futility will be performed when 50% of the PFS events required for the final PFS analysis have occurred. Both interim and final PFS analyses will be based on BICR of disease progression by modified RECIST version 1.1; however, a sensitivity analysis will be performed using the investigator-recorded assessment.

An interim analysis of OS will be performed at the time of the final analyses of PFS. A final analysis of OS will be performed when approximately 106 OS events have occurred.

Unblinded outputs for the interim analysis of PFS will be prepared by the International Drug Development Institute (IDDI). For the combined analysis of final PFS and interim OS, the study will be unblinded at PAREXEL. No measures for keeping team members blinded for the subsequent final OS analysis are required.

The study flow chart is in Appendix A: Study Flow Chart while the study schedule is in Appendix C: Study Schedule.

1.3 Number of Patients

The primary endpoint of the study is PFS. Approximately 145 patients will be randomised (3:2 ratio of olaparib:placebo) and the final PFS analysis will occur once approximately 87 PFS events (confirmed via a central review) have occurred. A single interim PFS analysis for futility will be performed when 50% of the PFS events required for the final analysis (approximately 44 PFS events) based on BICR have occurred.

The study is sized assuming a true treatment effect that is a PFS hazard ratio (HR) of 0.54 at the final analysis, assuming 80% power and 2.5% alpha (1-sided), with 3:2 randomisation (olaparib:placebo). Assuming PFS is exponentially distributed, a PFS HR of 0.54 equates to a 3.4 month improvement in median PFS over an assumed 4 month median PFS for placebo.

Patients are to be followed for the final analysis of OS and PFS2 (when approximately 106 death events have occurred). With 106 OS events the study has 80% power to show a

statistically significant difference in OS at the 1-sided 2.5% level if the assumed true treatment effect is a HR 0.57; this translates to an approximate 6-month improvement in median OS over an assumed 8 month median OS on placebo, assuming OS is exponentially distributed.

Assuming that the study accrual period will be approximately 15 months, 87 PFS events are anticipated to be observed approximately 18 to 19 months after the first patient is randomised in the study. It is estimated that 44 PFS events will occur approximately 13 to 14 months after first patient in. It is estimated that 106 deaths will have occurred approximately 31 months after first patient in.

2. ANALYSIS SETS

2.1 Definition of Analysis Sets

Full Analysis Set

Intention to treat (ITT): The primary statistical analysis of the efficacy of olaparib will include all randomised patients and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received or discrepancy between local and Myriad gBRCA results. Patients who were randomised but did not subsequently go on to receive study treatment are included in the Full Analysis Set (FAS). Therefore, all efficacy endpoints will be summarised and analysed using the FAS on an ITT basis.

In addition, key sensitivity analysis of efficacy endpoints will be performed in the subgroup of patients in the FAS that have a gBRCA mutation confirmed by the Myriad test.

Safety Analysis Set

All patients who received at least one dose of randomised investigational product, olaparib or placebo, will be included in the safety analysis set. Throughout the safety results sections, all patients who received at least one dose of olaparib will be accounted for in the olaparib treatment group. Erroneously treated placebo patients (those randomised to placebo but actually received at least one dose of olaparib) will be accounted for in the olaparib treatment group. Any mis-randomisations will be discussed on an individual basis and decisions will be documented at the blind data review meeting (BDRM) for the final analysis of PFS and at the data review meeting (DRM) for the final analysis of OS and PFS2.

Patient Reported Outcome Analysis Set

The analysis population for patient reported outcome (PRO) data will be a subset of the FAS (ITT) population who have evaluable baseline EORTC QLQ-C30 or QLQ-PAN26 forms where evaluable means that at least one sub-scale baseline score can be determined from at least one of the two forms.

Table 1 Summary of Outcome Variables and Analysis Populations

Outcome Variable	Populations
Efficacy Data	
Primary analysis: PFS	FAS (ITT), Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup
Secondary analysis:	
OS, PFS2, TFST, TSST, TDT	FAS (ITT), Myriad confirmed gBRCAm subgroup
Objective response rate (ORR)	FAS (ITT) (patients with measurable disease at baseline)
Disease control rate (DCR), Duration of response (DoR)	FAS (ITT)
EQ-5D-5L	FAS (ITT)
PRO Data (EORTC QLQ-C30/PAN26)	
Adjusted mean change from baseline in global HRQoL score	PRO
Time to sustained clinically meaningful deterioration (TCMD) in HRQoL	
Demography	FAS (ITT)
Safety Data	
Exposure, AEs, Laboratory measurements; ECGs, Vital signs, ECOG, Physical examinations	Safety

2.2 Violations and Deviations

Important protocol deviations are those that could have a heavy influence on the interpretation of any analysis based on addressing the primary efficacy and secondary safety objectives of the trial. This section will define important protocol deviations so that instances can be identified and reported in the CSR.

Major protocol deviations are deviations from the protocol that are likely to have an impact on the subject's rights, safety, well-being, and/or on the validity of the data for analysis. This will include all important deviations to be reported in the CSR.

Major and important protocol deviations will be listed for the FAS analysis set. Important protocol deviations will be summarised by randomised treatment group for the FAS analysis set. None of the deviations will lead to any patients being excluded from any of the analysis sets described in Section 2.1.

A per-protocol analysis excluding patients with important protocol deviations is not planned; however, a 'deviation bias' sensitivity analysis will be performed excluding patients with those important deviations that may affect the efficacy of the trial therapy if >10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock or data freeze for the final analysis on PFS and will be documented prior to the study being unblinded and the analysis being conducted.

The full definition of important protocol deviations and any action to be taken regarding the exclusion of subjects (for the sensitivity analysis) are defined in the project-specific Protocol Deviation Specification. The dataset of protocol deviations that is received from the protocol deviation system will contain a variable DVACTION that can be used to identify patients to be excluded from the sensitivity analysis.

The following general categories will be considered important deviations from a statistical perspective and will be summarized, listed and discussed in the CSR as appropriate:

- Patients randomised but who did not receive olaparib/matching placebo.
- Patients who deviate from key study entry criteria (to be determined at the BDRM), which will be documented ahead of database lock.
- Baseline RECIST scan missing or > 28 days before start of study treatment.
- Baseline RECIST scan after randomisation.
- RECIST scan not performed according to protocol.

The categorisation of these as important deviations is not automatic and will depend on duration and the perceived effect on efficacy.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post-entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified.

Mis-randomisations in terms of errors in treatment dispensing, will also be considered as important protocol deviations. A mis-randomisation is when a patient is not randomised or treated according to the randomisation schedule. It is envisaged that there will be 2 subcategories of this:

(a) Patients who receive no treatment whatsoever for a period of time due to errors in dispensing of medication. Note, this is not due to tolerability issues where patients may stop taking drug.

(b) The patient receives a treatment pack with a different code from their randomisation code. However, the actual treatment may still match the randomised treatment. For example, a patient is given randomisation code 0001, which according to the randomisation schedule is olaparib. However, at the randomisation visit they are given treatment pack 0003, but this still contains olaparib.

The summary will include all patients with a dispensing error but will also include information on how many of those patients received at least one dose of the wrong treatment (olaparib/placebo) at any time.

Patients who receive the wrong treatment at any time will be included in the safety analysis set as described in Section 2.1. During the study, decisions on how to handle mis-randomisations will be made on an individual basis with written instruction from the study team leader and/or statistician.

The following table summarizes the important deviations discussed above. The last column flags the deviations that if observed in >10% of FAS patients would lead to a sensitivity analysis. For the full specification please refer to the project-specific Protocol Deviation Specification.

Table 2 Important protocol deviations

PD term	Criteria to identify PD	Sensitivity analysis
Not the intended disease or indication	Relevant in- or exclusion criteria are not fulfilled.	Yes
Did not receive any randomised therapy	Patient was randomised and did not receive any study treatment.	Yes
Deviation from other key entry criteria	Patients who deviate from key entry criteria other than the intended disease or indication.	
Baseline RECIST missing	RECIST scan on or before first dose of study treatment is missing.	
Baseline RECIST scan too early	Baseline RECIST scan taken more than 28 days before start of study treatment.	
Baseline RECIST scan too late	Baseline RECIST scan taken after randomisation.	

RECIST scan not performed according to protocol	RECIST scan not in scheduled visit window on >2 occasions post-baseline regardless of whether visits were consecutive or not.	
Wrong treatment kit but correct study drug	The patient receives a wrong treatment pack. Actual treatment matches the randomised treatment.	
Wrong treatment kit with incorrect study drug	The patient receives a wrong treatment pack. Actual treatment does not match the randomised treatment.	
Treatment interrupted	Subject did not receive study treatment for a period of 28 consecutive days or more due to errors in dispensing of medication or non-compliance. This excludes drug interruptions due to adverse events or due to tolerability issues.	
Subject took concomitant medications or therapies prohibited whilst receiving study medication	Subject took disallowed medications or therapies starting on or after first dose of treatment. Refer to details of medication types in section 7.7 of the CSP.	
Non-compliance with study treatment	Severe non-compliance with treatment reported by site monitor in IMPACT.	
Deviation from ICH-GCP	Deviation of ICH Good Clinical Practice (GCP) reported by site monitor in IMPACT	

The categories listed in the table can be identified using the protocol deviation reference IDs that are defined for each type of protocol deviation in the project-specific specification.

For the final analysis of PFS / interim analysis of OS, the final classification of deviations will be made at the BDRM prior to database lock or data freeze and all decisions including the requirement of a sensitivity analysis will be made whilst blinded to study treatment allocation Decisions made at the BDRM for the final analysis of PFS will be documented and approved by AstraZeneca prior to analysis and unblinding.

For the final analysis of OS, new protocol deviations will be reviewed and classified at a DRM prior to DB lock. The study will be unblinded by that time, however, there is not sensitivity analysis planned for the analysis of OS.

3. PRIMARY AND SECONDARY VARIABLES

At each visit patients will be assigned a RECIST visit response of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE) or NED depending on the status of their disease compared to baseline and previous assessments, based on the BICR. This will be repeated using the Investigator assessed RECIST data.

3.1 Derivation of RECIST Visit Responses

Patients with measurable or non-measurable disease or NED assessed at baseline by computed tomography (CT) / magnetic resonance imaging (MRI) will be entered in this study. RECIST has been modified to allow the assessment of progression due to new lesions in patients with NED at baseline (inclusion criteria #4).

For all patients, the RECIST tumour response data will be used to determine each patient's visit response according to modified RECIST version 1.1. It will also be used to determine if and when a patient has progressed in accordance with RECIST and also their best overall response.

Baseline radiological tumour assessments are to be performed no more than 28 days before start of study treatment and ideally as close as possible to the start of study treatment and prior to randomisation. Tumour assessments are then performed every 8 weeks (±1 week) up to 40 weeks and then every 12 weeks (±1 week) following randomisation until disease progression.

If an unscheduled assessment was performed and the patient had 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.

At each visit, an overall visit response will be provided by the BICR and separately by the investigator - using the information from target lesions (TL), non-target lesions (NTL) and new lesions.

3.1.1 Target lesions

Measurable disease is defined as having at least one measurable lesion, not previously irradiated, which is ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded, then measurements from the one that is closest to and prior to randomisation will be used to define the baseline sum of TLs. 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.

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

Note: For patients who do not have measurable disease at entry (ie, no TLs) but have non-measurable disease, evaluation of overall visit responses will be based on the overall NTLs assessment and the absence/presence of new lesions (see Section 3.1.3 of the Clinical Study Protocol (CSP) for further details). If a patient does not have measurable disease at baseline, then the TL visit response will be not applicable (NA).

For patients with NED at baseline (ie, no TLs and no NTLs), evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be NED.

Table 3 TL Visit Responses

Visit Responses	Description
CR	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
PR	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
PD	At least a 20% increase in the sum of diameters of TLs, 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 indicate an absolute increase of at least 5 mm.
NE	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
NA	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs, percentage changes from baseline and previous minimum should be rounded to 1 decimal place before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable, all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded.
- A NTL visit response of PD is recorded.
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm from nadir, even assuming the non-recorded TLs have disappeared. Note: the nadir can only be taken from assessments where all the TLs had a longest diameter (LD) recorded, including non-missing TLs which have had intervention during the study and prior to any scaling of the measurements.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

Lymph nodes

For lymph nodes, if the size reduces to < 10 mm then these are considered non-pathological. However, a size will still be given, and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10 mm and all other TLs are 0 mm, then although the sum may be > 0 mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

A CR can only be followed by CR, PD or NE. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met ie, if a lymph node LD increases by 20% but remains < 10 mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or < 10 mm for lymph nodes), then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is also met.
- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD, then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined, the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure, this should be indicated in the database and a size ('x') above which it cannot be accurately measured should be recorded. If using a value of x in the calculation of TL response would not give an overall visit response of PD, then this will be

flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and entered a smaller value that can be reliably measured. If a TL response of PD results, then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (ie, lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolization), should be handled in the following way and once a lesion has had intervention then it should be treated as having had intervention for the remainder of the study, noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD this will remain as a valid response category.

- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements, then scale up as described below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.

  Scaling will be based on the measurements at the nadir visit, to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-intervention lesions to the nadir sum of diameters excluding the lesions with interventions.

Table 4 Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1	7.2	7.1
2	6.7	6.4
3	4.3	4.0
4	8.6	8.5
5	2.5	Intervention
Sum	**29.3**	**26**

Lesion 5 has had an intervention at the follow-up visit.

The sum of lesions 1 to 4 at the follow-up is 26 cm. The sum of the corresponding lesions at baseline visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4cm$$

- Step 3: If after both steps PD has not been assigned, then if appropriate, a scaled sum of diameters will be calculated (as long as ≤ 1/3 of the TLs have missing measurements), treating the lesion with intervention as missing, and PR or SD, then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or < 10 mm for lymph nodes) and the lesions that have been subject to intervention also have a value of 0 recorded. If scaling-up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

At subsequent visits the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up where appropriate (as per step 2 above).

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0 mm.

Change in method of assessment of TLs

Computed tomography (CT) and MRI are the only methods of assessment that can be used within the trial. If a change in method of assessment occurs between CT and MRI, this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (eg, CT changes to clinical examination), any affected lesions should be treated as missing.

3.1.2 NTLs and new lesions

At each visit an overall assessment of the NTL response should be recorded. This section provides the definitions of the criteria used to determine and record overall response for NTL at each visit.

The NTL response will be derived based on the overall assessment of NTLs as follows:

Table 5 NTL Visit Responses

Visit Responses	Description
CR	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
PD	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
NE	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
NA	Only relevant if there are no NTLs at baseline.

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

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

New lesions will be identified on the electronic case report form (eCRF). The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

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

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.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present and should be treated as NE in the derivation of overall visit response.

'Symptomatic deterioration' is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs. 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.

3.1.3 Overall visit response

Table 6 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 6 Overall Visit Responses

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

NA is only relevant if there were no TL/NTL at baseline.

3.1.4 Independent review

A planned BICR of all radiological imaging data will be carried out using modified RECIST version 1.1 and these data will be used for the interim and primary analyses of PFS. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca appointed Contract Research Organisation (PAREXEL Imaging) for central analysis. Prior radiotherapy and location of screening biopsy lesion reports will also be provided to the BICR to allow the selection of appropriate TLs. The imaging scans will be reviewed by 2 independent radiologists using modified RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data (for patients with TLs at baseline: CR, PR, SD, PD, NE; for patients with NTLs only: CR, SD, PD or NE; for patients with no disease identified at baseline: PD, NED, NE). If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD).

RECIST assessments/scans contributing towards a particular visit may be performed on different dates and for the central review the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression, either for the adjudicated reviewer selecting PD or of the first reviewer where both select PD as time-point response and there is no adjudication.

Results of this independent review will not be communicated to Investigators and the management of patients will be based solely upon the results of the modified RECIST 1.1 assessment conducted by the Investigator.

On an ongoing basis, patients who are determined to have progressed according to modified RECIST 1.1 criteria by the investigator will have scans centrally reviewed for confirmation of objective disease progression. Radiological scans will only be sent for BICR up until the date of RECIST progression determined by the investigator. However, if disease progression is not confirmed at BICR, an additional RECIST assessment will be requested at the next scheduled RECIST visit. After the final PFS analysis, BICR of scans will no longer be required, regardless of progression status.

Further details of the BICR will be documented in the BICR Charter.

3.2 Outcome Variables

For each patient, an overall RECIST visit response of CR, PR, SD, PD, NED, NE, will be determined from the BICR as described in Section 3.1.4 above. The outcome variables involving RECIST data, i.e. PFS, best overall response, ORR and DCR, will be derived using overall visit responses and relevant dates from the BICR (which is considered to be the primary RECIST dataset), unless otherwise stated.

Separately, investigator-assessed site measurements/assessments (TLs, NTLs, new lesions) will be used to programmatically derive an investigator assessment of overall visit response.

3.2.1 Progression-Free Survival

Progression-free survival is defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy prior to disease progression (i.e. date of RECIST progression/death or censoring – date of randomisation + 1). 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 (prior to the missing visits). 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 an extra two weeks for early and late visits. After 40 weeks, two missing visits will equate to more than 26 weeks. If two missed visits occur over the period when the scheduled frequency of RECIST assessments changes (ie, from every 8 weeks to every 12 weeks), this will equate to more than

22 weeks (allowing for an early assessment at Week 32 and a late assessment at Week 52). Please refer to the appendix for a graphical display of the allowed time gap in RECIST assessments (Appendix D: Visualisation of Censoring Rule for Progression Free Survival).

The baseline RECIST assessment should be performed prior to randomisation but if an evaluable RECIST assessment occurs after randomisation but before treatment then this assessment will be used as the baseline assessment. 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 tumour assessment visits of randomisation (16 weeks plus 1 week allowing for a late assessment within the visit window).

If a patient has two missing visits between two evaluable RECIST assessments with outcome not equal to progression at the second evaluable RECIST assessment, but then subsequently progresses, the patient will not be censored when analysing for PFS. For example, if RECIST assessments were performed at week 8 with outcome SD, week 32 with outcome SD and week 40 with a progression event (weeks 16 and 24 were missed), the patient will be analysed from time of randomisation until progression event at week 40 without considering the interruptions.

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

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

(a) For BICR data, the date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a time point response and there is no adjudication.

(b) For investigational site assessments, date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that triggered the progression.

(c) For both BICR data and investigational site assessments, 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 by the investigator and BICR 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 TLs (compared to previous minimum sum) and an absolute increase of > 5 mm, or an overall NTLs assessment of progression or a new lesion.

The primary analysis will be based on the programmatically derived PFS based on the BICR of the radiological scans, and using all scans regardless of whether they were scheduled or not.

A sensitivity analysis based on the derived PFS based on investigator-recorded assessments will be carried out.

3.2.2 Overall Survival

Overall Survival is defined as the time from the date of randomisation until death due to any cause (i.e. date of death or censoring – date of randomisation + 1). 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. This analysis will be based on the "date subject last known to be alive" variable which is recorded within the survival status module of the eCRF (SURVIVE module).

Note: Survival calls will be made in the week following the date of 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. If a patient has died but the date of death cannot be determined, then the patient will be censored based on the last recorded date on which the patient was known to be alive (although every effort needs to be made to determine the date of death). The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. If 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.

3.2.3 Time from randomisation to second progression

The time from randomisation to second progression (PFS2) is defined as the time from the date of randomisation to the earliest of the second progression event as assessed by the investigator or death (ie date of PFS2 event or censoring – date of randomisation + 1). The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of objective radiological or symptomatic progression or death. The RECIST assessments will not be collected for assessment of PFS2. The date of the PFS2 assessment and investigator opinion of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

Second progression status will be reviewed every 8 weeks following the investigator assessment of the first objective progression and status recorded. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression, ie, censored at the latest of the RECIST assessment or PFS2 assessment dates. If a patient progresses for the second time or dies after two or more missed visits, the patient will be censored for PFS2 at the time of the latest evaluable investigator – recorded assessment.

Censoring will need to be applied for some patients prior to the first progression and for others after the first progression, depending if the patient had a first progression at the time of

analysis or not. The duration of two missed visits is depending on the respective visit schedule:

- If the patient was progression-free at the time of analysis, then patients will be censored as described for PFS (Section 3.2.1), i.e. using the latest RECIST scan.
- If the patient died in the absence of any progression after two or more missed visits, then the censoring visit rule as described for PFS (Section 3.2.1) needs to be applied.
- If a patient is alive and had only the first progression assessed at the time of analysis, then the censoring will be based on the latest investigator assessment of no progression in the follow-up phase. If there are no follow-up results recorded, then the date of the latest scan contributing to the investigator assessment of first progression will be used for censoring.
- If the patient had progressed once and then died or progressed for the second time after two or more visits, then those two or more missed visits equate to more than 18 weeks, since the patient is in the follow-up phase (16 weeks plus allowing an extra two weeks for early and late visits), i.e., if the latest follow-up assessment prior to second progression or death was are more than 18 weeks ago, then the patient is censored with the date of this last investigator assessment. If no follow-up results are recorded, and the investigator assessment of first progression is more than 18 weeks ago, then the date of the latest scan contributing to this first progression assessment will be used for censoring.

3.2.4 Time to first subsequent therapy or death

As a supportive summary to PFS, TFST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks, in line with survival follow-up visits. The TFST is defined as the time from randomisation to the earlier of first subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of first subsequent cancer therapy/death or censoring – date of randomisation + 1). Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received subsequent cancer therapy, ie, the last follow-up visit where this was confirmed.

3.2.5 Time to second subsequent therapy or death

As a supportive summary to PFS2, TSST will be assessed at the 30-day follow-up visit following study treatment discontinuation and then every 8 weeks, in line with survival follow-up visits. The TSST is defined as the time from randomisation to the earlier of the second subsequent cancer therapy start date following study treatment discontinuation, or death (i.e. date of second subsequent cancer therapy/death or censoring – date of randomisation + 1). Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type will be censored at the last known time to have not received second subsequent cancer therapy, ie, the last follow-up visit where this was confirmed.

3.2.6 Time to study treatment discontinuation or death

The TDT is defined as the time from randomisation to the earlier of the date of study treatment discontinuation or death (i.e. date of study treatment (olaparib/placebo) discontinuation/death or censoring – date of randomisation + 1). Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive. Patients who were randomised but never exposed to study treatment will be censored at day 1.

3.2.7 Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST assessment (Table 6). It is the best response a patient has had following randomisation but prior to starting any subsequent cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on the RECIST criteria using the following order of response categories: CR, PR, SD, NED (applies only to those patients entering the study with no disease at baseline), PD and NE. Patients entering the study with no measurable disease at baseline who would qualify for CR are considered as SD and summarized separately as "stable disease (complete response without measurable disease)".

BoR will be determined programmatically from the overall visit response using BICR data. In addition, this will also be reported using investigator-recorded assessment.

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 7 weeks (ie, 8 weeks minus 1 week to allow for an early assessment within 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 ≤ 17 weeks (ie, 16 weeks +1 week to allow for a late assessment within the assessment window) after randomisation then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurred > 17 weeks (ie, 16 weeks +1 week) after randomisation then BoR will be assigned to the NE category.

Progression events that have been censored due to them being more than two missed visits 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 following randomisation, prior to RECIST progression and prior to starting any subsequent cancer therapy.

3.2.8 Objective response rate

For each treatment group, the ORR is the number of patients with a BoR of CR and PR according to the BICR data divided by the number of patients in the treatment group with measurable disease at baseline where 'measurable' is defined by the BICR data. Only patients with measurable disease at baseline can achieve an objective response of CR or PR.

As supportive summaries, duration and time to onset of objective response in patients with an objective response (derived using BICR data) will be calculated using a Kaplan-Meier technique.

Duration of response 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 (using BICR data). 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 subject does not progress following a response, then the patient will be censored at the same timepoint that was used for the censored PFS analysis.

Time to onset of objective response will be defined as the time from randomisation to the date of first documented response.

ORR, duration of response and time to onset of objective response will also be calculated using investigator-recorded assessment, with 'measurable' disease at baseline defined according to investigator assessment.

3.2.9 Disease control rate

The DCR is defined as the percentage of patients who have at least one visit response of CR or PR or have demonstrated SD or NED for at least 15 weeks (ie, 16 weeks minus 1 week to allow for an early assessment within assessment window) prior to any evidence of progression. In the case of SD and NED, follow-up assessments must have met the SD or NED criteria for a minimum interval of 15 weeks following randomisation. This will be calculated using BICR data, in addition to investigator-recorded assessment.

3.3 Patient Reported Outcome Variables

3.3.1 EORTC QLQ-C30 (Version 3) and EORTC QLQ-PAN26

The EORTC QLQ-C30/PAN26, validated PRO questionnaires in the target patient population, will be used to evaluate disease symptoms, functional impacts (e.g., physical functioning), and HRQoL and characterise clinical benefit from the patient perspective. The EORTC QLQ-C30 was developed to assess general cancer related symptoms, functional impacts (e.g., physical functioning) and HRQoL while the EORTC QLQ-PAN26 was developed specifically to assess pancreas cancer-specific symptoms (e.g. pancreatic pain) and impact.

The EORTC QLQ-C30 comprises 30 questions designed for all cancer types. Questions can be grouped into the following scales:

- 5 multi-item functional scales (physical, role, emotional, cognitive and social)
- 3 multi-item symptom scales (fatigue, pain, nausea vomiting)
- A 2-item global health status / QoL scale
- 5 single items assessing the following common cancer symptoms:
  - dyspnoea
  - loss of appetite
  - insomnia
  - constipation
  - diarrhoea
- 1 item on the financial impact of the disease.

The pancreas cancer module, EORTC QLQ-PAN26, is intended for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation, or palliative chemotherapy. The module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreas cancer, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes).

Data from these questionnaires will be analysed according to the visit as collected, ie no visit remapping will take place. Baseline is defined as the last result on or before the first day of study drug. For patients who are randomised but not treated, baseline is defined as the last result on or before the date of randomisation.

EORTC QLQ-C30/PAN26 scoring:

The EORTC QLQ-C30 / QLQ-PAN26 will be scored according to the EORTC scoring manual (Fayers et al 2001) and the draft scoring procedure for QLQ-PAN26 (Johnson 2007).

All the EORTC scales range from 0 to 100 (through transformation of scores as detailed below). The EORTC QLQ-C30 scales can be interpreted as following: 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. The interpretation of the EORTC QLQ-PAN26 depends

on the symptoms or problems. For digestive symptoms, altered bowel habit, hepatic, sexuality and body image, a higher score represents worse QoL, while a lower score represents a better outcome. For the health care satisfaction scale (items 53 and 54), a higher score represents better outcome while a lower score represents worsening.

Transformation of scores

Each scale will be transformed to a 100-point scale as follows:

For all scales, the Raw Score (RS) is the mean of the component items:

$$RS = (I_1 + I_2 + \cdots + I_n)/n$$

To obtain the score S, the following linear transformation will be applied:

Table 7 Linear Transformation of EORTC Scales

Scale	Item number QLQ-C30	Item number QLQ-PAN26*	Calculation of score
Functional scale	1-7, 20-27	NA	$S = \left\{1 - \frac{RS-1}{range}\right\} * 100$
Symptom scales	8-19, 28	31, 33-37, 44-49	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Global Health Status / QoL	29, 30	NA	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Health care satisfaction scale	NA	53, 54	$S = \left\{\frac{RS-1}{range}\right\} * 100$
Sexuality	NA	55, 56	$S = \left\{1 - \frac{RS-1}{range}\right\} * 100$

Range is the difference between the maximum possible value of RS and the minimum possible value.
*A few items of the QLQ-PAN26 questionnaire are not part of the table as they are not part of a multi-item scale (ie, item number 32, 38, 39-43, 50-52). Nevertheless, they need to be transformed in the same way as for symptom scales.

The QLQ-C30 / QLQ-PAN26 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6.

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. 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 items 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.

EORTC QLQ-C30/PAN26 Score Interpretation - Clinically Meaningful Change & Best Overall Response:

Clinically Meaningful Change

Definition of clinically meaningful changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al 1998) (Table 8). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. At each postbaseline assessment, the change in global health status/QoL, symptoms, and functioning score from baseline will be categorized as improvement, no change, or deterioration as shown in Table 8. Similarly, a change of at least 10 points in the QLQ-PAN26 will be considered as a clinically meaningful (Serrano et al 2014).

Table 8 EORTC QLQ-C30/PAN26 Clinically Meaningful Visit Response

Score	Change from baseline	Visit response
EORTC QLQ-C30 symptom scales	≥ +10 or patient too ill to complete measure	Deterioration
	≤ -10	Improved
	Otherwise	No change
EORTC QLQ-C30 Global QoL score and functional scales: physical, role, emotional, cognitive and social	≥ +10	Improved
	≤ -10 or patient too ill to complete measure	Deterioration
	Otherwise	No change
EORTC QLQ-PAN26 scales*: pancreatic pain, digestive symptoms, altered bowel habit, hepatic, sexuality and body image multi item scales and single item measures	≥ +10 or patient too ill to complete measure	Deterioration
	≤ -10	Improved
	Otherwise	No change
EORTC QLQ-PAN26 scales*: Satisfaction with health care	≥ +10	Improved
	≤ -10 or patient too ill to complete measure	Deterioration
	Otherwise	No change

*The change from baseline of 10 points for detecting a deterioration or improvement in the pancreas cancer module is based on recent investigations by Serrano et al 2014.

Note for some patients it will not be immediately possible to obtain a visit response for a particular subscale, for example:

- Patients with no baseline score for a particular subscale, or no baseline data at all
- Patients whose baseline subscale score is too close to the maximum or minimum possible score to allow an increase or decrease of the specific size to be observed.
  - For patients whose baseline score is greater than the maximum possible score for that subscale minus the score needed to satisfy improvement, the best visit response possible will be "No Change".
  - For patients whose baseline score is less than the threshold needed for worsening all post-baseline visit responses will be considered not-calculable.

Best overall response in HRQoL

A patient's best overall QoL response will be derived as the best QoL response the patient achieved, based on evaluable QoL data collected from randomisation up to the earliest of starting any subsequent cancer therapy or death. The criteria in Table 9 will be used to assign a best QoL response for HRQoL based on each QoL score. Improvement rate will be defined as the proportion of patients whose best overall QoL response was "Improved".

Table 9 Best Overall Response in HRQoL

Overall Score Response	Criteria
Missing	Patient has no evaluable baseline or post-baseline PRO assessments.
Improved	Patient meets one of the following criteria: 1. Has 2 consecutive visit responses of "improvement" at least 21 days apart. 2. Has 1 visit response of "improvement" and no further assessments and did not die within 2 PRO assessment visits.
No Change	Patient does not qualify for an overall score response of "improved" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "no change" at least 21 days apart. 2. Has 1 visit response of "no change" and no further assessments and did not die within 2 PRO assessment visits.
Deterioration	Patient does not qualify for an overall score response of "improved" or "no change" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "deterioration" at least 21 days apart. 2. Has 1 visit response of "deterioration" and no further assessments. 3. Has 1 visit response of "improvement" or "no change" followed by death within 2 PRO assessment visits.
Other	Patient does not qualify for one of the above.

Visit responses are considered consecutive and at least 21 days apart if the next response is within a window of 21 to 42 days. Within 2 PRO assessment visits is defined as within 62 days.

3.3.2 EORTC QLQ-C30/PAN26 time to sustained clinically meaningful deterioration

Time to sustained clinically meaningful deterioration of HRQoL will be calculated for the EORTC QLQ-C30 Global QoL score, the QLQ-C30 symptom and functional scales, the QLQ-PAN26 multi-item scales and the QLQ-PAN26 single item scales.

It will be defined as the time from date of randomisation until the earliest of the date of a sustained clinically meaningful deterioration in the respective score or death (by any cause in the absence of a sustained clinically meaningful deterioration), provided death occurs within two HRQoL assessment visits of the last HRQoL assessment where the respective score could be evaluated, and regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to deterioration in HRQoL (i.e. date of deterioration/death or censoring – date of randomisation + 1).

A sustained clinically meaningful deterioration will be defined as a deterioration per definition in Table 8, which must be sustained at the next scheduled visit and there must be no response of "improved" or "no change" between the two visit responses of "deterioration".

Patients whose respective score has not shown a sustained clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last HRQoL assessment where the respective score could be evaluated. Also, if the respective score shows a sustained clinically meaningful deterioration after two or more missed HRQoL assessments or the patient dies after two or more missed HRQoL assessment visits, the patient will be censored at the time of the last HRQoL assessment where the respective score could be evaluated. However, if a patient has two missing visits between two evaluable QoL assessments with outcome not equal to deterioration at the second assessment, but then subsequently shows sustained clinically meaningful deterioration, the patient will not be censored.

Time to sustained clinically meaningful deterioration for a respective score will only be evaluated if a patient has a baseline score that is far enough from the maximum or minimum possible score to allow for such a deterioration to occur.

3.3.3 EORTC QLQ-C30/PAN26 compliance

Summary measures of overall compliance and compliance over time will be derived separately for the EORTC QLQ-C30/PAN26 questionnaire forms. These will be based upon:

- Received forms = number of EORTC QLQ-C30/PAN26 questionnaire forms received back plus the number not received back where the reason was 'Subject too affected by symptoms of disease under investigation'.

- Expected forms = number of patients still under QoL follow-up at the specified assessment time excluding patients in countries with no available translation.

- Evaluable forms = subset of expected EORTC QLQ-C30/PAN26 questionnaire forms with at least one subscale that can be determined; or where the reason questionnaire not completed is ticked as 'Subject too affected by symptoms of disease under investigation'.

For each form, compliance over time will be calculated separately for each visit, including baseline, as the number of patients with an evaluable baseline form and a form at the time point (as defined above), divided by number of patients still expected to complete forms at that visit. Similarly, the evaluability rate over time will be calculated separately for each visit, including baseline, as the number of evaluable forms (per definition above), divided by the number of received forms.

For each form, the overall compliance rate is defined as number of patients with an evaluable baseline and at least one evaluable follow-up form (as defined above), divided by the number of patients expected to have completed at least a baseline form.

3.3.4 EQ-5D-5L

The EuroQoL five dimensions five level (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 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 EQ-5D 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.

The evaluable population will comprise all patients in the FAS.

3.4 Safety

Safety and tolerability will be assessed in terms of AEs (including serious AEs [SAEs]), deaths, laboratory data, vital signs, ECGs, physical examination, ECOG performance status, and exposure. These will be collected for all patients.

3.4.1 Adverse events

Adverse events and SAEs will be collected throughout the study, from informed consent until 30 days after the last dose of olaparib/placebo. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as possibly related to the study treatment should also be reported as an AE.

Adverse Event of special interest

Some AEs that follow clinical concepts are considered as adverse events of special interest (AESIs). They are grouped into the following three categories: Myelodysplastic syndrome / acute myeloid leukemia (MDS/AML), new primary malignancies and pneumonitis. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician will confirm the list of AEs of special interest (group terms and the specific preferred terms) and provide them for analysis. They will be confirmed at the BDRM prior to the final analysis for PFS and at the DRM prior to the final analysis of OS and PFS2.

3.4.2 Treatment exposure

Exposure will be defined as follows:

Total (or intended) exposure of olaparib/placebo:

- Total (or intended) exposure in days = last dose date - first dose date + 1

Actual exposure of olaparib/placebo:

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above. Dose interruptions are any periods when the patient does not take any treatment.

To calculate actual exposure, dose interruptions will include those where a patient forgot to take a dose.

Number of days on 300 mg olaparib/placebo bis in die (bid)

- Number of days on 300 mg olaparib/placebo bid = actual exposure for the dose assigned. Any days with changes in doses will not be counted.

Mean total daily dose per time period

- Sum of the total dose actually received in the time period of interest (considering interruptions and dose reductions) divided by number of days patient on dose for that time period (including interruptions and reductions).

Compliance will be assessed by calculating the actual exposure in days (total planned days - days of interruption) divided by the total exposure in days (last dose date - first dose date + 1) in percent. In addition, patient's individual drug accountability will be listed.

3.4.3 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression. Both will be derived using study treatment data up to the date of objective disease progression as defined by RECIST using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this will not be included in the derivation of dose intensity.

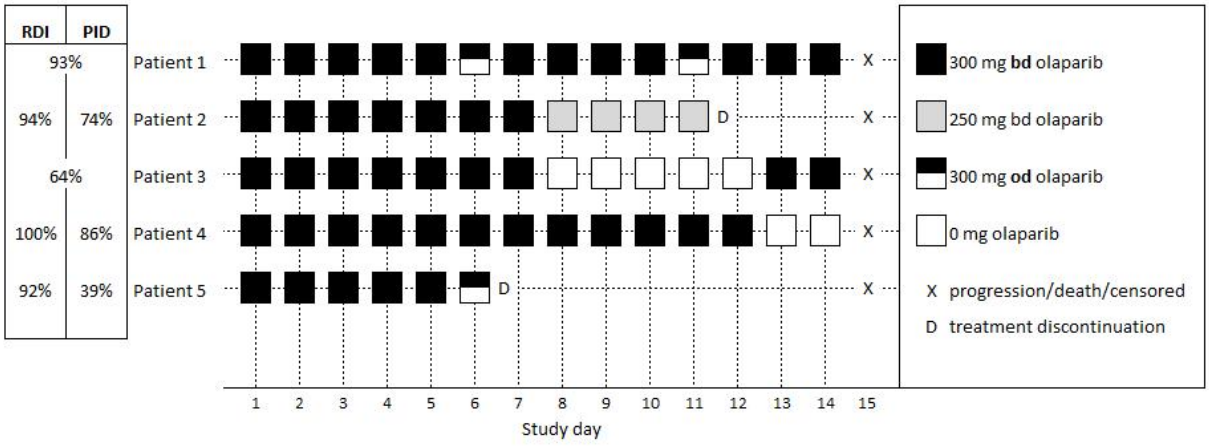
RDI and PID will be defined as follows:

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

- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or a censoring event) and D is the intended (or planned) cumulative dose up to progression (or a censoring event). D is the total dose that would be delivered, if there were no modification to dose or schedule.

For olaparib administered daily for the first two weeks of the cycle, the intended cumulative dose, D, will include all doses received up to midnight on the day of the last non-zero dose. Figure 1 provides examples of how dose intensity is calculated for olaparib.

Figure 1 Example of dose intensity calculations for olaparib



In this example, patients 1-4 progressed or were censored on Day 15. All four patients received less treatment than intended due to:

- Missed/forgotten doses (Patient 1)
- Dose reduction and early stopping (Patient 2)
- Dose interruption (Patient 3)
- Progression whilst on dose interruption (Patient 4)
- Early stopping (Patient 5)

Patient 1: RDI = PID = ((12 * 300 mg * 2) + (2 * 300 mg)) / (14 * 300 mg * 2) = 93%

Patient 2: RDI = ((7 * 300 mg * 2) + (4 * 250 mg * 2)) / (11 * 300 mg * 2) = 94%

PID = ((7 * 300 mg * 2) + (4 * 250 mg * 2)) / (14 * 300 mg * 2) = 74%

Patient 3: RDI = PID = (9 * 300 mg * 2) / (14 * 300 mg * 2) = 64%

Patient 4: RDI = (12 * 300 mg * 2) / (12 * 300 mg * 2) = 100%

PID = (12 * 300 mg * 2) / (14 * 300 mg * 2) = 86%

Patient 5: RDI = ((5 * 300 mg * 2) + (1 * 300 mg)) / (6 * 300 mg * 2) = 92%

PID = ((5 * 300 mg * 2) + (1 * 300 mg)) / (14 * 300 mg * 2) = 39%

3.4.4 Laboratory data

Laboratory data will be collected throughout the study, from screening to 30-day follow-up visit as described in Appendix C. Blood and urine samples for determination of pregnancy, haematology, clinical chemistry, and urinalysis will be collected as described in Section 5.2.1 of the CSP. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.5 Electrocardiograms

Electrocardiogram data will be collected during screening within 7 days prior to starting study treatment and when clinically indicated afterwards. For derivation of post baseline visit values considering visit window and how to handle multiple records present in any visit window, derivation rules as described in Section 3.4.9 below will be used.

3.4.6 Vital signs

Vital signs data including body temperature, height, weight, pulse and blood pressure will be collected as described in Appendix C. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.4.9 below will be used.

3.4.7 Physical examination

Physical examination data including 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 will be collected as described in Appendix C.

3.4.8 ECOG performance status

ECOG data will be collected as described in Appendix C. For derivation of post baseline visit values considering visit window, derivation rules as described in Section 3.4.9 below will be used.

3.4.9 General consideration for safety assessments

Time windows

Time windows will need defining for any presentations that summarise safety values by visit (ie. vital signs [incl weight and height], ECG, laboratory, and ECOG). The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.

- All unscheduled visit data should have the potential to be included in the summaries.

- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2, ie. the day after the first dose of study drug). The visits Screening, Cycle 1 Day 1, Treatment Discontinuation, 30-Day Follow-up and Survival Follow-up visits will be excluded from remapping. The equation to be used to calculate the time windows for each post-baseline visit is:

  Lower limit of interval=Upper limit of previous visit's time window +1

  Upper limit of interval=Nominal day at visit + ([nominal day at $visit_{i+1}$ - nominal day at $visit_i$]/2), where i = 3, 4, 5, 5.1, 5.2..., etc.

  If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

  For example, the visit windows for vital signs data with 28 days between scheduled assessments are:

  – Day 29, visit window 2 – 42

  – Day 57, visit window 43 – 70

  - Day 85, visit window 71 – 98
  - Day 113, visit window 99 – 126
  - ...

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit-based summaries:
  - If there is more than one value per patient within a time window, then the closest value should be summarised, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, for each treatment group visit data should only be summarised if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed. For example, if 150 patients were dosed in the study (1/3*150 = 50), data at a particular visit would be summarised if the number of observations is greater than min (20, 50). This would be in each treatment group. Eg, if olaparib arm at Visit 6 has > 20 observations and placebo arm has < 20 observations, the visit data will be summarised for the olaparib arm but not the placebo arm. If both had < 20 patients, the data for that visit will be presented as 'NC' (Not Calculated).
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment (olaparib or placebo). Any assessments made on day 1 will be considered pre-dose. If an assessment on day 1 is identified as baseline, then it will not be considered as "on treatment". Where safety data are summarised over time, study day will be calculated in relation to date of first treatment (olaparib or placebo).

Imputation of missing safety data

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (ie, below the lower limit of quantification) or "> x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

Imputation of missing age

- Age at randomisation: Age at randomisation (baseline) will be calculated from the date of birth. Due to country specific regulations the full date of birth will not be available for all patients. In this case the "age as collected" from the demographics CRF will be used instead.

- Age calculation after randomisation: If order to identify reference ranges for laboratory parameters during the study, the age of a patient needs to be calculated at the timepoint of the collection of the sample. If the date of birth of a patient is only partially collected, then the following rule will be applied: (a) if only day is missing, then calculate age using the first day of the month; (b) if day and month are missing, then calculate age using the first of July. Then use the maximum of this calculated age and of the age as collected at screening for identification of reference ranges. If the date of birth is completely missing, then age as collected will be used.

Imputation of missing dates

For **AEs**, imputation methods will be used on completely missing start dates. Missing AE stop dates are not imputed. Imputation for partial dates is not applicable because partial adverse event dates are not collected in this study. Imputed start dates are used to decide if an observation is treatment emergent and for calculation of the AE event rates. Data listings will show actual date values. Missing AE start dates will be imputed with the first dose date unless the end date indicates it started prior to first dose date, in which case impute the 1st January of the year where the AE stopped as the start date.

For **concomitant medications**, start and stop dates are captured on the CRF with no partial dates being entered in the CRF. If the drug started prior to study start, then this is indicated by a flag "Yes" and the start date is missing. If the treatment with the medication continues, then this is indicated by a flag "Yes" and the stop date is missing. For the analysis of medications, it is required to decide if the medication was taken during the time of study treatment. Such a medication may have started before, on or after the first dose of study drug and was taken in the time frame up to and including 30 days following the last dose of study drug. For patients on study treatment at the time of the PFS analysis, the DCO date will be used as the last dose of study drug.

Therefore, medications are considered as treatment emergent (taken during study treatment) if they:

- started on or before first dose and (stopped on or after first dose or are ongoing) OR
- started after first dose but prior to or on date of last dose plus 30 days.

The following conservative imputation rules will be applied:

- Start and stop date of medication present: apply the rules above
- Start date present but no stop date of medication: assume that medication is ongoing and apply the rules above.

- Start date missing and stop date is not missing and "treatment prior to study start" is "Yes": Temporarily set start date to the earliest of (date of first dose of study drug, stop date of medication) and apply the rules above
- Start date missing and stop date is missing and "treatment prior to study start" is "Yes": Temporarily set start date to the date of first dose of study drug, assume the medication is ongoing and apply the rules above
- Start date missing and stop date is not missing and "treatment prior to study start" is missing: Temporarily set start date to the earliest of (date of first dose of study drug, stop date of medication) and apply the rules above
- Start date missing and stop date is missing and "treatment prior to study start" is missing: Temporarily set start date to the date of first dose of study drug, assume the medication is ongoing and apply the rules above

3.5 Resource Use

Resource use outcome variables include the following:

- Total number of hospitalisations
- Length of hospital stay
- Reasons for hospitalisation
- Total number of ICU admissions
- Length of any time spent in an intensive care unit (ICU)
- Reasons for ICU admission

The length of hospital stay will be calculated as the difference between the date of hospital discharge (or death date when occurred during hospital stay) and the start date of hospitalisation (length of hospital stay = end date of hospitalisation – start date of hospitalisation + 1). If the start of study drug is after the start of hospitalisation, then the start of study drug will be used instead (length of hospital stay = end date of hospitalisation – start date of study drug + 1). If a patient was never treated with study drug and the date of randomisation is after the start date of hospitalisation, then the date of randomisation will be used instead (length of hospital stay = end date of hospitalisation – date of randomisation + 1). For patients without an end date at the time of the PFS analysis, the date of death will be used if available; otherwise the DCO date will be used.

Sum of total duration of hospital stay will be considered for analysis if patient was admitted to hospital more than one time during study period.

Hospital and ICU admissions will be counted as a single event if a patient is re-admitted on the same day.

The length of ICU stay will be calculated using the same method as detailed above for the length of hospital stay. However, if the end date of the ICU stay is not available, but the end date of the corresponding hospitalisation period is given, then the end of the ICU stay will be imputed using this date, instead of using the DCO date.

4. ANALYSIS METHODS

4.1 General Principles

Efficacy data will be summarised and analysed using the FAS on an ITT basis while HRQoL data will be analysed using the PRO analysis set (see Section 2.1) and will compare the treatment groups on the basis of randomised treatment, regardless of the treatment actually received. In addition, as sensitivity to the main analyses of PFS, PFS2, OS, TDT, TFST and TSST, analyses of these endpoints will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless specified otherwise. Median and corresponding 95% CI of time to event data (PFS, OS, PFS2, TFST, TSST, TDT) will be calculated using a Kaplan-Meier technique.

When assessing safety and tolerability, summaries will be produced based on the safety analysis set and will compare the treatment groups on the basis of treatment actually received. The safety data will be summarised descriptively and will not be formally analysed.

4.1.1 Presentation of results in summary tables

If not stated otherwise, tabulations will be presented by treatment group as follows:

- Olaparib 300 mg bid
- Placebo bid
- Total

Data listings will include at least the following details:

- Patient identifier
- Centre identifier
- Actual / randomised treatment group

Data listings will be sorted by treatment group (planned or actual) and patient ID, if not stated otherwise.

4.2 Analysis Methods

A single interim PFS analysis for futility will be performed when 50% of the final number of progression events has been reached (approximately 44 PFS events). A final PFS analysis will be performed when approximately 87 progression events have occurred (60% maturity). No further analyses of PFS are planned beyond this point.

One interim analysis for OS will be performed at the time of the final PFS analysis (approximately 87 PFS events). A final analysis of OS will be performed when approximate 106 death events have occurred.

Individual efficacy response data will be listed in a by-patient listing.

Timing of the statistical analysis is given in Table 10.

Table 10 Timing of Statistical Analyses

Timing of analysis	Outcome Variable
Interim PFS when ~44 PFS events reported	PFS
Final PFS when ~87 PFS events reported	PFS, PFS2, TDT, TFST, TSST, OS, ORR, BoR, DoR and adjusted mean change from baseline in global HRQoL score.
Final OS when ~106 OS events reported	OS, PFS2, TDT, TFST, TSST, and adjusted mean change from baseline in global HRQoL score.

Safety variables will be analysed at each analysis time point.

The treatment comparison is olaparib 300 mg bid versus placebo.

The following table details which efficacy endpoints are to be subject to formal statistical analysis, together with pre-planned sensitivity analyses making clear which analysis is regarded as primary for that endpoint.

Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
PFS	**Primary analysis**: log-rank test using BICR data
	Key sensitivity analyses: log-rank test using BICR data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
	Additional sensitivity analyses:

Table 11 Formal Statistical Analyses to be Conducted and Pre-Planned Sensitivity Analyses

Endpoints Analysed	Notes
	1) Evaluation time bias analysis; log-rank test using BICR data
	2) Attrition bias analysis (using alternative censoring rules); log-rank test using BICR data
	3) Ascertainment bias analysis; log-rank test using investigator data
	4) Deviation bias analysis (if meaningful to do); log-rank test using BICR data
OS	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test data in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
	Supportive analysis: Kaplan-Meier (KM) plot of time to censoring for OS
PFS2	**Primary analysis**: log-rank test using investigator assessment of second progression
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TDT	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TFST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
TSST	**Primary analysis**: log-rank test
	Key sensitivity analysis: log-rank test in randomised patients confirmed as gBRCA mutation positive by the Myriad test (if subset of FAS)
ORR	**Primary analysis**: logistic regression using BICR data
	Sensitivity analysis: logistic regression using investigator data
Adjusted mean change from baseline in global HRQoL score	**Primary analysis**: mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit **Supportive analysis**: logistic regression on global HRQoL score improvement rate.
Time to sustained clinically meaningful deterioration in HRQoL	**Primary analysis**: log-rank test **Supportive analysis**: attrition bias analysis (log-rank test using alternative censoring rules)

4.2.1 Multiplicity

In order to describe the nature of the benefits of olaparib maintenance treatment, PFS and OS will be tested at a 1-sided significance level of 2.5%.

In addition to these planned analyses, which will be performed and reported in the CSR, in order to strongly control the type I error at 2.5% 1-sided for key label claims, a multiple testing procedure (MTP) will be employed across the primary endpoint (PFS) and key secondary endpoint (OS).

A hierarchical testing strategy will be employed where PFS is tested first using the full test mass (full test mass = alpha 2.5% 1-sided) and the key secondary endpoint of OS will then be tested using a MTP with a recycling strategy (ie, the MTP will recycle the test mass to the endpoint not yet rejected in the hierarchy outlined in Figure 2).

The MTP is detailed below.

Figure 2 Multiple Testing Procedure

The OS will only be tested if the null hypothesis (of no difference) is rejected for PFS. One interim analysis for OS will be performed at the time of the final PFS analysis (approximately 87 PFS events). The Lan and DeMets approach that approximates the O'Brien & Fleming spending function will be employed to preserve the overall 1-sided type-I error rate of 2.5% (Lan and DeMets 1983). If the interim analysis for OS occurs at exactly 57% of the 106 OS events (60 OS events), statistical significance for OS will be declared if the null hypothesis for PFS is rejected and the observed p-value for OS is $p<0.003$, which equates to a HR ≤ 0.49. The significance level at the interim and the final analysis will be determined based on the exact number of events at the time of the interim and final analyses and documented in the minutes of the blind data review meeting prior to DB lock. If the interim analysis for OS occurs at exactly 57% of OS events and the number of OS events at the final analysis is approximately 106 then the 1-sided significance level to be applied for the final analysis will be 2.4%. Statistical significance for OS will be declared if the observed p-value for OS is $p<0.024$, which equates to a HR ≤ 0.68.

4.2.2 Primary variable - progression free survival

A summary of PFS will be prepared to present the number of patients with progression and no progression. Tabulation will detail the total number of progressions and no progressions, the

number of patients with progression identified by RECIST (separately for TLs, NTLs, and new lesions) and death as well as details about non-progressed patients including the number of patients progression-free at time of DCO, lost to follow-up, withdrawn consent, and prematurely censored (RECIST or death) if they did not progress and if the latest scan prior to DCO was more than one scheduled tumour assessment interval (+ 2 weeks) prior to the DCO date. The summary will be presented by treatment group.

The PFS as defined in Section 3.2.1 will be analysed using a log-rank test for generation of the p-value and using the Breslow approach for handling ties in the following manner:

```
PROC LIFETEST DATA=...;
  TIME pfsTime*censor(1);
  TEST trtn;
RUN;
```

By using the TEST-Statement within LIFETEST procedure the test statistics U and the covariance matrix will be averaged over the possible orderings of the tied failure times (SAS Lifetest 2008).

The HR and its CI will be estimated from the log-rank (U and V statistics) follows directly from the LIFETEST model as used above for calculation of p-values (Berry et al 1999 and Sellke et al 1983)

$$HR = EXP(\frac{U}{V})$$

$$95\%\ CI = \left[EXP\left(\frac{U}{V} \pm \frac{1.96}{\sqrt{V}}\right)\right]$$

Where $U = \sum_i (d_{1j} - e_{1j})$ is the log-rank test statistic (with d_{1j} and e_{1j} the observed and expected events in group 1); and V the variance of the log-rank test statistic. U and V will be obtained directly from LIFETEST procedure; U will be taken from the table "*Rank Statistics*" while V will be taken from the table "*Covariance Matrix for the Log-Rank Statistics*".

The log-rank test statistic, the HR (olaparib vs. placebo) together with its corresponding 95% CI and p-value will be presented (a HR less than 1 will favour olaparib).

The median and 95%-CI of PFS and the proportion of patients progression-free at 6 months, 12 months, 18 months, 24 months, 36 months and 48 months will be summarised and presented by treatment group.

In addition, duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to be non-progressor) in censored (not progressed) patients only, presented by treatment group.

The following KM plots of PFS will be presented by treatment group. The KM plot will be prepared using LIFETEST procedure and selecting ODS graphics. The plot will identify censored patients using a different symbol and include patients at risk at specific time points:

- PFS
- PFS with censoring and event flags reversed

The assumption of proportionality will be assessed. The results of these model checks will not be presented in the CSR as part of the formal outputs; however, any deviation from this assumption will be considered in the interpretation. 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 producing 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 complementary log-log plot will be directly produced in SAS LIFETEST procedure using ODS graphics option PLOTS=(LLS) in the PROC-Statement. The graph will be assessed visually. Two parallel lines favour the proportionality assumption. To support the proportionality assessment a Cox proportional hazard's model will be constructed containing the interaction of treatment and the logarithm of PFS_time (treatment*log(PFS_time)). The p-value obtained from the Wald Chi-squared test for the time dependent covariate will be presented. The following SAS-code may be used:

```
PROC PHREG DATA=...;
  CLASS trtn (REF='placebo') / PARAM=REFERENCE;
  MODEL pfs_Time *censor(1)=trtn timeDependent / TIES=EFRON;
  timeDependent = trtn*LOG(pfs_Time);
  proportionality_test: TEST timeDependent;
RUN;
```

A further analysis of PFS (using investigator assessed RECIST) may be performed at the time of the final OS analyses, if requested by health authorities. A final decision will be made at the BDRM for the final OS analysis.

4.2.2.1 Progression-free survival sensitivity analyses

As a sensitivity analysis to the primary endpoint of PFS, the primary analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test. The same methodology and model will be used as for the primary analysis and the HR and associated 95% CI will be reported. A KM plot of PFS in this subset of patients will be presented by treatment group.

(a) 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 their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

A by-patient listing will be produced similar to the PFS listing but including only patients who progressed but were censored for the primary analysis due to missing of two, or more, non-evaluable tumour assessments. The actual PFS times will be reported.

(b) Evaluation-time bias

A sensitivity analysis 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 log-rank test, as described for the primary analysis of PFS, will be repeated using the midpoint between the time of progression and the previous evaluable RECIST assessment to derive PFS time for patients with RECIST progression events. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Chen and Sun 2010). This approach will use the BICR RECIST assessments.

To support this analysis, the individual mean time difference between RECIST assessments (patient inter-assessment times) will be calculated and summarised using descriptive statistics.

(c) Ascertainment bias

The primary analysis of PFS (log-rank test) will be repeated using investigator assessed RECIST data. The HR and 95% CI will be presented. A KM plot of PFS based on the investigator assessed RECIST data will be presented by treatment group.

Ascertainment bias will be assessed through the use of two measures proposed by Amit (Amit, et al., 2011): the early discrepancy rate (EDR) and late discrepancy rate (LDR). The EDR represents the positive predictive value of Investigator assessment and quantifies the frequency with which the Investigators declare progression early relative to BICR within each arm as a proportion of the total number of Investigator assessed PD's. The LDR quantifies the frequency that the Investigators declare progression later than BICR as a proportion of the total number of discrepancies within the arm. If the distribution of discrepancies is similar between the arms, then this suggests the absence of evaluation bias favouring a particular arm.

EDR and LDR are calculated as:

$$EDR = \frac{\left(\begin{array}{c}\text{number of times Inv. declares PD when BICR does not} \\ + \text{number of times Inv. declares PD earlier than BICR}\end{array}\right)}{\left(\begin{array}{c}\text{number of times both Inv. and BICR declare PD} \\ + \text{number of times Inv.declares PD when BICR does not}\end{array}\right)}$$

$$LDR = \frac{\left(\begin{array}{c}\text{number of times BICR declares PD when Inv. does not} + \\ \text{number of times Inv. declares PD later than BICR}\end{array}\right)}{\left(\begin{array}{c}\text{number of times Inv. declares PD when BICR does not} \\ + \text{number of times BICR declares PD when Inv. does not} \\ + \text{number of times Inv. declares PD later than BICR} \\ + \text{number of times Inv. declares PD earlier than BICR}\end{array}\right)}$$

The EDR and LDR will be calculated for each treatment arm and the differential discordance around each measure will be defined as the rate on the experimental arm minus the rate on the control arm.

If there is an important discrepancy between the primary analysis using BICR assessments and this sensitivity analysis using investigator assessments, the proportion of patients with site but no central confirmation of progression will be summarised by treatment group and the primary analysis will be repeated for this subset of patients. The approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value, but only if an important discrepancy exists. Discrepancy between the primary analysis using BICR assessments and investigator assessments of progression will be discussed at the BDRM. The study team will decide whether the discrepancy between assessments is of importance and whether or not additional analyses are required.

A by-patient listing will be produced to present patients where at least one assessment differs between investigator and central reviews of RECIST progression.

(d) Deviation bias

As a sensitivity analysis to the primary endpoint of PFS, an analysis excluding patients with "important" deviations that may affect the efficacy of the trial therapy will be performed if the following deviations were reported for > 10% of patients:

- did not have the intended disease or indication or
- did not receive any randomised therapy

A log-rank test will be repeated using the BICR RECIST data, using the same method as described for the primary analysis of PFS. The HR and 95% CI will be presented.

The treatment status at progression by patients who have progressed / censored including the number of patients and percentage of on-treatment or discontinued will be tabulated. The number of days from treatment discontinuation to progression for patients who have discontinued treatment will be summarised descriptively. Data will be presented by treatment group.

Patients censored for progression at more than 14 weeks before the DCO ('censored > 14 weeks before DCO', 'censored <= 14 weeks before DCO') will be tabulated and presented by treatment group.

A by-patient listing will be produced including patients with an important deviation only.

4.2.2.2 Progression-free survival subgroup analyses

Subgroup analyses will be conducted comparing PFS between treatments. The purpose of the subgroup analyses is to assess the consistency of treatment effect across potential or expected prognostic factors. KM plots will be produced for each subgroup according to treatment group.

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 5 events in a subgroup in at least one treatment group), the results of the subgroup analysis (HR and 95% CI) will not be presented, however, all patients with non-missing subgroup data will be included in the Cox model used for the analysis (see below).

The following subgroups will be analysed for PFS:

- Previous chemotherapy (FOLFORINOX variants, gemcitabine/cisplatin, other); Reference=FOLFORINOX variants
- Type of previous chemotherapy (doublets, triplets, other); Reference=doublets
- Time on first-line treatment till randomisation (≤ 6 months vs > 6 months); Reference=≤6 months
- Best response on first-line treatment (SD vs PR/CR); Reference=SD

These will be determined from the "Metastatic Pancreas Cancer Therapy" (CAPRX2) module of the eCRF at screening by medical review.

- Presence or absence of biliary stent; Reference=Presence of biliary stent

This will be determined from the "Surgical History" (HISS) module of the eCRF at screening by medical review.

- Measurable versus non measurable disease / NED at baseline; Reference=non measurable disease / NED at baseline

This will be determined programmatically from the baseline BICR results.

- gBRCA mutation type (BRCA1, BRCA2, BRCA1/2 (both), non-gBRCAm); Reference=BRCA1

This will be determined programmatically from the Myriad central laboratory test results.

- Age at randomisation (>= 65 vs < 65); Reference=< 65
- Race (White vs Other); Reference=White
- Sex (Male vs Female); Reference=Male

These will be determined programmatically from the "Demography" (DEM) module of the eCRF at screening.

Other baseline variables may also be assessed if there is clinical justification. A final decision will be made at the BDRM.

For each subgroup, the HRs (olaparib: placebo) and associated CIs will be calculated from a Cox proportional hazards model (TIES = Efron) that contains the treatment group, factor (subgroup) and treatment-by-factor interaction term. All patients with non-missing subgroup category data will be included in the Cox model. Statistics produced by the Cox model, i.e. HR/CI will only be displayed in subgroup categories with a sufficient number of events available (at least 5 events in both treatment groups), otherwise, only the total number of patients and events will be displayed. Reference cell coding will be used introduced by the PARAM=REFERENCE option in the CLASS-Statement. Individual reference levels will be defined using the REF= option within the CLASS-Statement for each subgroup. The treatment effect HRs for each treatment comparison along with their CIs will be obtained for each level of the subgroup from this single model. Analysis will be carried out using PHREG procedure in SAS in the following manner:

```
PROC PHREG DATA=...;
  CLASS trtn (REF='placebo') chemoType (REF='doublets')
    / PARAM=REFERENCE;
  MODEL pfs*censor(1)=trtn chemoType trtn*chemoType
    / TIES=EFRON;
RUN;
```

The HRs and 95% CIs will be presented in an overview table as well as on a forest plot including the HR and 95% CI from the overall population (using the HR and 95% CIs from the primary analysis).

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 PFS.

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 two-sided 10% significance level. If a covariate does not have more than 5 events per level in both treatment groups (of the covariate) it will be included as a covariate in the model but the covariate-by-treatment interaction term will be omitted. 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 1985.

A by-patient listing will be produced for presenting individual PFS data.

4.2.3 Overall Survival

A summary of survival status at the time of analysis will be produced. This will summarise the number of patients who have died, who are still in survival follow-up, who are lost to follow-up or who have withdrawn consent. Results will be presented by treatment group.

Overall survival as defined in Section 3.2.2 will be analysed at the time of the final analysis for PFS and will use the same methodology and model (provided there are sufficient events available for a meaningful analysis [> 5 deaths in both treatment groups], if not descriptive summaries only will be provided). A further analysis of OS will be performed when approximately 106 deaths have occurred.

Median OS and corresponding 95% CI will be summarised including the number of deaths, and survival at month 6, 12, 18, 24, 36 and 48. Results will be presented by treatment group.

The analysis will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test.

The sensitivity analyses outlined for PFS in Section 4.2.2 will not be repeated for OS with the exception of a KM plot. Two KM plots will be produced. The first KM plot will show time to censoring of OS and the second KM plot will show will show time to censoring where the censoring indicator is reversed (median time to follow-up where events will be censored and previously censored patients will be treated as events). The first KM plot will be repeated excluding any patients who did not have a gBRCA mutation status confirmed by the central Myriad test.

OS data will be listed in a by-patient listing.

Similar subgroup analyses (except the interaction test) will be conducted comparing OS between treatments as detailed for PFS in Section 4.2.2.2, using the same methodology and model. KM plots will be produced for each subgroup according to treatment group. 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 5 events in a subgroup in at least one treatment group), the relationship between that subgroup and OS will not be formally analysed. In this case, only descriptive summaries (number of patients, number (%) of events, and KM plots) will be provided.

4.2.4 Time from randomisation to second progression

The status of PFS2 as defined in Section 3.2.3 will be summarised by the number and percentage of patients experiencing a PFS2 event and the type of progression (objective progression by RECIST, symptomatic progression or death). Results will be presented by treatment group.

The analysis of PFS2 will use the same methodology and model as the primary analysis of PFS. No multiplicity adjustment will be applied as this is viewed as a supportive endpoint.

A KM plot of PFS2 will be provided by treatment group. A KM plot of the time to censoring where the censoring indicator of the PFS2 analysis is reversed will be produced (called median time to follow-up where events will be censored and previously censored patients will be treated as events).

As a key sensitivity, the analysis of PFS2 will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. A KM plot of PFS2 in this subset of patients will be presented by treatment group.

The median and 95%-CI of PFS2 and the proportion of patients with no second progression at 6, 12, 18, 24, 36 and 48 months will be summarised and presented by treatment group.

Days between second progression and last assessment prior to second progression will be summarised descriptively by treatment group.

A by-patient listing will be produced including details about time of second progression.

4.2.5 Time to first subsequent therapy or death

The TFST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TFST and 95% CI for each treatment group.

As a key sensitivity, the analyses of TFST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TFST and 95% CI

will be reported by treatment group. In addition, a KM plot of TFST will be presented by treatment group.

The time between progression and starting subsequent cancer therapy will be summarised.

In addition, best overall RECIST response to first subsequent cancer therapy by treatment group will be provided.

Individual TFST will be presented in a by-patient listing.

4.2.6 Time to second subsequent therapy or death

The TSST will be analysed using the same methodology and model as the primary analysis of PFS. The HRs for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TSST and 95% CI for each treatment group.

As a key sensitivity, the analyses of TSST will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TSST and 95% CI will be reported by treatment group. In addition, a KM plot of TSST will be presented by treatment group.

In addition, best overall RECIST response to second subsequent cancer therapy by treatment group will be provided.

Individual TSST will be presented in a by-patient listing.

4.2.7 Time to study treatment discontinuation or death

The TDT will be analysed using the same methodology and model as the primary analysis of PFS. The HR for the treatment effect together with 95% CIs will be presented. A KM plot will be presented by treatment group, together with status, median TDT and 95% CI for each treatment group.

As sensitivity, the analyses of TDT will be repeated in those patients whose gBRCAm status is confirmed by the Myriad test. In this subset of patients, median TDT and 95% CI will be reported by treatment group. In addition, a KM plot of TDT will be presented by treatment group.

Individual TDT will be presented in a by-patient listing.

4.2.8 Best objective response and objective response rate

For each treatment group, BoR as defined in Section 3.2.7 will be summarised by n (%) for each category (CR, PR, SD, NED, PD, NE) based on the BICR data. This will also be summarised based on the investigator-assessed data. No formal statistical analyses are planned.

ORR as defined in Section 3.2.8 will be summarised descriptively, ie, number of patients (%) by treatment group, and using logistic regression, based on the BICR data, in patients in the FAS (ITT population) with measurable disease at baseline defined according to BICR. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). If there are not enough responses for a meaningful analysis using logistic regression then a Fisher's exact test will be presented.

ORR will also be summarised based on the investigator-assessed data in the FAS (ITT population) with measurable disease at baseline defined according to investigator assessment using the same methods as for the BICR data. Any patients who experienced CR or PR which was first observed whilst receiving subsequent therapy after discontinuation of olaparib will be identified and not treated as responders per definition of BoR in Section 3.2.7.

In addition, the duration and time to onset of objective response in patients with objective response (by BICR and by investigator assessment) will be summarised by treatment group.

BoR will be presented in a by-patient listing. In addition, a listing will be prepared including objective responders (confirmed CR or PR) only.

4.2.9 Disease control rate

The DCR as defined in Section 3.2.9 will be summarised (ie, n, %) by treatment group. The DCR will be presented based on the BICR data and also the investigator recorded data.

4.2.10 Target lesion summary and other efficacy

Target lesion size, and percentage change from baseline will be summarised by treatment group and time point using descriptive statistics. Lesion data according to BICR and also by investigator assessment will be listed in by-patient listings.

Subsequent cancer therapy relative to progression will be summarised using frequency counts and percentages. The tabulation will detail any patients receiving any further therapy for cancer by time of therapy ('After progression', 'Before progression', 'No progression'). Tabulation will include the number of patients where no subsequent cancer therapy was recorded as well. Data will be presented by treatment group.

4.2.11 Patient reported outcomes

The analysis population for PRO data will be the PRO analysis set as defined in Section 2.1. Derivations and rules for transformation of PRO data are defined in Section 3.3.

Impact of olaparib on HRQoL

The impact of olaparib on HRQoL will be assessed through an analysis of the global health status / QoL gathered from items 29 and 30 of EORTC QLQ-C30.

Descriptive statistics including change from baseline score will be produced by time point for the EORTC QLQ-C30 global health status / QoL score. Results will be presented by treatment group. Arithmetic mean (± standard deviation) plots of scores versus time point will be produced in linear scale.

Adjusted mean change from baseline in global QoL score will be analysed using a mixed model for repeated measures (MMRM) analysis of all of the post-baseline scores for each visit and will be presented by treatment group. Only visits with at least 25% of non-missing values in both treatment arms (calculated separately by treatment arm) are included in the model. The study treatment discontinuation visit and the safety follow-up visit will be excluded from this analysis. Restricted maximum likelihood (REML) estimation will be used. The model will include randomised treatment group, visit and treatment by visit interaction as explanatory variables and the baseline QoL score as a covariate along with a baseline QoL score by visit interaction. Treatment, visit and treatment by visit interaction will be fixed effects in the model. The treatment by visit interaction will remain in the model regardless of significance.

An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The following provides sample code for implementing the MMRM analysis:

```
* Model 1 (adjusted means by treatment and visit);
PROC MIXED DATA=… METHOD=REML;
   CLASS trt visit patient;
   MODEL cfb = trt visit trt*visit base base*visit / S DDFM=KR;
   REPEATED visit / TYPE=UN SUBJECT=patient;
   LSMEANS trt*visit / SLICE=visit AT MEANS DIFF PDIFF ALPHA=0.05 CL;
RUN;

* Model 2 (adjusted means by treatment, averaging over all visits);
PROC MIXED DATA=… METHOD=REML;
   CLASS trt visit patient;
   MODEL cfb = trt visit trt*visit base base*visit / S DDFM=KR;
   REPEATED visit / TYPE=UN SUBJECT=patient;
   LSMEANS trt / AT MEANS PDIFF ALPHA=0.05 CL;
RUN;
```

where TRT is the randomised treatment group, VISIT is the visit, CFB is the change from baseline in the global QoL score, and BASE is the baseline global QoL score.

If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be tried in order until convergence is reached: Toeplitz with heterogeneity, autoregressive with heterogeneity, Toeplitz, and autoregressive.

The adjusted mean change from baseline estimates (obtained from LSMEANS-Statement as the calculated least square means adjusted for the random component of the model), standard error, and corresponding 95% CIs will be presented by visit for each treatment group. Corresponding plots over time will be presented.

An overall adjusted mean estimate will also be derived that will estimate the average treatment effect over all visits giving each visit equal weight. For this overall treatment comparison, adjusted mean estimates per treatment group and corresponding 95% confidence intervals will be presented along with an estimate of the treatment difference, 95% confidence interval and p-value. Also, for each visit, an estimate of the treatment difference and a 95% confidence interval will be presented.

A by-patient listing will be produced for the EORTC QLQ-C30 global QoL scale presenting raw scores (overall health and overall quality of life items) and the transformed score by time point.

As a supportive analysis, EORTC QLQ-C30 global QoL score improvement rate will be analysed using a logistic regression model. The model will include a binary variable as response (improvement=1; no improvement=0) and treatment group as an explanatory variable in the MODEL-Statement together with the option CLPARM=PL to compute profile likelihood CIs and p-values. Explanatory variables will be introduced using a reference cell coding (option PARAM=REFERENCE) while the option REF= will be used to identify the reference. The following provides sample SAS code for implementing the analysis:

```
PROC LOGISTIC DATA=… ALPHA=0.05;
   CLASS trt(REF='PLACEBO') / PARAM=REFERENCE;
   MODEL improvement(EVENT='1') = trt / CLPARM=PL;
   EXACT trt / ESTIMATE;
RUN;
```

If the overall improvement rate is < 5%, no analysis will be performed (note that if the response rate in only one of the treatment groups is < 5% but ≥ 5% in the other treatment group then the analysis will still be performed). If the overall response rate is low (< 20%) a Fisher's exact test (for an example SAS code see below) will be considered and mid p-values used. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood CIs and p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

```
PROC FREQ DATA=…;
   TABLE improvement * trt / FISHER;
   EXACT OR / ALPHA=0.05;
RUN;
```

In addition, a summary table of EORTC QLQ-C30 global QoL score best overall QoL response will be provided (improvement, deterioration, no change).

Compliance

The EORTC QLQ-C30 and EORTC QLQ-PAN26 compliance (overall compliance and by visit compliance, separately for each form) will be summarised and presented by treatment group.

4.2.12 Exploratory analyses

EORTC QLQ-C30 functional and symptom scales and EORTC QLQ-PAN26 scales

The analysis as described above to assess the impact of olaparib on HRQoL will be repeated for selected EORTC QLQ-C30 functional and symptom scales as well as for selected EORTC QLQ-PAN26 scales. This involves the following, presented by treatment group:

- Descriptive statistics including change from baseline
- Arithmetic mean (±standard deviation) plots of scores versus time point
- Adjusted mean change from baseline (95% CI) over time (summary tables and plots)
- Frequency tables of best overall QoL response (improvement, deterioration, no change)

The following scores will be analysed in the exploratory analysis:

- QLQ-C30 Functional scale: Physical score (items 1-5), role score (items 6, 7), emotional score (items 21-24), cognitive score (items 20, 25), social score (items 26, 27)
- QLQ-C30 Multi-item symptom scale: Pain score (items 9, 19), fatigue score (items 10, 12, 18), nausea/vomiting score (items 14, 15)
- QLQ-C30 Single-item symptom scale: Loss of appetite (item 13), insomnia (item 11)
- QLQ-PAN26 Multi item scale: Pancreatic pain score (items 31, 33-35), digestive symptoms score (items 36, 37), hepatic score (items 44, 45)
- QLQ-PAN26 Single item scale: Worried about low weight (item 41)

These additional sub-scales are considered exploratory to support the primary EORTC QLQ-C30 global QoL and will be used to assess whether any observed differences in the global measure are driven by particular domains of functioning, symptoms, or group of symptoms. P-values will not be calculated for these supportive analyses.

A by-patient listing will be produced presenting the EORTC QLQ-C30 functional and symptom scales. A separate by-patient listing will be produced for EORTC QLQ-PAN26 scales. Listings will include the raw scores for each item and the transformed scores by time point.

Time to sustained clinically meaningful deterioration in HRQoL

A supportive analysis of time to sustained clinically meaningful deterioration will be performed, using the same methodology and model as described for the primary analysis of PFS (log-rank test). For each type of score, the analysis will be carried out for a subset of patients from the PRO set, i.e. only for those patients that have the potential for a clinically

meaningful deterioration to occur. The following scores will be analysed (requirement for baseline score):

- QLQ-C30 Global Health Status / QoL score (baseline score ≥ 10)
- QLQ-C30 Functional scale: Physical score (baseline score ≥ 10)
- QLQ-C30 Multi-item symptom scale: Pain score, fatigue score, nausea/vomiting score (baseline score ≤ 90)
- QLQ-C30 Single-item symptom scale: Loss of appetite (baseline score ≤ 90)
- QLQ-PAN26 Multi item scale: pancreatic pain (baseline score ≤ 90)
- QLQ-PAN26 Single item scale: worried about low weight (baseline score ≤ 90)

A KM plot of time to sustained clinically meaningful deterioration will be presented by treatment group. Summaries of the median time to sustained clinically meaningful deterioration of HRQoL for each treatment will be produced.

A sensitivity analysis will be performed to assess the impact of attrition bias. This will be assessed by repeating the time to sustained clinically meaningful deterioration analysis except that the actual times to deterioration of HRQoL, rather than the censored times, of patients who experienced sustained clinically meaningful deterioration or died immediately following two, or more, non-evaluable assessments will be included. In addition, patients who take subsequent therapy prior to their last evaluable HRQoL assessment or prior to sustained clinically meaningful deterioration of HRQoL or death will be censored at their last evaluable HRQoL assessment prior to taking the subsequent therapy.

EQ-5D-5L health state utility index

The evaluable population will comprise all patients in the FAS.

Health state utility index and visual analogue scale (VAS) for health status will be summarised using descriptive statistics. The change from baseline and the percentage change from baseline will be calculated for each time point and presented by randomised treatment group, and both will be presented graphically using arithmetic mean (±standard deviation) plots. EQ-5D-5L five-point dimension scales will also be summarised over time by randomised treatment group.

By-patient listings will be produced presenting the individual EQ-5D-5L raw scores and review assessments.

Resource use

Total length of hospital stay and total length of ICU stay (number of days) will be summarised by randomised treatment group. Total number of days spent in hospital and in ICU, the number of hospitalisations and reasons for hospitalisation will also be summarised by randomised treatment group.

A by-patient listing will be produced presenting details of hospital and ICU stay.

ECOG

A by-patient listing will be produced presenting details of ECOG performance status.

Impact of Switching to PARP inhibitors (or other potentially active investigational agents) on Overall Survival Analysis

Exploratory analyses of OS adjusting for impact of subsequent PARP inhibitor trial or treatment may be performed if a sufficient proportion of patients receive the therapies of interest. Decision will be made at the BDRM.

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 patients receiving physician's choice of chemotherapy, splitting between those that have and haven't received a PARP inhibitor at the time of the analyses. Further detail will be provided in the Payer Analysis Plan under the responsibility of AstraZeneca. These analyses are intended to support reimbursement appraisals.

Biomarkers

Collection details for biomarker samples will be listed in a by-patient listing.

4.2.13 Safety

Safety data will be summarised and listed only. No formal statistical analyses will be performed on the safety data. All safety data will be summarised by actual treatment group (olaparib or placebo). However, some listings such as AEs listings will display the actual dose the patient received at onset of an AE.

Adverse events

All AEs, both in terms of Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and Common Toxicity Criteria for Adverse Events (CTCAE) grade, will be listed and summarised descriptively by count (n) and percentage (%) for each treatment group. MedDRA dictionary will be used for coding. Any AE occurring before olaparib/placebo treatment (ie, before Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

The summary tables will include all AEs that occurred after the start of treatment up until the end of the 30 day follow-up period. The 30 day follow-up period will be defined as 30 days following discontinuation of olaparib/placebo treatment. Any untoward event occurring subsequent to the 30-day follow-up AE reporting period that the investigator assesses as

possibly related to the study treatment will also be included in the AE listings, but not in the summary tables.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved), investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each PT will be presented (ie, multiple events per patient will not be accounted for apart from on the episode level summaries).

Summary information (the number and percent of patients by actual treatment) will be tabulated for:

- All AEs
- All AEs causally related to study medication
- AEs with CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, causally related to study medication
- AEs leading to dose modification of olaparib/placebo
- AEs leading to dose interruption of olaparib/placebo
- AEs leading to dose reduction of olaparib/placebo
- AEs with outcome of death
- AEs with outcome of death causally related to study medication
- All SAEs
- All SAEs causally related to study medication
- DAEs
- AEs leading to discontinuation of olaparib/placebo, causally related to study medication

An overall summary of the number and percentage of patients in each category will be presented.

In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarised by PT, by decreasing frequency. This cut-off may be modified after review of the data.

Each AE event rate (per 1000 patient years) will be summarised by system organ class (SOC) and also by PT within each SOC. The event rate will be calculated as the number of patients

with an AE in that SOC or with that PT divided by the sum of the duration of therapy (for patients without such an event) and the time to the AE (for patients with such an event) in each group multiplied by 1000. The denominator defines the time at risk for an event with:

- Duration of therapy (days) calculated as:
  MINIMUM([date of last dose + 30-day safety follow-up period], OS date, DCO) – date of first dose + 1

- Time to the AE (days) calculated as date of first occurrence of the AE – date of first dose + 1 (in days), imputed AE start dates can be used in case of missing start dates.

The formula for calculating the event rate for a specific PT is as follows:

$$eventRate_{PT} = \frac{\#patients_{PT}}{(\sum durationTherapy_{\neq PT} + \sum timeToAE_{PT})/365.25} * 1000$$

PT = Patients with the event reported; eg, all patients with an AE where PT equals to 'Headache'.

$\neq PT$ = Patients without the event; eg, all patients who never experienced an AE where PT is equal to 'Headache'.

Similarly, the formula for calculating the event rate in as SOC is as shown below:

$$eventRate_{SOC} = \frac{\#patients_{PT\ in\ SOC}}{(\sum durationTherapy_{no\ PT\ in\ SOC} + \sum timeToAE_{PT\ in\ SOC})/365.25} * 1000$$

PT in SOC = Patients with any reported event in the respective SOC

$no\ PT\ in\ SOC$ = Patients who did not report any event in the respective SOC

AEs will be assigned CTCAE grades (National Cancer Institute CTCAE version 4.0) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, SOC, PT and actual treatment group. Tabulation will be repeated to present AEs with a CTCAE grade 3 or higher and separately those AEs, causally related to study treatment by SOC and PT. Fluctuations observed in CTCAE grades within the same PTs during study will be listed.

Tabulation of AEs causally related to study treatment will be summarised by SOC and PT and presented by treatment group.

Summaries of the number and percentage of patients with AEs leading to dose modification of olaparib/placebo and also separately with AEs leading to dose reductions and drug interruptions of olaparib/placebo will be presented by PT and treatment group.

A summary table will be prepared presenting AEs which started prior to first dose or > 30 days following date of last dose by SOC and PT. Data will be presented by treatment group.

Death

A summary of all AEs resulting in deaths will be provided with number and percentage of patients by actual treatment group, categorised as:

- Related to disease under investigation
- AE outcome=death
- Both related to disease under investigation and with AE outcome=death
- AE with outcome=death ≥30 days after last treatment dose
- Deaths ≥ 30 days after last treatment dose, unrelated to AE or disease under investigation
- Patients with unknown reason for death

In addition, AEs with outcome of death will be summarised. The following summary tables will be prepared and presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT
- Death will be listed as part of TLFs for part 11 of the CSR

Serious AEs

The following SAE summaries and listings will be prepared. Summaries will be presented by treatment group:

- By SOC and PT
- Causally related to study treatment by SOC and PT
- Listing of key information

Discontinuation

AEs leading to discontinuation of study treatment will be summarised by SOC and PT. In addition, AEs leading to discontinuation of study treatment, causally related to study treatment will be summarised by SOC and PT. Details of AEs leading to discontinuation will be presented in a by-patient table.

Listings

By-patient listings will be produced as following:

- A by-patient listing of AEs, including flags for AESIs
- A by-patient listing of AEs causally related to olaparib
- A by-patient listing of SAEs
- A by-patient listing of AEs with CTCAE grade 3 or higher (separately for causally related to olaparib)
- A by-patient listing of AEs leading to dose reduction or dose interruption
- A by-patient listing of AEs presenting any events that occur prior to dosing or starting more than 30 days after discontinuing therapy

Laboratory assessments

Laboratory data is collected by local laboratories. Results will be converted to standard units for reporting purposes. Reference ranges from the local laboratories are collected in the CRF and will be used to determine reference range indicators (low, normal, high). If the same parameter is found as measured in serum and in plasma, then the summaries will not distinguish between them (e.g. values from plasma Albumin and serum Albumin will be summarised under Albumin). If the same parameter is found as measured in serum and in plasma within the same patient, which would be a rare case, then the change from baseline will only be calculated for those post-baseline values using the same source, i.e. only within plasma or serum. If one patient has multiple toxicity grades, because they are derived separately from serum and plasma, then the maximum value of the two will be considered.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

Shift tables for laboratory values (excluding electrolytes) from baseline to worst value on-treatment categorized using the common toxicity criteria (CTC) grading based on local reference ranges will be produced. On-treatment is defined as data collected up until the last dose of olaparib/placebo. For parameters with no CTC grading, shift tables from baseline to worst value on-treatment will be provided using normal ranges for categorization. Shift tables for urinalysis values from baseline to worst grade on-treatment will also be provided.

Box-plots of absolute values for continuous laboratory assessments will be presented, with AZ project defined reference ranges indicated.

A scatter plot of alanine aminotransferase (ALT) versus total bilirubin, both expressed as multiples of the upper limit of normal (ULN), will be produced with reference lines at 3×ULN

for ALT, and 2×ULN for total bilirubin. The scatter plot will be repeated for aspartate aminotransferase (AST) versus total bilirubin with reference lines at 3×ULN for AST, and 2×ULN for total bilirubin. In each plot, total bilirubin will be in the vertical axis.

Liver biochemistry test results over time for patients who show elevated ALT or aspartate aminotransferase (AST) (≥3xULN) and elevated total bilirubin (≥ 2xULN) (elevated results do not need to be present at the same visit), or a total bilirubin of ≥ 5xULN will be tabulated and plotted.

All laboratory summaries and listings will be presented by actual treatment group.

By-patient listings of laboratory assessments will be provided showing at least: laboratory parameters, actual time point, measurements/results, CTC grade (if available), and the change from baseline value (for continuous data) (if appropriate). In addition a flag will indicate if the value was out of normal range, if appropriate:

- Laboratory reference ranges
- Haematology
- Serum chemistry
- Urinalysis
- Individual patient data with elevated ALT or AST plus total bilirubin
- Pregnancy report data

Electrocardiograms

If available, overall evaluation of ECG will be summarised by visit as normal, abnormal or borderline.

All ECG data will be listed by actual treatment group.

Vital signs

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, body temperature and weight) will be summarised by time point in terms of absolute values, changes from baseline and percentage changes from baseline at each scheduled measurement by actual treatment group. A shift table comparing baseline to maximum value on treatment will be summarised for SBP, DBP and pulse rate by actual treatment group, using the following normal ranges: SBP = 100 - 160 mmHg; DBP = 60 - 95 mmHg; pulse rate = 55 - 95 bpm.

Box plots for absolute values in SBP, DBP, pulse rate, body temperature, and weight will be presented.

Vital signs data will be listed.

Other

- Any concomitant procedures patients experiencing during the study will be listed in a by-patient listing
- Patients experiencing a Hy's Law incident will be tabulated and details will be included in by-patient listings. Hy's Law incidents are those cases where a patient shows an AST or ALT ≥ 3xULN or total bilirubin ≥ 2xULN. Please refer to Appendix D of the CSP for further instructions.

4.2.14 Demographic and baseline characteristics data

The following will be listed and summarised by randomised treatment group using the FAS analysis set:

- Listing of patients receiving the various batches of investigational product
- Listing of randomisation scheme and codes
- Patient disposition (including screening failures and reason for screening failure, reasons for patients prematurely withdrawing from study, patients with a mis-randomisation [treatment dispensing error] and patients who were unblinded, discontinuation of study treatment), to be repeated also for Myriad confirmed gBRCAm subgroup
- Important deviations including patients with a dispensing error and the number of patients received at least one dose of the wrong study treatment (see Section 2.2)
- Inclusion and exclusion from analysis populations; exclusions from full, safety and PRO analysis set
- Demographics (age in years, age group in years (<35, 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, >= 85), sex, race, and ethnicity), to be repeated also for Myriad confirmed gBRCAm subgroup
- Patient characteristics (baseline height [cm], baseline weight [kg], baseline body mass index [BMI] [kg/m²], weight group [< 70 kg, 70 kg to 90 kg, > 90 kg], BMI group [Normal (< 25), Overweight (25 - 30), Obesity (> 30)]), to be repeated also for Myriad confirmed gBRCAm subgroup
- Patient recruitment by country and centre
- All (allowed) concomitant medications on entry and during the study

- Disallowed concomitant medications on entry and during the study (defined at the BDRM)
- Disease characteristics at baseline including BRCA testing (local and Myriad, including a comparison of local versus Myriad results) and pathology at time of diagnosis, to be repeated also for Myriad confirmed gBRCAm subgroup
- Extent of disease
- Disease related medical history per CRF
- Relevant surgical history per CRF
- Pregnancy at baseline (entry)
- Physical examination at baseline (entry)
- Archival paraffin embedded tumour tissue or cytology sample
- Blood transfusion
- Previous radiotherapy and radiotherapy post randomisation (including current and subsequent radiotherapy)
- Post-discontinuation cancer therapy, defined as any therapy received after discontinuation of study treatment
- Patients who subsequently received a PARP inhibitor or entered a PARP inhibitor trial will be summarised and listed by treatment group according to line of subsequent therapy, ie, immediately after olaparib or as a later line, in addition to patients in the placebo arm who subsequently received olaparib
- Previous disease-related treatment modalities (metastatic pancreas cancer therapy)
- Previous non-disease-related treatment modalities
- Initial vomiting and nausea data will be listed only

WHO drug dictionary will be used for concomitant medication coding.

Patients who were unblinded (a) prior to disease progression and (b) prior to or on the day of treatment discontinuation will be listed.

4.2.15 Treatment exposure

The following summaries related to study treatment will be produced for the Safety Analysis Set by actual treatment group:

- Total exposure of olaparib/placebo
- Actual exposure of olaparib/placebo
- Number of days on 300 mg olaparib/placebo bid = actual exposure for the dose assigned
- Reasons for dose reductions, dose interruptions, and dose modifications of olaparib/placebo. Dose reductions and dose interruptions will be based on investigator initiated dosing decisions. Dose interruptions/reductions due to "Subject Forgot to Take Dose" will be omitted from these summaries
- Number of dose reductions, dose interruptions, and dose modifications of olaparib/placebo that last for a period of three days or more
- PID and RDI of olaparib/placebo (entire intended treatment period)
- Mean total daily dose per time period

For patients on study treatment at the time of the PFS analysis, the DCO date will be used to calculate exposure.

Treatment compliance will be summarised by treatment group using descriptive statistics. Tabulation will be presented by actual treatment group.

All treatment information data will be listed:

- Study treatment compliance
- Administration of investigational product
- Duration of exposure
- Overdose report

5. INTERIM ANALYSES

A single interim PFS analysis for futility will be performed when 50% of the PFS events required for the final PFS analysis have occurred (approximately 44 PFS events) based on BICR. The interim analysis will be performed by an Independent Data Management Committee (IDMC) and full details will be provided in the IDMC charter. Safety data including death rates will also be reviewed at this time.

The futility assessment will be based on the probability of eventually showing statistical significance for the primary endpoint when the final number of PFS events (n=87) is reached

(Lachin 2005). The determination of this probability will be conditional on the observed data at the time of the interim analysis and on the assumed hazard ratio for the alternative hypothesis (PFS HR=0.54). If the probability is less than 20%, the IDMC will consider the option of declaring futility.

The exact figure used for the futility boundary will be calculated by AstraZeneca and sent to the IDMC at the time of the interim analysis, based on the number of events which have occurred at that time. As an example, if exactly 50% of the PFS events required for the primary PFS analysis have occurred at the time of the interim analysis (44 events), then the HR that corresponds to 20% conditional power for the interim analysis will be 1.02. Therefore, if the observed HR for PFS at the interim is more than 1.02, the IDMC will consider the option of declaring futility.

An interim analysis of OS will be performed at the time of the final analyses of PFS (~87 PFS events). A final analysis of OS will be performed when approximately 106 OS events have occurred.

6. CHANGES OF ANALYSIS FROM PROTOCOL

The definition of the Patient Reported Outcome analysis set has been changed in order to add clarification. The previous definition required a patient to have "evaluable baseline EORTC QLQ-C30 and QLQ-PAN26 forms". Now it has been decided to specify this in more detail by saying that it must be possible to determine at least one sub-scale baseline score from at least one of the two forms.

Analysis of time to sustained clinically meaningful deterioration in HRQoL has been added.

7. REFERENCES

Amit et al 2011
Amit, O. et al., 2011. Blinded independent central review of progression in cancer clinical trials: results from a meta analysis. European Journal of Cancer, 47(12), pp. 1772-8.

Berry et al 1999
Berry G, Kitchin RM, Mock PA. A comparison of two simple hazard ratio estimators based on the logrank test. Statistics in Medicine 1991; 10:749-755.

Chen and Sun 2010
Sun X, Chen C. Comparison of Finkelstein's method with the conventional approach for interval-censored data analysis. Stat Biopharm Research 2010; 2(1):97-108.

Chen and Sun 2011

Chen C, Sun LZ. Quantification of PFS Effect for accelerated approval of oncology drugs. Stat Biopharm Research 2011; 3(3):434-444.

Fayers et al 2001
Fayers et al. EORTC QLQ-C30 Scoring Manual (Third Edition). Belgium: EORTC Quality of Life Group, 2001.

Gail and Simon 1985
Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1985; 41(2):361-72.

Johnson 2007
Johnson C. Draft scoring procedure for the EORTC-PAN26, 2007.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983; 70: 659-63.

Lachin 2005
Lachin, J. M. A review of methods for futility stopping based on conditional power. Statist. Med. 2005; 24: 2747–2764.

Osoba et al 1998
Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16(1):139-144.

Pintilie 2006
Pintilie M. Competing risks - a practical perspective. 1st ed. West Sussex (England) John Wiley & Sons; 2006.

SAS Lifetest 2008
SAS Institute Inc. 2008. SAS/STAT® 9.2 User's Guide. Cary, NC: SAS Institute Inc.

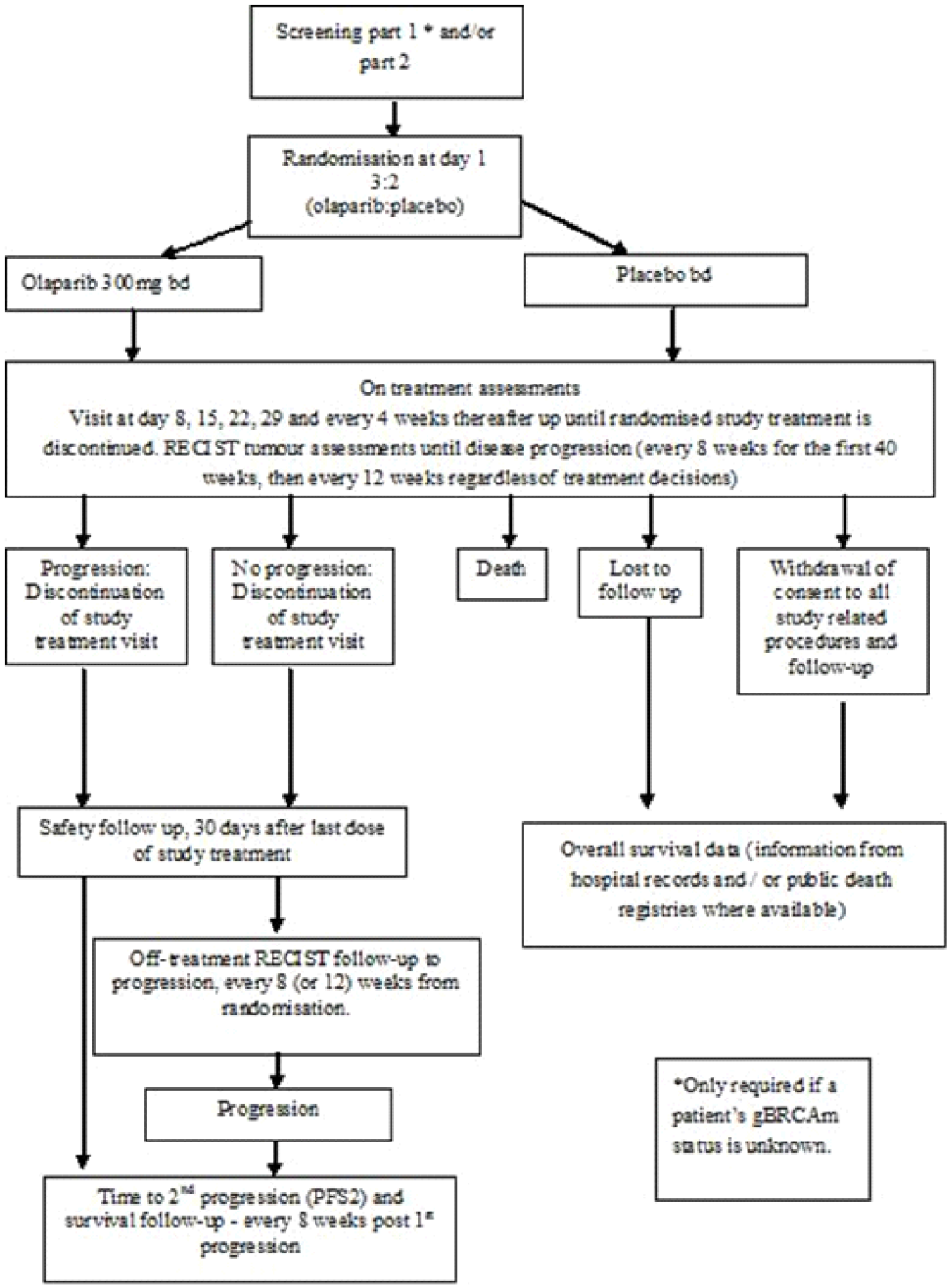
Sellke et al 1983
Sellke, T., Siegmund, D. Sequential analysis of the proportional hazards model. Biometrika 1983; 70:315-326.

Serrano et al 2014
Serrano PE, Herman JM, Griffith KA, et al. Quality of life in a prospective, multicenter phase 2 trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation in patients with resectable or borderline resectable pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys 2014; 90(2):270–277.

APPENDIX

Appendix A: Study Flow Chart

Figure 3 Study Flow Chart



Appendix B: Draft scoring procedure for EORTC-PAN26

Draft scoring procedure for the EORTC-PAN26

This is a list of hypothesised scales for the PAN26.

Issue	Item Numbers in QLQ-PAN26
Pancreatic pain	31, 33-35
Digestive symptoms	36 and 37
Altered bowel habit	46 and 47
Hepatic	44 and 45
Body image	48 and 49
Satisfaction with health care	53 and 54
Sexuality	55 and 56

Scoring algorithm

The following section is the scoring algorithm for the scales. This has been described in a similar fashion to the scoring for the EORTC QLQ-C30.

For each scale, calculate the total score by addition of the responses to each item in the scale. For the first 5 scales (symptom related) a higher score represents *worse* QoL. For these scales, and for satisfaction scale, use a linear transformation to standardise the raw score, so that scores range from 0 to 100;

Symptom scales / items: $S = (RS - 1)/range \times 100$

Satisfaction scale / items: $S = (RS - 1)/range \times 100$

Sexual function is also scored so that high score represents worse function: $S = (1-(RS-1)/range)x100$

Range is the difference between the maximum possible value of RS and the minimum possible value. Single items are scored 1 to 4, giving range = 3.

If reporting scale level data, it is highly recommended that some basic psychometric analyses be carried out. Minimally, the internal consistency of the scales should be examined using the reliability program of SPSS or a similar software package that calculates a Cronbach's alpha coefficient. That coefficient should preferably be above 0.70 for any given multi-item scale (for purposes of group comparisons). You do not need to recode the items to perform the reliability analysis.

If forming a scale appears to be justified, then the same algorithm can be used as is presented in the scoring manual for the QLQ-C30 for linearly converting items and/or scales to 0-100 scales.

The module items can also be reported individually. If this is done, it may be more useful to report the percentage of patients endorsing each of the response categories, rather than mean scores. It may be even more useful to recode the response categories to yield a dichotomous outcome per item (e.g., "not at all" and "a little" vs. "quite a bit" and "very much"). This allows one, for example, to report the percentage of patients with moderate to severe symptoms or problems. If item mean scores are being presented, the items should first be linearly converted to a 0 to 100 scale.

Appendix C: Study Schedule

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Informed consent	X	X									
Randomisation f			X f								
Demographics	X	X									
Medical and surgical history, including blood transfusions a		X									
Prior cancer therapies including radiotherapy		X									
Inclusion/exclusion criteria	X (all * criteria) b	X									
Blood samples for gBRCA status c	X		X d								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Archival paraffin embedded tumour tissue or cytology sample e	X	X									
Concomitant medications		X	X	X	X	X	X	X	X	X	
ECOG performance status		X					X	X	X	X	
Vital signs		X g	X g				X	X	X	X	
Physical examination h		X					X	X	X	X	
ECG i		X	As clinically indicated								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Tumour assessment (modified RECIST) j		X (no more than 28 days before start of treatment) j	Every 8 weeks (± 1 week) until week 40 then every 12 weeks (±1 week), relative to the date of randomisation j						If patient does not have disease progression at the time of treatment discontinuation tumour assessments should be continued per the CSP schedule k		
Haematology/clinical chemistry		X	X l				X	X	X	X	
Coagulation m		X	As clinically indicated								

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Urinalysis n		X	As clinically indicated								
Pregnancy test o	X	X	X								
Biomarker blood sample p			X					X (only at progression)			
EORTC QLQ-C30 q		X					X	X	X	X	
EORTC QLQ-PAN26 q		X		X	X	X	X	X	X	X	
Euro QoL EQ5D		X	X				X	X	X	X	
Hospital Resource Use			X	X	X	X	X	X	X	X	

Table 12 Study Schedule

	Screen PART 1 (Patients with unknown BRCA status only)	**Screen PART 2 (All patients)**	**Treatment Duration**						**Study treatment discontinued**	**30-Day follow-up**	**Survival Follow-up [v]**
Cycle/ Visit			**1 (28 days)**				**2**	**3+ (every 28 days)**			
Day		**-28 to 0**	**1**	**8**	**15**	**22**	**29**	**57+**			**Every 8 weeks**
Visit window				**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**±7d**	**±7d**	**±7d**
Adverse event r	SAEs related to study procedure s only	X	X	X	X	X	X	X	X	X	
Study drug dispensing s			X				X	X			
Study drug return							X	X	X	X	
Subsequent cancer treatment t										X	X
Second progression assessment u											X u
Survival status v											X v

a Include history of blood transfusion within previous 120 days from start of study treatment and the reasons eg, bleeding or myelosuppression.
b These screening assessments do not need capturing on the eCRF, but they must be recorded in the patient's notes.

c Patients must have a known deleterious or suspected deleterious *BRCA* mutation to be randomised to the study; this can be either a local lab result or a Myriad test result. Patients for whom their *gBRCA* status is already known, should be consented to the study within 28 days prior to day 1 of study treatment. Any patient who consents to study related Myriad *gBRCA* status testing, must also have a blood sample taken at the same time for the purpose of developing and validating a future diagnostic test(s) for g*BRCA* mutations.

d Samples to be taken on Day 1 only for patients with known *gBRCA* mutation who have not completed PART 1 Screening. The screening *gBRCA* test and method performed at site must be recorded in the eCRF.

e Collection of an archival tumour sample is requested, if available, for all patients. These samples will be collected from the site pathologist during the screening Part 1 for patients with unknown *gBRCA* status and screening Part 2 for patients with known local *gBRCA* test.

f Patients will be randomised within 6 weeks after their last dose of chemotherapy (last dose is the day of the last treatment) and treatment started as soon as possible but no less than 4 and no more than 8 weeks of the last chemotherapy dose. At the time of starting protocol treatment, all previous chemotherapy treatment should be discontinued.

g Vital signs performed on day 1 before every cycle. If vital signs assessed within 7 days before starting study treatment, it does not need to be repeated on Day 1 of study treatment unless investigator believes that it is likely to have changed significantly.

h Physical examination should be performed according to the schedule. After the baseline assessment it is not necessary to record the details on the eCRF, any clinically significant changes not unequivocally related to disease progression, should be reported as adverse events.

i ECG assessments to be completed within 14 days before starting treatment if patient is eligible following completion of all other PART 2 assessments. After screening, ECGs will only be required if clinically indicated.

j Baseline RECIST assessments will be performed using CT scans of the chest, abdomen and pelvis (or MRI where CT is contraindicated) and should be performed no more than 28 days before start of study treatment and as close as possible to randomisation. A randomisation must be within 6 weeks of last chemotherapy. Treatment should be started as soon as possible but no less than 4 weeks and no more than 8 weeks after their last dose of chemotherapy. RECIST follow-up assessments will be performed every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) irrespective of treatment decisions. Follow-up assessment will include CT assessments of chest, abdomen and pelvis (or MRI where CT is contraindicated) for all patients. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until disease progression assessed using modified RECIST criteria. 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. Prior to primary analysis for PFS, all scans will be submitted for independent review. If progression is not confirmed at central review an additional RECIST assessment will be requested at the next scheduled visit.

k For patients who discontinue study treatment prior to disease progression, RECIST assessments will continue until objective disease progression (every 8 weeks (±1 week) for the first 40 weeks, then every 12 weeks (±1 week) relative to date of randomisation, until objective disease progression as defined by modified RECIST.).

l Haematology and clinical chemistry should be performed at screening and day 1 of every cycle. Safety blood samples do not need to be repeated on Day 1 of study treatment if assessed at least 3 weeks after the last dose of chemotherapy but within 7 days before starting study treatment, unless the investigator believes that it is likely to have changed significantly.

m Coagulation test should be performed at screening and if clinically indicated.

n Urinalysis should be performed at screening. After screening, urinalysis will only be required if clinically indicated.

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

p Mandatory blood samples for biomarker analysis to be taken prior to dosing on Cycle 1 Day 1 and at disease progression.

q Questionnaires to be completed prior to randomisation once eligibility has been confirmed and then until objective radiological disease progression, at discontinuation of study treatment visit and then 30 days post last dose. Questionnaires should be completed prior to dosing on all administrations.

r Adverse events must be captured from time of consent. Only SAE's related to blood sampling for the Myriad gBRCA test will be collected at this visit.

s Continuous Olaparib 300mg/ placebo twice daily dosing. Sufficient study treatment should be dispensed for at least each treatment period plus overage, however additional treatment can be dispensed to patients to last longer in accordance with local practice.

t All anti-cancer treatments (including, but not limited to, chemotherapy and targeted agents), and the Investigator's opinion of response to them, plus the date of progression post discontinuation of study treatment, need to be recorded.

u Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of; objective radiological or symptomatic progression or death. Subsequent therapy will be collected for these patients from the time of treatment discontinuation.

v The status of ongoing, withdrawn (from the study) and 'lost to follow-up' patients at the time of an OS analysis should be obtained by the site personnel by checking the patients notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. 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 (see Section 3.10 of the CSP). In addition to their regular 8 weekly contact, patients will be contacted in the 7 days following a specified date (data cut-off date) for each survival analysis.

Appendix D: Visualisation of Censoring Rule for Progression Free Survival