AstraZeneca

POLO
BRCAm Pancreatic Cancer

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# 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

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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 February 2015 | | |
| 3 | 30 August 2019 | | |

# 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

**International Co-ordinating Investigator:** PPD **MD** PPD
PPD **MD** PPD

**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 | Q1 2021 | |

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### 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)<br>• Time from randomisation to second progression (PFS2)<br>• Time from randomisation to first subsequent therapy or death (TFST)<br>• Time from randomisation to second subsequent therapy or death (TSST).<br>• Time from randomisation to study treatment discontinuation or death (TDT)<br>• Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients<br>• 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: |
|---|---|
| • CCI [redacted] | • CCI [redacted] |


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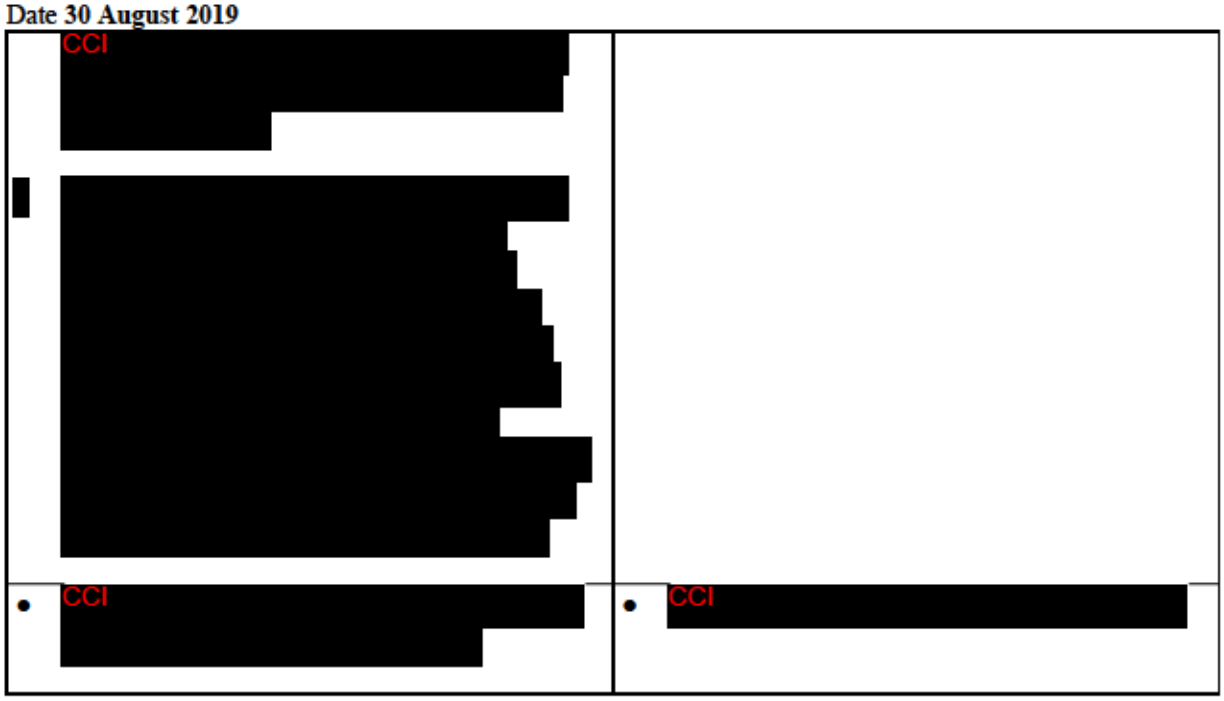
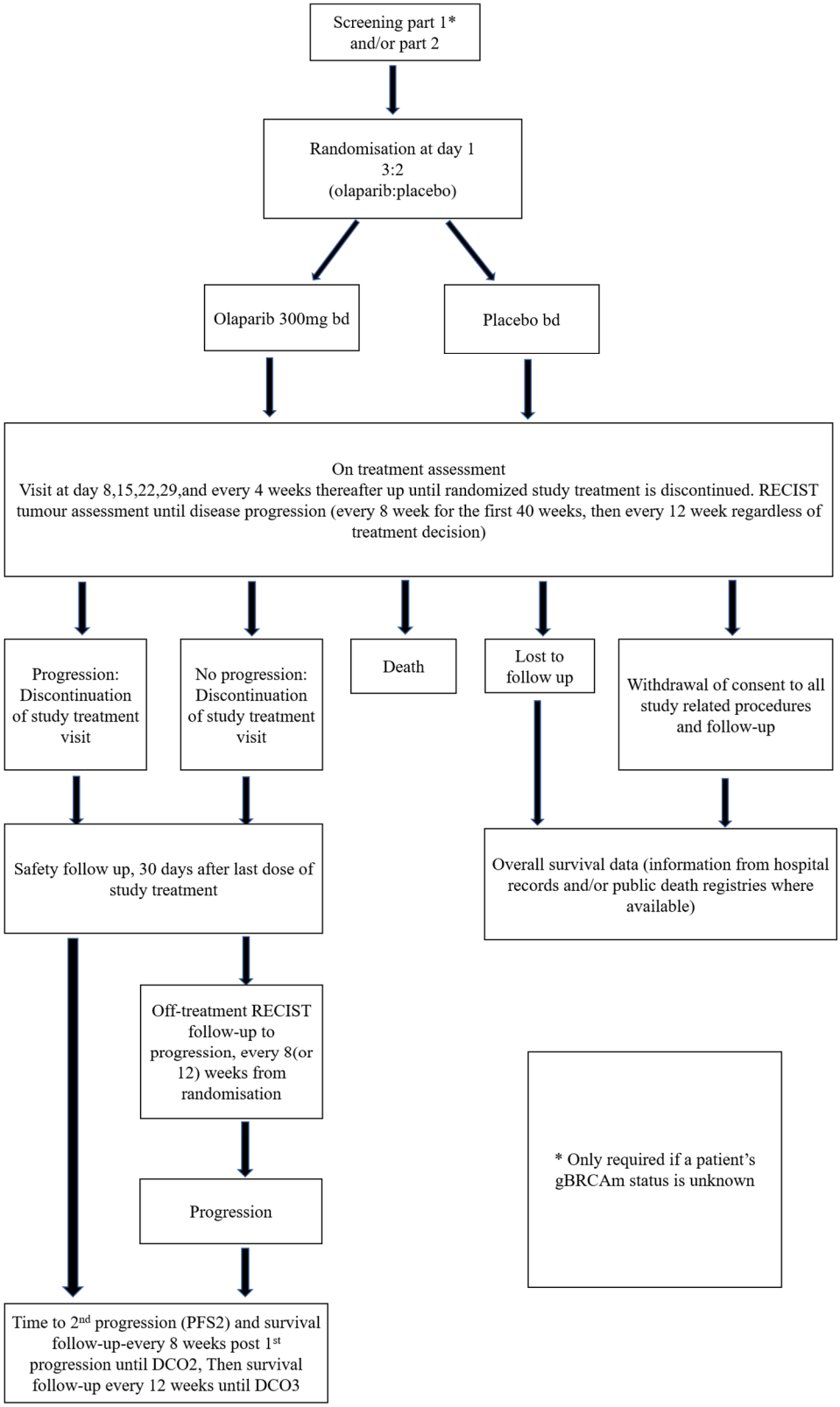



The exploratory analyses may not be reported in the clinical study report (CSR). If not, they will be reported separately.

## 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.


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 CCI [redacted]. 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, DCO1) have occurred. A single interim PFS analysis for futility will be performed when 50% of the final number of progression **events** 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, DCO2). 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. CCI [redacted]

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 formal analysis of OS will be performed when approximately 106 death events have occurred (DCO2) and a multiplicity adjustment will be made to account for the different analyses. CCI [redacted]

At the time of the PFS analysis (DCO1), CCI [redacted] at the final analysis will be derived using a weighted sum of the observed OS data and the predicted OS value using primary PFS data available at DCO1.

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PFS2 analyses will be performed at the same time as the primary analysis of PFS, at the time of the final OS analysis, 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.

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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 |
| DCO1 | Data Cut Off for primary PFS analysis |
| DCO2 | Data Cut Off for final formal OS analysis |

| | |
|---|---|
| CCI | [redacted] |
| 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) |
| CCI | [redacted] |
| 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 |
| CCI | [redacted] |
| [redacted] | [redacted] 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 |

| | |
|---|---|
| CCI | [redacted] |
| 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 |
| CCI | [redacted] |
| 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 *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 (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

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[redacted] 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 CCI 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 *gBRCA* pancreas cancer. The preliminary analysis of [redacted] suggests selecting patients with tumours which are not known to be platinum resistant would increase the likelihood of benefit. [redacted] 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 [redacted] testing because it has [redacted]. Myriad keeps a comprehensive [redacted]. 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. CCI [redacted]

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% [CCI redacted]. 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 CCI (0.7%) of CCI that received placebo or comparator in the Olaparib trial programme (1 patient on placebo in CCI and 1 patient on paclitaxel in CCI). 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 CCI. 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 CCI 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 CCI, 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 CCI

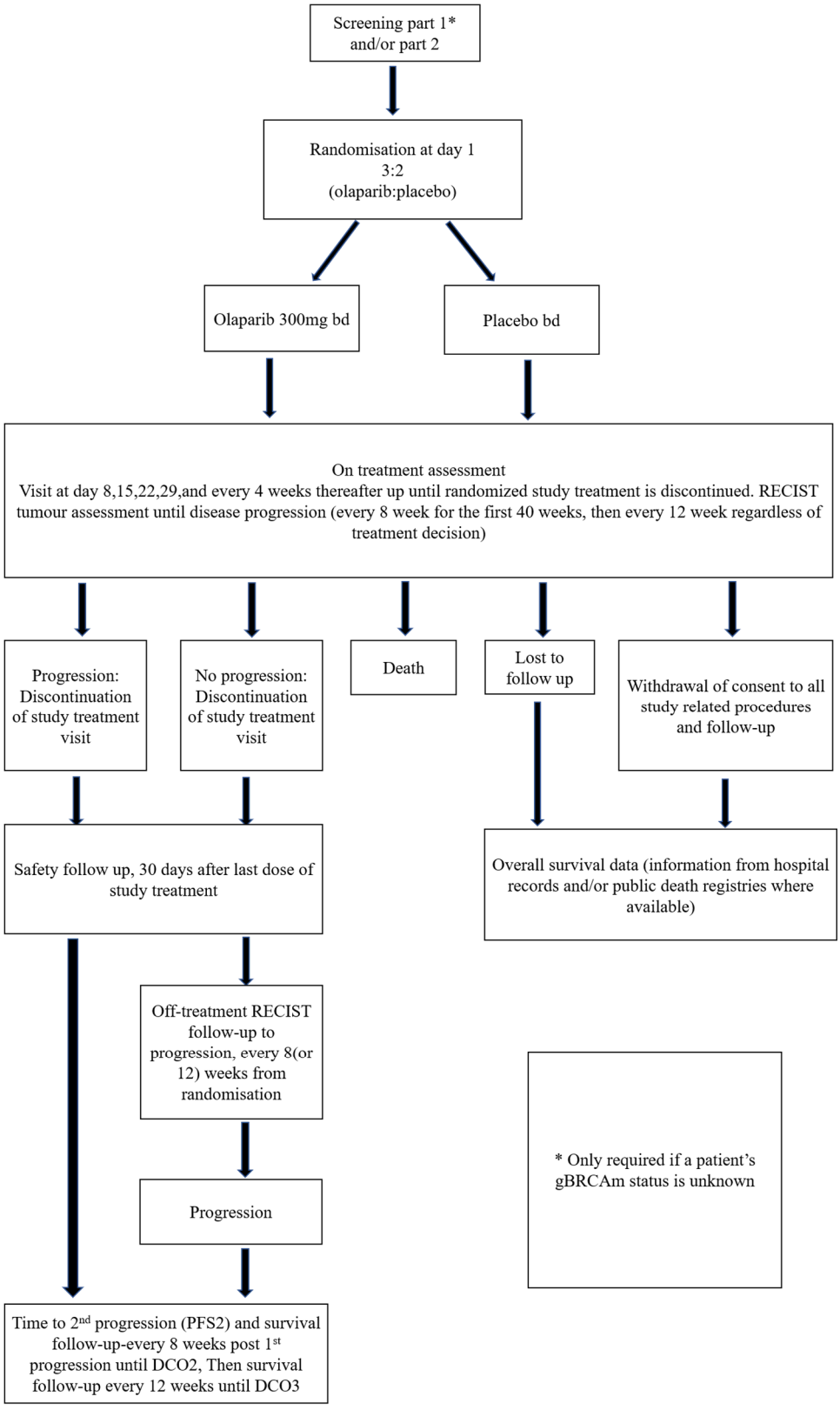
CCI [redacted] The progression-free survival (PFS) following Olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.35; 95% CI: 0.25, 0.49; p<0.00001) in the overall population. In the subgroup of patients with *BRCA* mutant ovarian cancer, the effect was even greater 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. CCI [redacted] 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 CCI [redacted] in ovarian cancer and CCI [redacted] 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. CCI [redacted]

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.

CCI [redacted]

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)<br>• Time from randomisation to second progression (PFS2)<br>• Time from randomisation to first subsequent therapy or death (TFST)<br>• Time from randomisation to second subsequent therapy or death (TSST).<br>• Time from randomisation to study treatment discontinuation or death (TDT)<br>• Objective Response Rate by BICR using modified RECIST 1.1 criteria for evaluable patients<br>• 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: |
|---|---|
| • CCI | • CCI |
| • CCI | |


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. CCI

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.

If a patient is continuing to derive benefit from olaparib at the end of the study (at DCO3), then they may continue to receive treatment as open labelled drug via manual supply outside of the study setting once the IVRS/IWRS has been closed.

### 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) 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)** | | | **Until DCO2** | **Between DCO2 & DCO3** |
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **22** | **29** | **57+** | | | **Every 8 weeks** | **Every 12 Weeks** |
| **Visit window** | | | | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±7d** | **±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 | | | | | | | | | | |

| | 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) | | | Until DCO2 | Between DCO2 & DCO3 |
| **Day** | | -28 to 0 | 1 | 8 | 15 | 22 | 29 | 57+ | | | Every 8 weeks | Every 12 Weeks |
| **Visit window** | | | | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d | ±7d | ±7d | ±7d |
| 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 | | |
| CCI [redacted] | | [redacted] | | | | | [redacted] | [redacted] | [redacted] | [redacted] | | |
| Vital signs | | X [g] | X [g] | | | | X | X | X | X | | |
| Physical examination [h] | | X | | | | | X | X | X | X | | |
| ECG [i] | | X | As clinically indicated | | | | | | | | | |

| | **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)** | | | **Until DCO2** | **Between DCO2 & DCO3** |
| **Day** | | **-28 to 0** | **1** | **8** | **15** | **22** | **29** | **57+** | | | **Every 8 weeks** | **Every 12 Weeks** |
| **Visit window** | | | | **±3d** | **±3d** | **±3d** | **±3d** | **±3d** | **±7d** | **±7d** | **±7d** | **±7d** |
| 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 | | |
| Coagulation [m] | | X | As clinically indicated | | | | | | | | | |
| Urinalysis [n] | | X | As clinically indicated | | | | | | | | | |
| Pregnancy test [o] | 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) | | | Until DCO2 | Between DCO2 & DCO3 |
| **Day** | | -28 to 0 | 1 | 8 | 15 | 22 | 29 | 57+ | | | Every 8 weeks | Every 12 Weeks |
| **Visit window** | | | | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d | ±7d | ±7d | ±7d |
| Biomarker blood sample [p] | | | X | | | | | X (only at progression) | | | | |
| EORTC QLQ-C30 [q] | | X | | | | | X | X | X | X | | |
| CCI [redacted] | | [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | | [redacted] | [redacted] | | | | [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | | | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | | |
| 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 | | | | |

| | 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) | | | Until DCO2 | Between DCO2 & DCO3 |
| **Day** | | -28 to 0 | 1 | 8 | 15 | 22 | 29 | 57+ | | | Every 8 weeks | Every 12 Weeks |
| **Visit window** | | | | ±3d | ±3d | ±3d | ±3d | ±3d | ±7d | ±7d | ±7d | ±7d |
| Study drug return | | | | | | | X | X | X | X | | |
| Subsequent cancer treatment [t] | | | | | | | | | | X | X | X |
| Second progression assessment [u] | | | | | | | | | | | X[u] | |
| Survival status [v] | | | | | | | | | | | X[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 CCI , must also have a blood sample taken at the same time for the purpose of developing and validating a CCI .
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 [redacted]

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 need to be recorded until end of study period (DCO3), 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 until end of study period (DCO3).

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 until final formal analysis of OS (DCO1 & DCO2). Post DCO2 period, patients will be contacted every 12 weeks for survival status and in the 7 days following the specified date of DCO3 for [redacted].

## 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
- CCI
- 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 CCI 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
- CCI

- 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.

- CCI [redacted]

- CCI [redacted]

[redacted]

[redacted]

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

Survival data should be collected, every 8 weeks until final formal survival analysis (DCO2) and every 12 weeks until the CCI [redacted] (DCO3), 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. In addition, patients should be contacted in the week following the data cut-off for the primary PFS (DCO1), final formal survival analyses (DCO2, at 106 OS events) and at the CCI [redacted] to provide complete survival data.

Patients will be followed up as per Table 1 to the point of CCI [redacted] 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 (DCO3) for the final statistical analysis of the study will be established 12 months after the time 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] |

| **Haematology/Haemostasis (whole blood)** | **Clinical Chemistry (serum or plasma)** |
|---|---|
| B-Absolute differential white cell count<br>– (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]<br>S-Aspartate transaminase [AST]<br>S- alanine transaminase [ALT]<br>S-Urea or blood urea nitrogen [BUN]<br>S-Total protein<br>S-Albumin<br>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.

CCI [redacted]

[redacted]

[redacted]

### 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 women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment, at the time points shown in Table 1 during study treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

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 0

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

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

| [redacted] | [redacted] |
| --- | --- |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |

CCI [redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

Patients will be required to provide:

- CCI [redacted]

[redacted]

## 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 | |
| CCI | | | | |
| 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 any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

## 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.

Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

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.

#### 6.3.1.1 Adverse events after the 30 day follow up period

At any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify AstraZeneca, Patient Safety.

If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion (after DCO3) then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe. After study completion (after DCO3) SAE reporting to be followed using paper reporting process.

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

### 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.

### Olaparib adverse events of special interest

Adverse events of special interest [AESI] are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterise the event and gain a better understanding regarding the relationship between the event and study treatment.

## 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

### 6.4.1 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

## 6.5 Overdose

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

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The Maximum Tolerated Dose is 300 mg twice daily (tablet).

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) occurring from the date of the first dose of study medication until 1 month after the last dose of study medication 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 (Table 8) Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once dose is reduced, escalation is not permitted

### 6.7.1 Management of haematological toxicity Olaparib

#### 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. Anaemia should be managed as described in Table 6.

**Table 6 Management of anaemia**

| Haemoglobin | Action to be taken |
|---|---|
| **Hb ≥ 8 g/dl (CTCAE Grade 1 or 2)[a]** | **First occurrence:**<br>Give appropriate supportive treatment and investigate causality.<br>Investigator judgement to continue *study treatment* with supportive treatment (eg transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to > 9g/dl.<br>**Subsequent occurrences:**<br>If Hb**< 10** *but* **≥ 9 g/dl** investigator judgement to continue *study treatment* Consideration could be given to supportive treatment (eg transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).<br>If Hb**< 9** *but* **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 9 g/dl and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). |
| **Hb < 8 g/dl (CTCAE Grade 3)[a]** | Give appropriate supportive treatment (e.g. transfusion) and investigate causality.<br>Interrupt *study treatment* for a maximum of 4 weeks until improved to Hb ≥ 9 g/dl.<br>Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease. |

[a] CTCAE Version 4.

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases management of anaemia may require blood transfusions. 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.**

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to guidance later in this section for the management of this.

#### 6.7.1.2 Management of neutropenia, leukopenia and thrombocytopenia

Adverse event of neutropenia, leukopenia and thrombocytopenia should be managed as described in Table 7.

**Table 7 Management of neutropenia, leukopenia and thrombocytopenia**

| Toxicity | Study treatment dose adjustment |
|---|---|
| CTCAE Grade 1-2 | Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation |
| CTCAE Grade 3-4 | Dose interruption until recovered to CTCAE gr 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce <<*select olaparib or study treatment*>> to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step |

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.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or worse), refer to guidance later in this section for the management of this.

**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 and/or development of platelet transfusion dependence (Platelets < 50 x $10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. 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. Study treatment should be discontinued if blood counts do not recover to CTC gr 1 or better within 4 weeks of dose interruption.

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.

**Table 8 Dose reductions for study treatment**

| Initial Dose | Following re-challenge post interruption: Dose reduction 1 | Dose reduction 2 |
|---|---|---|
| 300 mg twice daily | 250 mg twice daily | 200 mg twice daily |

### 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)

### 6.7.4 Renal impairment

If subsequent to study entry and while still on study therapy, a patient's estimated CrCl falls below the threshold for study inclusion (≥51 ml/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test of between 31 and 50 ml/min) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg twice daily.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

## 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. If a patient is continuing to derive benefit from olaparib at the end of the study (at DCO3), then they may continue to receive treatment as open labelled drug via manual supply outside of the study setting once the IVRS/IWRS has been closed.

## 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. Please refer to Section 3.7.
- 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 9 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.

CCI [redacted]

**Table 9 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 |
| [redacted] | CCI [redacted] |
| -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 **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.

#### 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.

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## 8.8 Methods for statistical analyses

A single interim PFS analysis for futility will be performed when 50% of the 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 12

**Table 12 Timing of statistical analyses**

| Timing of analyses | Outcome Variable |
|---|---|
| | Efficacy Data |
| Interim PFS analyses (~ 44 PFS events) | - PFS |
| Final PFS (~ 87 PFS events, DCO1) | - PFS, PFS2, TDT, TFST, TSST, OS, adjusted mean change from baseline in global QoL score |
| Final formal OS analyses (~106 OS events, DCO2) | - OS, PFS2, TFST, TSST, adjusted mean change from baseline in global QoL score |
| CCI [redacted] | [redacted] |

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 13 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 |
| | 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 |

| 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 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 |
| 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) (DCO1). A final formal analysis of OS will be performed when approximately 106

death events have occurred (DCO2). However, the multiple testing strategy will not apply to the CCI [redacted] and only descriptive analysis will be done for this analysis (DCO3). 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 (DCO1) 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 $p<0.003$, which equates to a HR $\leq 0.49$. The significance level at the final formal OS analysis (DCO2) will be determined based on the exact number of events at the time of the interim OS analyses (DCO1) and final formal OS analyses (DCO2). If the interim analysis for OS occurs at exactly 57% of events and the number of OS events at the final formal OS analysis is approximately 106 then the 1-sided significance level to be applied for the final formal OS 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 $\leq 0.68$.

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)

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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

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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).

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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

Interim OS data will be analysed at the time of the final analysis of PFS (DCO1) 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 final formal analysis of OS will be performed when approximately 106 deaths have occurred (DCO2). CCI [redacted] to take place 12 months after the analysis based on 106 deaths, will be a descriptive only analysis (DCO3) and will use the same methodology as the final formal OS analysis.

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.

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#### 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.

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#### 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

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## 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 **PFS** final analyses.

Patients are to be followed for the CCI [redacted] 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 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 analysis of OS will be performed at the time of the primary analysis of PFS (approximately 87 events) with the final formal OS analysis 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. CCI

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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.

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**Clinical Study Protocol Appendix B**

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| 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**

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| 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:

- CCI [redacted]

[redacted]

**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 | |
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| Drug Substance | Olaparib |
| Study Code | D081FC00001 |
| Edition Number | 2 |
| Date | 30 Aug 2019 |

# Appendix D
# Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

# TABLE OF CONTENTS PAGE

# 1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

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

# 2. DEFINITIONS

### Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication, irrespective of an increase in Alkaline Phosphatase (ALP).

### Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL 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:

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

# 4. FOLLOW-UP

## 4.1 Potential Hy's Law Criteria not met

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

- 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 (See Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team.

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patient's follow-up (including any further laboratory testing) 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. Completes follow-up SAE Form as required.

    - 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

# 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.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent 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.

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

**Where 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: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated 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 15 calendar days 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:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- 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 still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

# 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:

---

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. 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 for reporting PHL as an SAE.

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FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

[#] 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.

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| **Clinical Study Protocol Appendix E** | |
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# 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.<br>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.<br>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.

| Clinical Study Protocol Appendix G | |
|---|---|
| Drug Substance | Olaparib |
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| Clinical Study Protocol Appendix H | |
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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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| Drug Substance | Olaparib |
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# Appendix I

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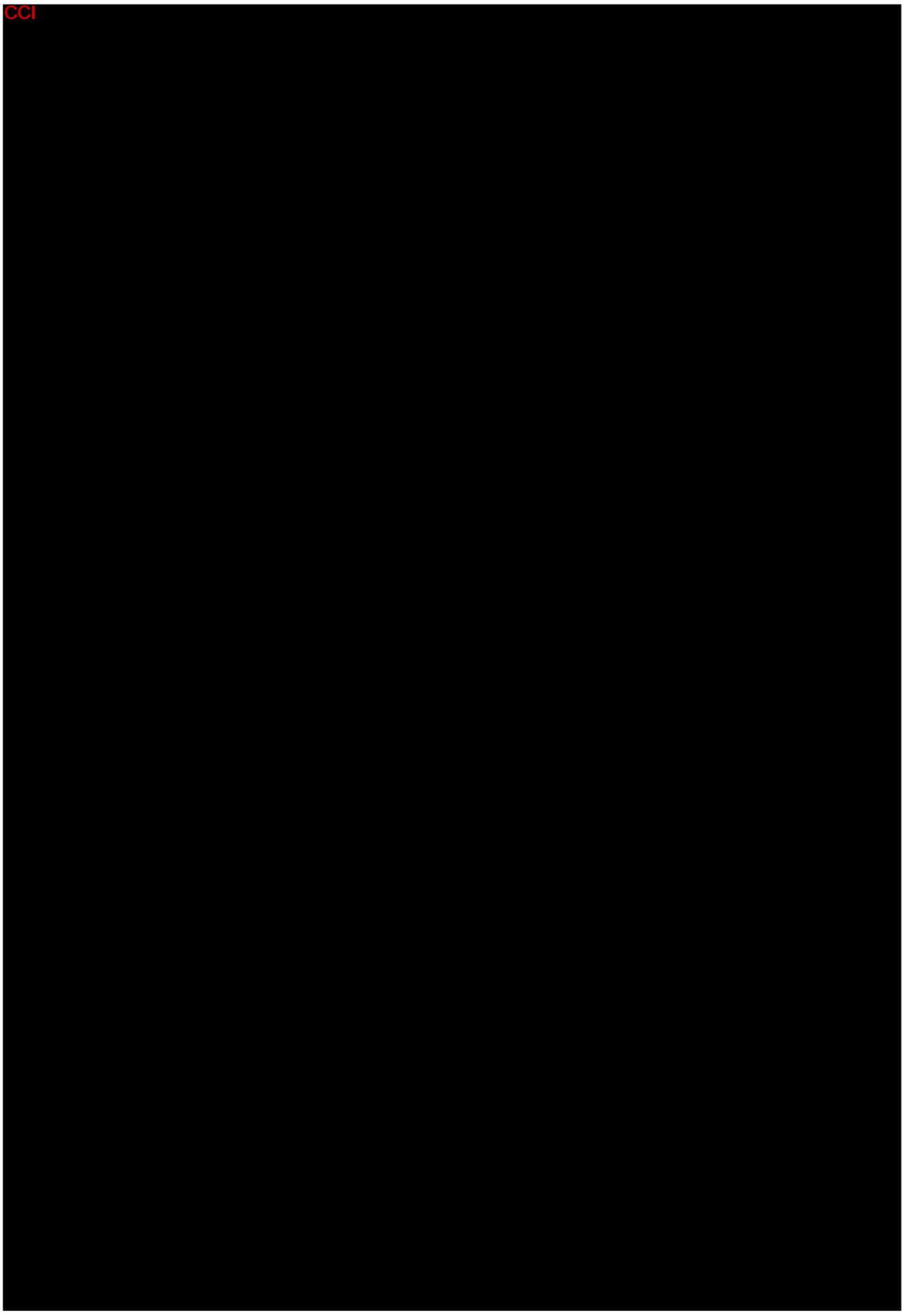
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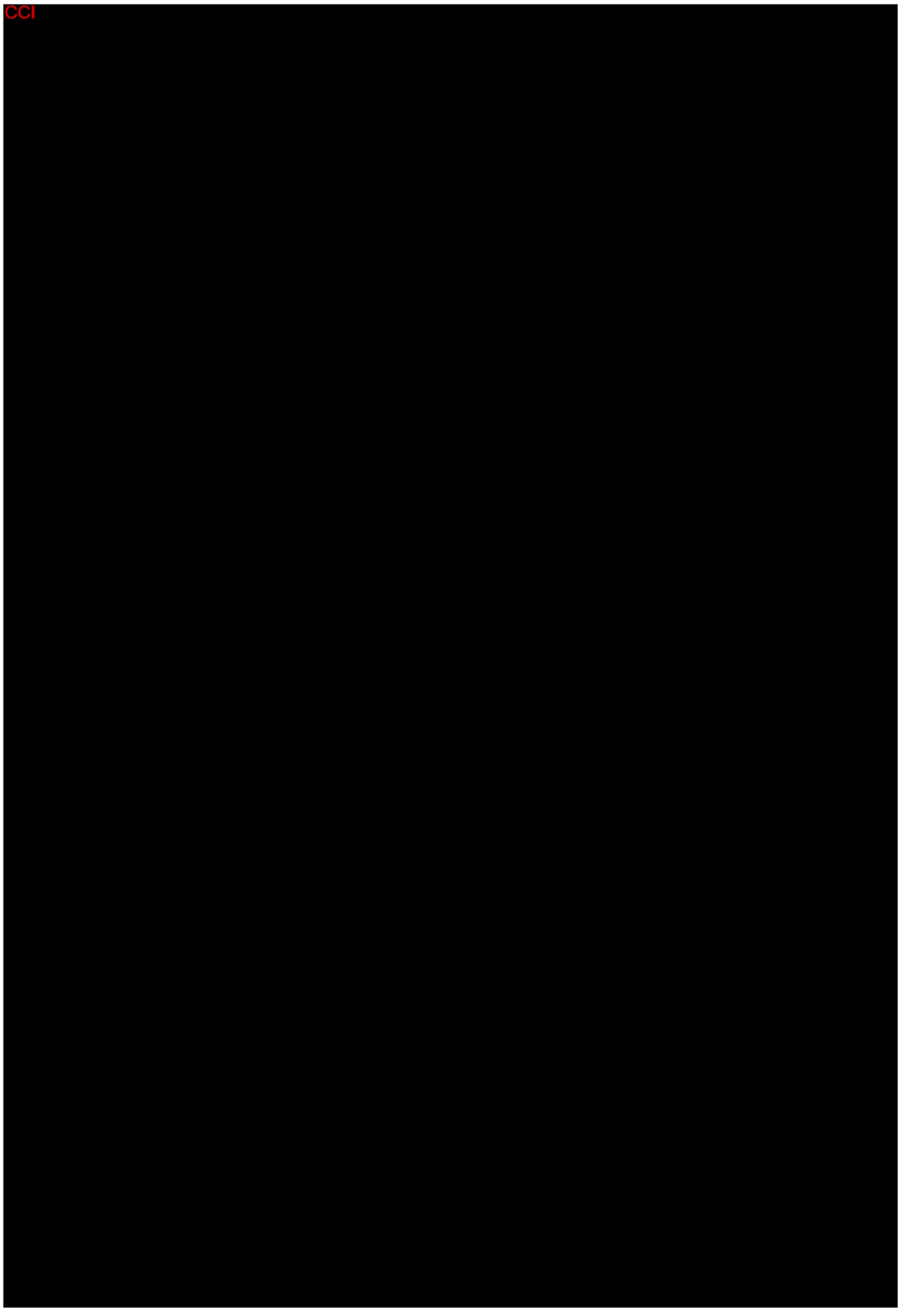
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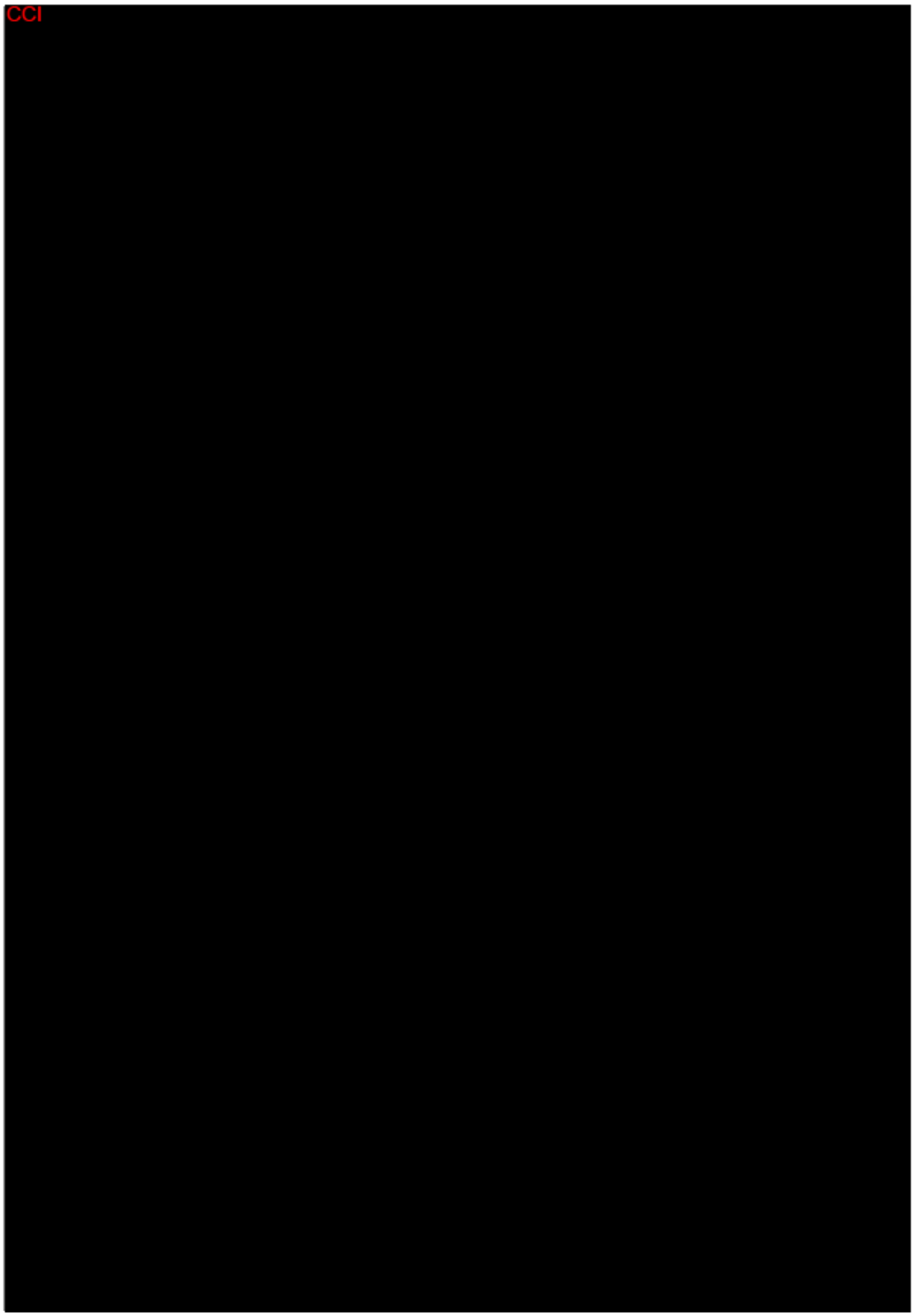
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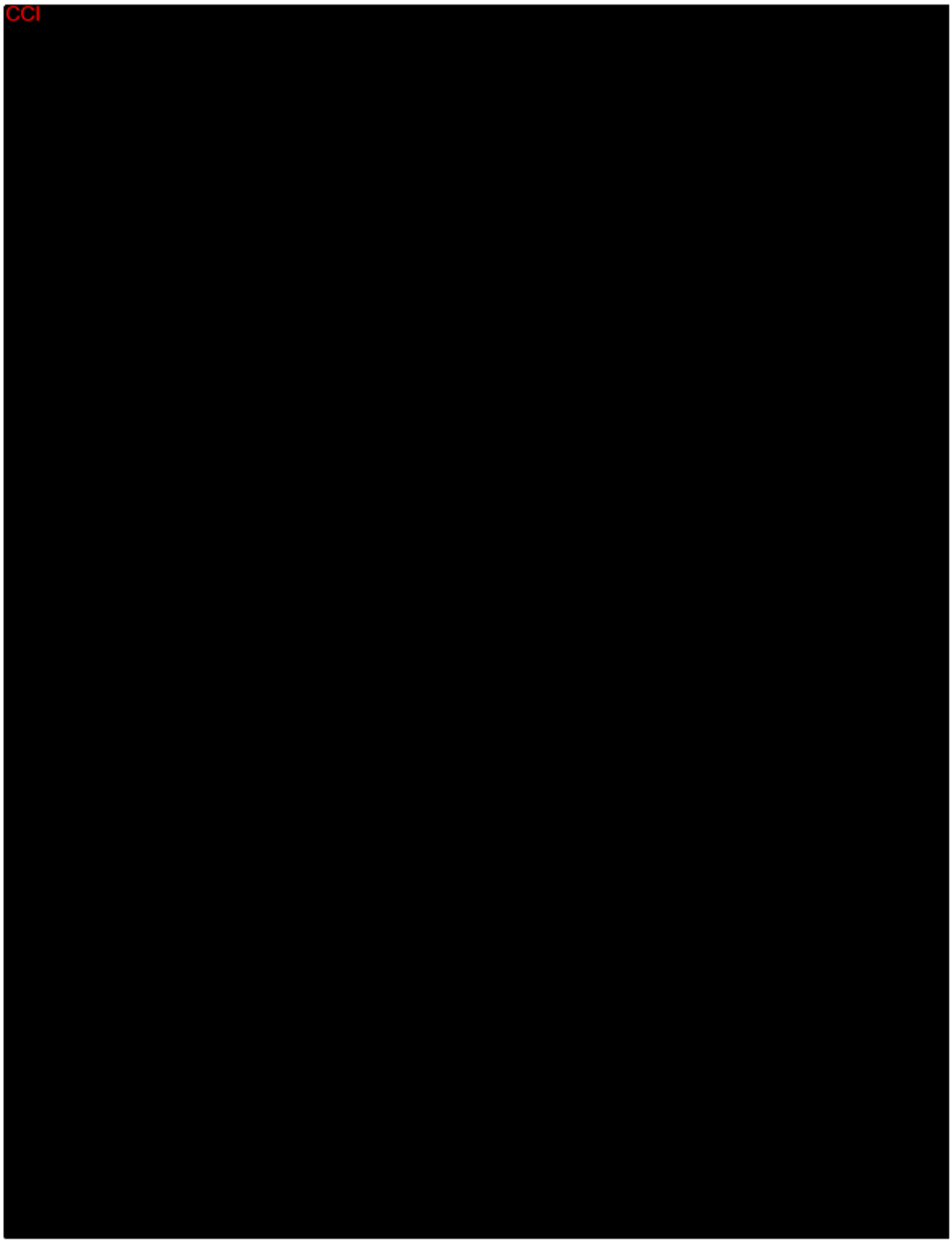
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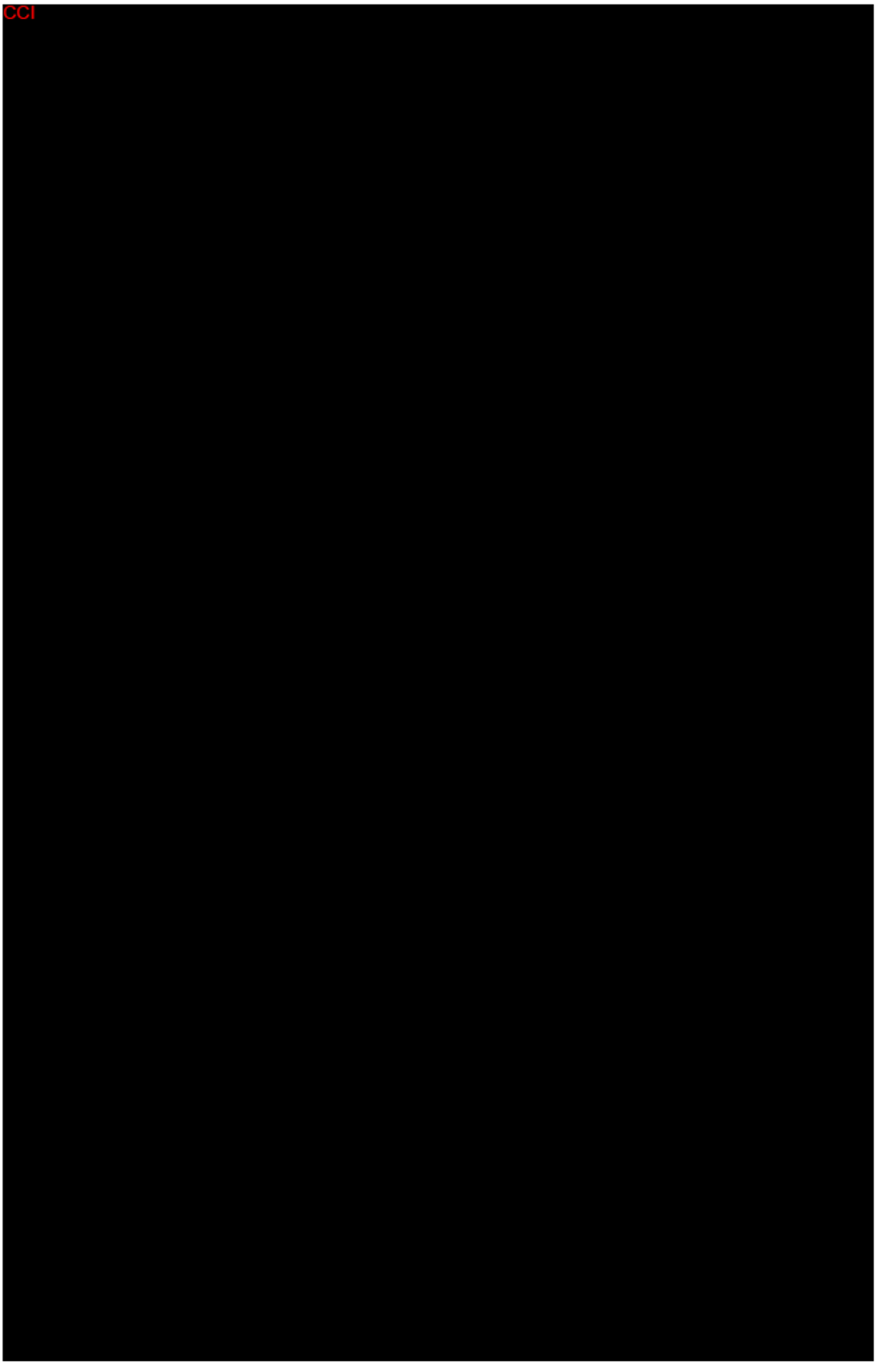
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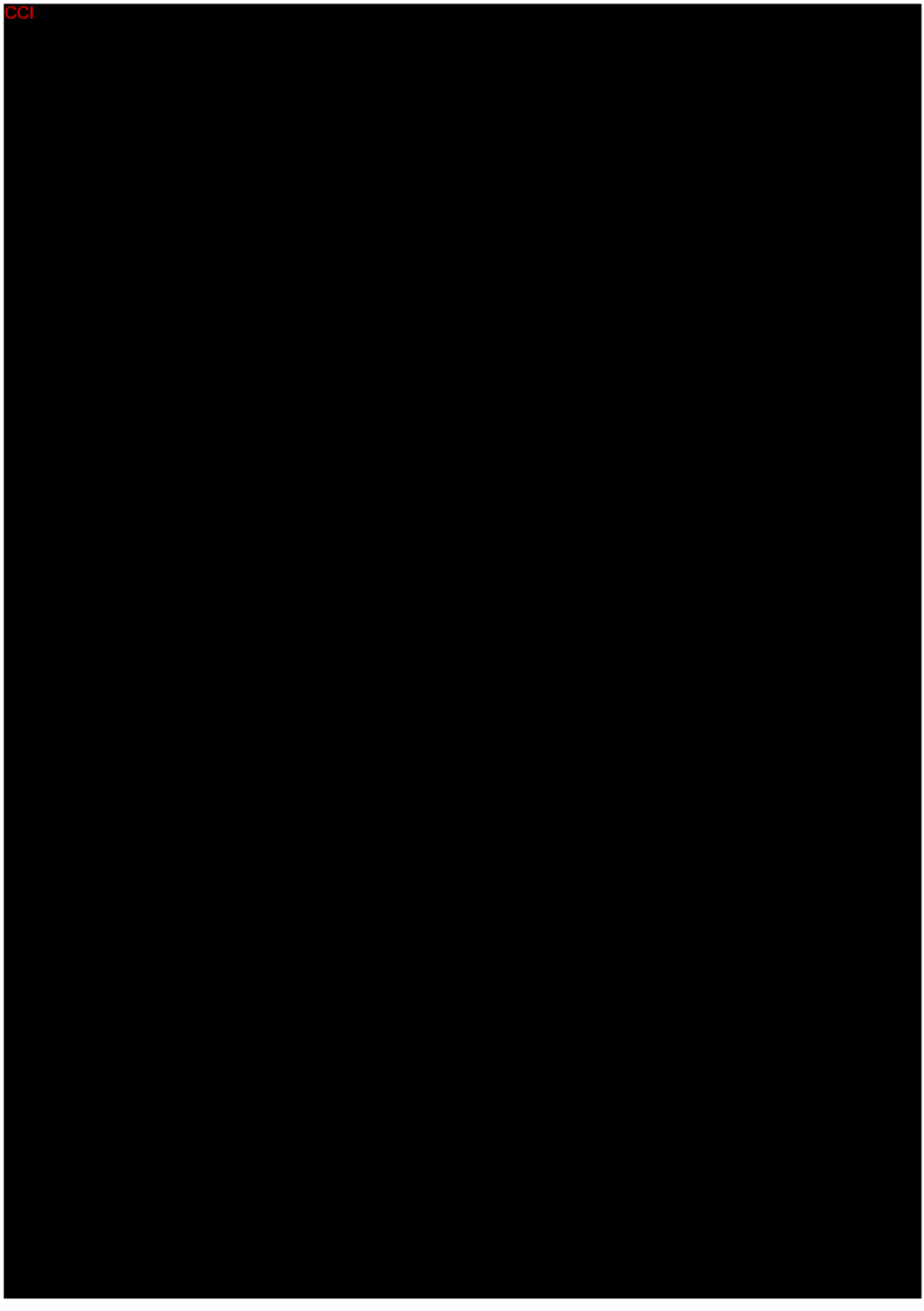
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