Protocol GEICAM/2015-06

"A Phase II **C**linical Trial to analyse **O**laparib Response in patients with *BRCA1 and/*or *2* Promoter **Met**hylation Diagnosed of **A**dvanced **Breast** Cancer"

"COMETA-Breast study"

SPONSOR:

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SUMMARY OF THE STUDY PROTOCOL

Study Title: "A Phase II **C**linical Trial to analyse **O**laparib Response in patients with *BRCA1 and/*or *2* Promoter **Met**hylation Diagnosed of **A**dvanced **Breast** Cancer (COMETA-Breast Study)"
Sponsor Study Code: GEICAM/2015-06
Sponsor: GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama)
Indication: Triple negative (TN) Advanced Breast Cancer (ABC)
Countries and approximate number of sites: Spain /16 sites approximately
Number of patients: Approximately 34 patients will be included in the study.
Study Rationale: Triple negative Breast Cancer (TNBC) represents approximately 12-17% of BC overall. This tumour subtype is characterized by the presence of stem cell precursors, a high proliferation rate and metastatic capacity and a worse prognosis than other BC subtypes. Median survival of advanced TNBC is at best 12 months, much shorter than the survival seen in other subtypes of advanced BC. Chemotherapy is the current mainstay of therapy for TNBC with varied impact on long-term prognosis. No targeted treatment has been developed for TNBC. Therefore, identification of specific targeted and more active therapies for TNBC patients remains an important clinical challenge. One of the most frequent molecular events in TN breast tumours is the presence of BRCA protein dysfunction. Among BC patients with a hereditary *BRCA1* mutation, over 80% is a TNBC. Sporadic TN tumours often show the same histological characteristics and clinical outcome as *BRCA1* mutation carriers so several studies have postulated that *BRCA1* inactivation might also have a role in sporadic TNBCs. The phenotype that some sporadic tumours share traits with familial *BRCA* cancer is called "*BRCA*ness". Approximately 15% of ovarian cancer patients and 5% of breast, pancreatic and prostate cancer patients have inherited mutations of *BRCA1* or *BRCA2*, and it has been suggested that a further ~20% of tumours display so-called "*BRCAness*" phenotype. The importance of defining such a group of tumours lies within the clinical management of these tumours. Inhibition of Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP) is a promising strategy for targeting cancers with defective DNA-damage repair, including *BRCA1* and *BRCA2* mutation-associated breast and ovarian cancers. After preliminary data showing minimal efficacy of PARP inhibitors (PARPi) in sporadic BC, some of the trials were amended to enrich the study cohorts for *BRCA*-associated tumours. Initial phase I testing olaparib as monotherapy in *BRCA*-associated breast, prostate and ovarian cancers showed that 47% of patients with *BRCA*-associated breast, ovarian, or prostate cancers treated with olaparib achieved a partial response, and 63% of them derived clinical benefit.

On December 2014, Marketing Authorisation Applications were approved in EU/EEA and US for the capsule formulation of LYNPARZA® (olaparib) monotherapy for the treatment of *BRCA*-mutated advanced ovarian cancer patients. Phase II clinical studies have investigated the effect of olaparib either as monotherapy or in combination with other chemotherapy agents in other cancer types. Tutt et al. reported efficacy of olaparib as monotherapy in 54 patients with advanced BC heavily pre-treated and germline *BRCA1*/2 mutations. At the maximum tolerated olaparib dose (400 mg b.i.d., capsule formulation) it was observed a 41% ORR, with a 54% ORR observed in the TNBC subgroup (7 out of 13 patients). The majority of completed studies have been performed with the capsule formulation of olaparib but most new studies, including the Phase III registration studies, are being performed with the tablet formulation which delivers the therapeutic dose of olaparib in fewer dose units than the capsule. Based on the totality of the efficacy, safety/tolerability profile and the patient convenience of a b.i.d. dosing schedule, the 300 mg b.i.d. tablet dose was chosen as the recommended Phase III monotherapy dose. Recently, OlympiAD (NCT02000622) trial comparing treatment with olaparib tablets versus a standard of care chemotherapy in patients with HER2-negative MBC harbouring germline *BRCA1* or *BRCA2* mutations showed that patients treated with olaparib have a statistically-significant and clinically-meaningful improvement in PFS compared with those who received chemotherapy[63].

Since August 2017, the tablet formulation has subsequently been approved in the US, EU and Japan for different types of ovarian cancer and in January 2018 has been approved by US for patients with deleterious or suspected deleterious gBRCAm, HER2-negative MBC who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting.

In addition to *BRCA* mutations, other alterations can be responsible for a dysfunctional BRCA protein. One of them is the epigenetic silencing by aberrant methylation of *BRCA1*/2 promoter, more frequently described in medullary and metaplastic tumours. In most cases, the methylation status leads to gene silencing. The methylation of *BRCA1*/2 promoter has been explored in multiple neoplasms, finding variable frequencies: ovarian 5-20%, gastric 50% and breast 29-59%. *BRCA1*-methylated sporadic breast tumours have been described in young women and display pathologic features similar to those of *BRCA1*-mutated BC. Interestingly, sporadic tumours with aberrant *BRCA1* promoter methylation can be clustered with tumours derived from women with inherited *BRCA1* germline mutations because of similarities in their global gene expression profiles.

Similarly to *BRCA* germline mutations, reduced function of other key proteins in the homologous recombination pathway results in increased sensitivity to PARPi and enhancement of chemotherapy and radiotherapy treatments. For these reasons, PARP inhibition represents a novel approach as an anti-tumour therapy and may address an unmet need in patients with *BRCA*-associated cancer.

Based on these results and data from the full clinical program to date, it is anticipated that orally active PARP inhibitor, olaparib, will have a positive benefit risk profile for the treatment of the small well-defined population of advanced TNBC patients with promoter methylation of *BRCA*.

Study Drug(s)/medications:

Dose/Route/Regimen

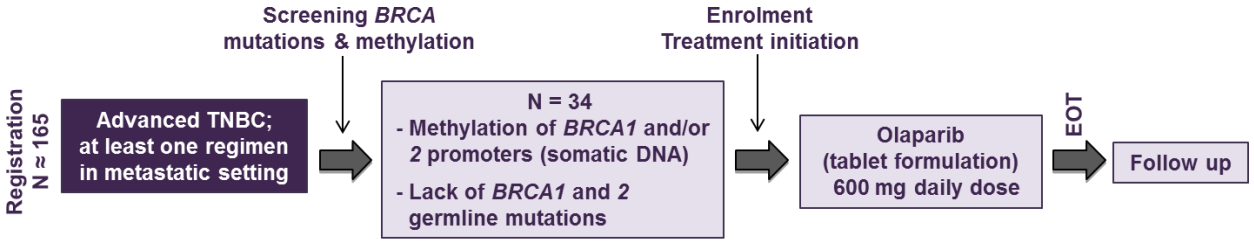
Eligible patients will be enrolled and treated with:

- ✓ Olaparib as single agent at 600 mg continuous daily dose (tablet formulation); given in two oral administrations (300 mg every 12 hours).

All patients included will receive study therapy until radiographic or symptomatic progression, unacceptable toxicity or withdraw of the informed consent, whatever occurs first.

Study Design and Treatment:

This is a multicenter single-arm phase II clinical trial to assess the efficacy and safety of olaparib in patients diagnosed of advanced TNBC with methylation of *BRCA1* and/or *2* promoters assessed in DNA from metastatic lesions and absence of *BRCA1* and 2 germline mutations. Patients must have received at least one previous regimen in the advance disease setting.



Potential eligible patients will be screened to assess germinal (g) *BRCA* mutational status at Myriad laboratory (unless the *BRCA* mutational status is already known based on a Myriad previous report).

Blood samples for mutational *BRCA* screening could be sent either 1) during the previous line of treatment prior to study enrolment, once the eligibility criteria have been reviewed and the patient is considered a potential candidate for the study (at least the patient must have measurable and biopsiable disease) or 2) after ending the line of treatment prior to study enrolment (simultaneously to the shipment of the tumour samples for methylation analysis). A specific ICF must be signed for this screening assessment.

Somatic (s) *BRCA* promoter methylation will be assessed also centrally at an external reference central laboratory selected by GEICAM. Tumour samples must be obtained from a metastatic lesion, it is strongly recommended to obtain the tumour sample after the treatment line

immediately previous to the study entry.

Patients with a positive methylation status on *BRCA1* and/or *BRCA2* and lacking of known deleterious or suspected deleterious mutations in both genes could be included in the study to receive olaparib tablet formulation at 600 mg daily dose (given in two oral administrations of 300 mg every 12 hours approximately).

Blood and tumour samples collected from all registered patients could be used for biomarker analysis planned in the study, including but not limited to the assessment of germline methylation status and gene expression levels of *BRCA1/2*.

An optimal two-stage Simon design will be used to analyse olaparib efficacy in the study population, the analysis of the stage 1 will be performed after 12 evaluable patients are enrolled; if at least 4 of them show tumour response, additional patients will be included to complete a total of 31 evaluable patients. Assuming a 10% dropout rate, the total number of patients to be enrolled is 34.

It is planned the participation of 16 Spanish sites, recruitment will be competitive approximately 2 or 3 patients should be enrolled per site; to achieve that is estimated that 7 or 8 patients approximately should be screened per site.

Primary Objective:

- To analyse the olaparib efficacy in the treatment of patients diagnosed of advanced triple negative breast cancer (TNBC) with *BRCA1* and/or *BRCA2* promoter methylation assessed in somatic DNA.

Primary End-point:

- Objective Response Rate (ORR) defined as Complete Response (CR) plus Partial Response (PR) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Secondary Objectives:

- To analyse other efficacy measures.
- To analyse olaparib safety.
- To explore changes in the methylation status of BRCA1/2 promoter in germline DNA prior and after treatment discontinuation for any reason and correlate germline BRCA1/2 methylation data with efficacy parameters.
- To correlate BRCA1/2 methylation between germline and somatic DNA and between primary tumour and metastatic lesions.
- To correlate BRCA1/2 expression with methylation status of *BRCA1/2* promoter and efficacy parameters.

Secondary End-points:

- Clinical Benefit Rate (CBR), Response Duration (RD), Progression Free Survival (PFS) and Overall Survival (OS).
- Adverse events defined by the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.0.
- The methylation status of *BRCA* 1 and 2 promoters will be measured in germline DNA from blood cells at the beginning of the study and after disease progression, or at the end of study treatment by other reason, and in paired primary and metastatic lesions. It will be analysed: 1) changes of germline methylation pre and post-treatment; 2) correlation between germline methylation status and efficacy outcome data; 3) correlation between germline and somatic methylation status and 4) correlation between primary and metastatic lesions.
- mRNA levels of *BRCA1* and *2* will be assessed in blood and available tumour samples. Expression data will be correlated with promoter methylation status of *BRCA* and outcome data.

Exploratory Objectives:

- To explore biomarkers of clinical activity in tumour and blood samples.

Exploratory End-points:

- Biomarker values from the primary or metastatic tumour tissue could be used for assessment of biomarkers related to breast tumour sensitivity and/or resistance to olaparib (e.g. may include but not limited to somatic *BRCA1*/2 mutational status or other genes related to cancer susceptibility or thought to be related to the drug mechanism of action). These samples will be instrumental to explore biomarkers of response or resistance to olaparib.

- DNA and RNA obtained from the blood samples collected during the study may be used for potential pharmacogenomics analyses related to drug response or adverse drug reactions (including but not limited to comparison of germline DNA or RNA patterns of patients who respond well and those who respond poorly to treatment). For example, genes coding drug metabolizing enzymes, drug transport proteins or genes involved in DNA repair pathways, cancer susceptibility or thought to be related to the drug mechanisms of action may be analysed.
- Specific mutations or epigenetic biomarkers identified in pre-therapy tumour specimens as potentially linked to treatment response could be tested in plasma DNA. A targeted NGS panel may be designed to study all the candidate mutations. Plasma DNA has also the potential to be a surrogate of tumour load and may also be instrumental to monitor disease.

Study population and main inclusion and exclusion criteria:

Inclusion Criteria:

Patients are eligible to be included in the study only if they **meet all** of the following criteria. Any asterisked* are also applicable as an inclusion criteria prior to perform the *BRCA* methylation testing via central testing; to perform the BRCA methylation test, investigator judgement of patient's potential eligibility to the study should be assessed as per Protocol Attachment 1. Study Schedule and by reviewing the below inclusion criteria:

1. *The patient has signed and dated the informed consent document and it has been obtained before conducting any procedure specifically for the study.
2. Female ≥ 18 years of age on day of signing informed consent.
3. Patient with histological confirmation of breast cancer with evidence of advanced disease not amenable to resection or radiation therapy with curative intent.
4. Documented **triple negative** disease by immunohistochemistry (IHC) and/or *in situ* hybridization based on local testing (preferably assessed on the most recent tumour biopsy available). TN is defined as **negative hormone receptor status** (< 1% of tumour cells with ER and PgR expression) and **HER2-negative status** (defined as IHC score 0/1+ or negative by *in situ* hybridization defined according to local criteria).
5. Patient must have received at least one previous regimen in the advance disease setting.
6. Absence of deleterious or suspected deleterious germline mutations in *BRCA1* and *BRCA2*. Germinal *BRCA* mutational status will be centrally assessed in Myriad laboratories to check eligibility unless the test has been previously performed at Myriad and absence of mutations has been determined.
7. Availability of a tumour tissue sample from the metastatic lesions (every effort should be done to obtain the sample after the previous therapeutic regimen for advanced disease) for central testing.

8. Documented methylation of *BRCA1* and/or *2* promoters based on central testing by analysis on the most recent tumour from metastatic lesions available.
9. At least one lesion measurable not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) or clinical examination and which is suitable for accurate repeated measurements according to RECIST v.1.1.
10. Patient must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
    - Haemoglobin ≥ 10.0 g/dL with no blood transfusions in the past 28 days
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase, SGOT) /Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase, SGPT)] ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case they must be ≤ 5 x ULN
    - Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min:

      $$\text{Estimated creatinine clearance} = \frac{(140\text{-age [years]}) \times \text{weight (kg)} \ (\times F)^{a}}{\text{serum creatinine (mg/dL)} \times 72}$$

      [a] where F=0.85 for females.
11. *Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see protocol attachment 2)
12. *Patient must have a life expectancy ≥ 16 weeks
13. *Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1.

    Postmenopausal patient is defined as a woman fulfilling any one of the following criteria (based on the NCCN definition of menopause [National Comprehensive Cancer Network 2008]):
    - Prior bilateral oophorectomy.
    - Age > 60 years.
    - Age ≤ 60 years and with amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone and estradiol in the postmenopausal range.
14. 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 as listed below. This should be started from the signing of the informed consent for study entry and continue throughout period of taking study treatment and for at least 1 month after last dose of study drug or they must totally/truly abstain from any form of sexual intercourse (see below).

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of the study treatment and for at least 1 month after one dose. Periodic abstinence (e.g., 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.
- Intrauterine Device (IUD) PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (e.g., Depo-Provera) PLUS male condom**.**
- Etonogestrel implants (e.g. Implanon or Norplan) PLUS male condom.
- Norelgestromin/ethinyl estradiol (EE) transdermal system PLUS male condom.
- Intrauterine system (IUS) device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom.
- Intravaginal device PLUS male condom (e.g. EE and etonogestrel).

15. *Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits, laboratory tests and examinations and other study procedures including follow up.

Exclusion Criteria:

Patients will be excluded from the study if they **meet any** of the following criteria. Any asterisked* are also applicable as an exclusion criteria prior to perform the BRCA methylation testing via central testing; to perform the *BRCA* methylation testing, investigator judgement of patient's potential eligibility to the study should be assessed as per Protocol Attachment 1. Study Schedule and by reviewing the below exclusion criteria):

1. Involvement in the planning and/or conduct of the study (applies to the sponsor and/or study site staff).
2. Previous enrolment in the present study.
3. Participation in another clinical study with an investigational product during the last 4 weeks.

4. *Any previous treatment with a PARP inhibitor, including olaparib.
5. *Patients with other malignancy within the last 5 years, except: adequately treated non-melanoma skin cancer (basal cell or squamous cell carcinoma), 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 inclusion. Patients with a history of localised breast cancer with tumour histology different to TN, with no evidence of disease for ≥ 5 years since they completed their adjuvant treatment.
6. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons), within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).
7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.
8. *Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks. Please refer to section 5.5.2.1 about strong and moderate CYP3A inhibitors.
9. *Concomitant use of known strong CYP3A inducers (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. Please refer to section 5.5.2.2 about strong and moderate CYP3A inducers.
10. *Persistent toxicities (> NCI-CTCAE grade 2) caused by previous cancer therapy (except alopecia or other toxicities not considered a safety risk for the patient at investigator´s discretion).
11. *Patients with myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) or with features suggestive of MDS/AML.
12. *Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Patients with brain metastases may be eligible for the study only if more than 4 weeks from treatment completion for these metastases (including radiation and/or surgery), are clinically stable at the time of study entry. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable

disease for 28 days.

13. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
14. *Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
15. *Breast feeding women.
16. *Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
17. *Patients with known active hepatitis (i.e., Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids.
18. *Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
19. *Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, severe hepatic impairment (according to Child-Pugh classification), an extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) or any psychiatric disorder that prohibits obtaining informed consent.
20. *Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
21. *Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria nº 10).

Justification of Sample size determination:

We have set the null hypothesis (H0) that ORR will be 30% (ORR achieved by TN patients treated with gemcitabine plus carboplatin[1]) versus the alternative hypothesis (H1) that ORR will be 54% (ORR showed by TN BRCA mutated patients treated with olaparib[2]). Using an optimal two-stage Simon model and considering an alpha error of 0.05 and a statistical power of 80%, it will be required to include 31 evaluable patients. Twelve evaluable patients will be analysed in the first stage, and if at least 4 patients of them have tumour response, additional patients will be recruited to get a total of 31 evaluable patients. Assuming a 10% dropout rate, the total number of patients to be enrolled is 34. Considering, these data the number of responders needed at the end of stage 2 to reject the null hypothesis is at least 14 responders.

Statistical Analyses:

- Demographics and Baseline Characteristics

  Standard descriptive statistics, such as the mean, median, range and proportion, will be used to summarize the patient sample and to estimate parameters of interest.

- Safety Analyses

  Adverse events data and serious adverse events will be reported in frequency tables (overall and by intensity). The safety analysis will be performed in the population that has received at least one dose of the study drug.

- Efficacy Analyses

  ORR will be calculated in the efficacy population and in the ITT population.

Study Duration:

The start date of study is the date of the first site initiation visit. This study will be considered complete following the data cut-off date and data-lock for the final analysis; the data cut-off date will be the date of last patient´s death or the date when there is sufficient data to achieve the final analysis, whichever comes first. It is estimated that the final analysis could be performed approximately 30 months after the enrolment of the first patient because, considering a median OS of 12 months, it is estimated that more than 50% of death events will have occurred at that time and OS analysis could be performed. The study is expected to start in Quarter 3 2017 and to end by Quarter 1 2020.

Performing exploratory objectives will be independent of the date of the end of the study.

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Abbreviations and Definitions

ABC	Advanced Breast Cancer
AE	Adverse Event
AEMPS	Spanish Agency for Medicines and Health Products
AESI	Adverse Event of Special Interest
ALT/ALAT (SGPT)	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST/ASAT (SGOT)	Aspartate Aminotransferase
BC	Breast Cancer
b.i.d.	Twice daily (from Latin *Bis In Die*)
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Rate
CI	Confidence Interval
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CT Scan	Computed Tomography Scan
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
DSB	Double Strand Break
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form (sometimes referred to as Clinical Report Form). An electronic form for recording study participants' data during a clinical study, as required by the protocol.
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Ethinyl Estradiol
End of Study (Trial)	This study will be considered complete following the data cut-off date and datalock for the final analysis, the data cut-off date will be the date of last patient´s death or the date when there is sufficient data to achieve the final analysis for primary and secondary objectives, whichever comes first
Enroll	The act of including a patient in the study. Patients who are enrolled in the trial are those who have been assigned a registration (or screening) numberand it will be confirmed that the patient will receive the study treatment.
Screen	The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. Patients who are entered in the trial will be assigned a registration (or screening) number.

EOT	End of Treatment
ER	Oestrogen Receptor
ERB/IRB/IEC	Ethical review board/Institutional review board/Independent Ethics Committee: A board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
ESR	Expedited Safety Report
et al	And collaborators
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
gBRCA	*BRCA1* and *2* in germinal line
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase
GMP	Good Manufacturing Practice
GLS	Geometric least squares
GEICAM	Fundación Grupo Español de Investigación en Cáncer de Mama
G-CSF	Granulocyte Colony-Stimulating Factor
HER2	Human Epidermal Growth Factor Receptor 2
Hgb	Haemoglobin
HL	Hy's Law
HR	Homologous Recombination or Hazard Ratio depending on the context
HRD	Homologous Recombination DNA pathway Deficiency
HRR	Homologous Recombination DNA Repair
IC_{50}	Concentration for 50% inhibition
ICD	Informed Consent Document
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the Investigator is the responsible leader of the team and may be called the Principal Investigator.
INR	International Normalised Ratio
ISH	In Situ Hybridization
ITT	Intent To Treat
LDH	Lactic dehydrogenase
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical trial.
LLN	Lower Limit of Normal
MDS/AML	Myelodysplastic Syndrome/ Acute Myeloid Leukemia
MBC	Metastatic Breast Cancer
MCH	Mean Cell Haemoglobin
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mRNA	Messenger Ribonucleic Acid

N.B.	Please note from Latin "*Nota bene*".
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OAE	Other Significant Adverse Event
o.d.	Once a day
ORR	Objective Response Rate
OS	Overall Survival
PARP	Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP)
Patient	A subject with a defined disease.
PD	Progressive Disease or Pharmacodynamic depending on the context
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PgR	Progesterone Receptor
PK	Pharmacokinetic
PR	Partial Response
PS	Performance Status
RBC	Red Blood Cells
RD	Response Duration
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase II Dose
RR	Response Rate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SSB	Single Strand Break
SD	Stable Disease or Standard deviation depending on the context
sBRCA	*BRCA1* and *2* in somatic line (tumour)
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TN	Triple Negative
TTP	Time To Progression
ULN	Upper Limit of Normal
WBC	White Blood Cells
WNL	Within Normal Limits

Study Title: **Protocol GEICAM/2015-06**

"A Phase II **C**linical Trial to analyse **O**laparib Response in patients with *BRCA1 and/*or *2* Promoter **Met**hylation Diagnosed of **A**dvanced **Breast** Cancer**"**

"**COMETA-Breast Study**"

1. Introduction

1.1. Overview of Breast Cancer

Breast cancer (BC) represents one of the most frequent cancers in general population and the first malignant tumour in women worldwide. In Europe, there were an estimated of 464,000 new cases of breast cancer in 2012, with a mortality of 131,000 cases[3]. Specifically in Spain, incidence is around 26,000 new cases per year and although a steady decrease in mortality has been demonstrated in the last decades, nearly 20% of the patients relapse and ultimately die of breast cancer, which represent a mortality of approximately 6,000 women per year in Spain[4].

1.2. Triple Negative Breast Cancer (TNBC)

Breast cancer has been classified in several subtypes by gene expression analyses including luminal, basal-like, HER2-enriched and claudin-low[5,6]. Each one represents an independent entity with different prognosis and potential response to specific therapeutic strategies[7]. Using immunostaining in tumour samples, it has been observed, that most of basal-like tumours are those that match with cancers that are defined by lack or low immunohistochemical (IHC) expression of oestrogen (ER), progesterone (PgR) and HER2 (IHC 0, 1+ or 2+/ISH not amplified); therefore, this particular subset of breast cancer has been termed triple negative breast cancer (TNBC)[8], which represents approximately 12-17% of breast cancer overall[9]. This tumour subtype is characterized by the presence of stem cell precursors, a high proliferation rate and metastatic capacity[10,11] and a worse prognosis than other breast cancer subtypes. These factors may be a major reason for the high-risk of relapse, and the shorter progression-free survival (PFS) and overall survival (OS) reported for this disease[12,13].

It is known that within this group there is differential expression of several genes that could have clinical relevance[14]. One of those differences with potential therapeutic implications is *BRCA1* expression. Turner et al reported low expression of *BRCA1/2* in approximately 70% of basal-like tumours[15]. Consistent with this, one of the most frequent molecular events in TN breast tumours is the presence of BRCA protein dysfunction[16]. Among breast cancer patients with a hereditary *BRCA1* mutation, over 80% is a TNBC[17]. As sporadic triple-negative tumours often show the same histological characteristics and clinical outcome as *BRCA1* mutation carriers, several studies postulated that *BRCA1* inactivation might also have a role in sporadic TNBCs[18,19]. The phenotype that some sporadic tumours share traits with familial *BRCA* cancer is called "*BRCA*ness"[20]. The importance of defining such a group of tumours lies within the clinical management of these tumours[21].

1.2.1. Treatment Options for Triple Negative Advanced Breast Cancer

Treatment options for advanced breast cancer (ABC) are numerous and varied, however the median survival for patients with metastatic disease is still only approximately 18 to 24

months[22] and the medical need for more active agents in this clinical setting remains very high, especially in triple negative tumours, a challenging situation where impact of the current treatments in overall survival is relatively low[23]. Median survival of advanced TNBC is at best 12 months, much shorter than the duration of survival seen in other subtypes of ABC. Chemotherapy is the current mainstay of therapy for TNBC patients with varied impact on long-term prognosis and no optimal cytotoxic regimen has been identified. Chemotherapeutic agents with proven activity in TNBC include anthracyclines, taxanes, platinum derivatives, capecitabine, gemcitabine, vinorelbine, eribulin, and ixabepilone[24,25].

At present, multiply efforts are being performed to improve the prognosis for these patients. It implies both optimization in selection and scheduling of cytotoxic agents or dose intensification strategies and introduction of new targeted agents. No targeted treatment has been developed for TNBC, in contrast to endocrine treatment and anti-HER2 treatments, which have significantly improved the clinical outcomes in ER/PgR positive and HER2 positive breast cancer patients, respectively. Therefore, identification of specific targeted and more active therapies for TNBC patients remains an important clinical challenge.

1.2.2. Methylation of BRCA Promoter and Breast Cancer Risk

It is known that germline mutations in one of the genes encoding BRCA proteins (*BRCA1* and *BRCA2*) increase the susceptibility to breast and ovarian cancer, in fact, these mutations are observed in 5-10% of breast tumours[26] and up to 20% of high grade serous ovarian tumours[27]. Both proteins have a key role in cellular homeostasis, making a fundamental contribution in the regulation of the ER expression and repair of double-stranded DNA breaks, mainly by the homologous recombination (HR) pathway[28]. DNA breaks can be leaded by multiple chemotherapeutic agents.

The association between *BRCA1* mutations and a common expression phenotype (CK 5/6+, ER- and mutated p53) could reflect a common aetiology for breast and ovarian tumours. However, the frequency of *BRCA1* mutations is much lower than the breast cancer basal subtype or the high grade serous ovarian cancer.

In addition to the mutational analysis of *BRCA*, other alterations can be responsible for a dysfunctional BCRA protein. One of them is the epigenetic silencing by aberrant methylation of *BRCA1*/2 promoter, more frequently described in medullary and metaplastic tumours. It is known that, in most cases, the methylation status leads to gene silencing. The methylation of *BRCA1*/2 promoter has been explored in multiple neoplasms, finding highly variable frequencies: ovarian 5-20%[29,30], gastric 50%[31] and breast 29-59%[32,33,34]. *BRCA1*-methylated sporadic breast tumours have been described in young women and display pathologic features similar to those of *BRCA1*-mutated hereditary breast cancers[35,36,37]. Among different breast cancer types, the level of tumour DNA methylation seems to be higher in TNBC cases and in tumours with high BRCA-like histopahological scores[38]. According to Tutt et al. up to 40% of TNBCs harbor methylated *BRCA1* genes; they

recently showed that CpG methylation was associated with transcriptional silencing of *BRCA1* mRNA. They were able to analyze primary tumors for 191 patients, of which mRNA and methylation status data were available for 184 and observed that Sixty-six percent of methylated tumor samples were gene-silenced[39]. Interestingly, sporadic tumours with aberrant methylation of the *BRCA1* promoter can be clustered with tumours derived from women with inherited *BRCA1* germline mutations because of similarities in their global gene expression profiles[18,40].

There are other causes leading deficiencies in the repair process of double-stranded DNA breaks by the homologous recombination mechanism, such as the loss of heterozygosity or the expression of negative regulators of BRCA, as ID4, or loss of function of proteins as RAD51, CHECK2 or ATM[41].

The methylation assessment can be performed both at tumour tissue and at germline level (DNA from nucleated peripheral blood cells), without necessarily existing a correlation between both measurements. Furthermore, methylation status is a changing and dynamic process, determined at tumour level by the own carcinogenic process and at germline level by multiple processes, including the different anti-tumour treatments.

The methylation status of *BRCA1* promoter assessed in germline DNA, isolated from peripheral blood cells, has been associated with breast cancer risk[42,43,44]. In the Bosviel dataset the methylation rate of *BRCA1* at the germline level in breast cancer patients (n=902) was 47.1%[45]. These results are consistent with other datasets such as those studied by Snell[46] or Iwamoto who detected methylation of *BRCA1* promoter in 43 out of 200 breast cancer patients (21.5%), a higher frequency than the rate observed in controls (27/200, 13.5%)[47]. These findings suggest that *BRCA1* promoter methylation is an event that occurs in normal tissues and can be associated with the development of breast cancers BRCA1-like[48].

Although there is limited information, the relationship between the methylation status in *BRCA1* promoter in germline and tumour DNA has been reported in several datasets[38,49]. According to Wong et al[49], this association suggest that the methylation at this level and in a constitutive manner could be the first event in the carcinogenesis process of a group of non-inherited breast cancers. Other authors have reported this correlation between germline and tumour methylation status, as Al-Moghrabi et al. who found correlation in 10 out of 15 analysed cases (66.7%)[50]. Sarah et al. showed that blood DNA methylation levels correlated with tumour methylation at most of the *BRCA1* CpG sites examined although those levels were higher in tumour DNA compared to matched blood DNA samples[38].

1.3. PARP Inhibitors in Breast Cancer

Inhibition of Polyadenosine 5'diphosphoribose [poly (ADP ribose] polymerisation (PARP) is a promising strategy for targeting cancers with defective DNA-damage repair, including *BRCA1* and *BRCA2* mutation-associated breast and ovarian cancers[51]. Several PARP inhibitors are currently in trials in the adjuvant, neoadjuvant, and metastatic settings for the treatment of ovarian, *BRCA*-mutated breast, and other cancers.

The observation that *BRCA*-mutated breast cancers show impairment in HR pathways[52], and that some sporadic TNBC are phenocopies of *BRCA1*-mutated cancers (i.e. they display a phenotype resembling *BRCA1*-mutated cancers without harbouring a *BRCA1* mutation, a feature also defined as "*BRCAness*"), led to exploration of the application of PARP inhibition to the treatment of breast cancer (*BRCA*-associated and TNBC).

Following the demonstration by Bryant and Farmer[53,54] of the cytotoxic effect of PARP inhibition in HR-deficient cells, there was interest in studying the activity of PARP inhibitors as monotherapy in solid tumours. In earlier studies, the population enrolled in these trials was not restricted to patients with known *BRCA* mutations, but encompassed also those whose cancer displayed a phenotype similar to *BRCA*-mutated cancers. Clinically, this group included triple-negative breast cancers and high grade serous or poorly differentiated ovarian cancer.

However, after preliminary data showing minimal efficacy of PARP inhibitors in sporadic breast cancers, some of the trials were amended to enrich the study cohorts for *BRCA*-associated tumours[55,56]. Initial phase 1 testing of olaparib as monotherapy in *BRCA*-associated breast, prostate and ovarian cancers showed encouraging results: 47% of patients with *BRCA*-associated breast, ovarian, or prostate cancers treated with olaparib achieved a partial response, and 63% of them derived clinical benefit (tumour marker decrease or radiologic response or stable disease for 4 or more months). A phase 1 study of niraparib in patients with advanced solid tumours enriched for *BRCA*-associated cancers reported an overall response rate of 40% (8 of 20) in patients with *BRCA*-associated ovarian cancer and 50% (2 of 4) in patients with *BRCA*-associated breast cancer[57]. Talazoparib monotherapy has shown antitumour activity in patients with *BRCA* mutations, with an objective response rate of 65% in ovarian and peritoneal tumours and 33% (2 of 6 patients) in breast cancers[58]. Data presented at ASCO 2014 on single agent rucaparib showed efficacy in BRCA-associated ovarian, breast, and pancreatic cancers[59].

Tutt et al.[2] reported efficacy of olaparib as monotherapy in 54 patients with advanced breast cancer and germline *BRCA1*/2 mutations. At the maximum tolerated olaparib dose of 400 mg b.i.d. (capsule formulation), a 41% ORR was observed, with responses in both TNBC and hormone receptor-positive HER2-negative patients. It is noteworthy that the ORR achieved by TN patients was 54%.

Kaufman et al[60] reported data of a phase 2 study of olaparib monotherapy in 298 patients with diverse recurrent cancers (mostly ovarian, breast, pancreatic, and prostate) and confirmed *BRCA1*/2 mutations (a study design called "basket trial"). Breast cancer tumour response rate was 12.9% in 62 patients, and 47% of patients had disease stabilization for ≥ 8 weeks. The lower objective response rate in this study compared with previous studies could be due to the fact that the study population was more heavily pre-treated than in other trials (mean of 4.6 prior chemotherapy regimens in the metastatic setting vs. 3 in Tutt et al[2]).

Randomized phase 3 studies of PARPi in MBC have been limited to patients with documented *BRCA1*/2 mutations. Three parallel study designs have already tested (EMBRACA and OlympiAD) or are currently testing (BRAVO NCT01905592)[61] oral PARPi monotherapy vs. physician's choice single agent chemotherapy in breast cancer patients with PARPi-naive metastatic disease with germline *BRCA1*/2 mutations. Study results from EMBRACA (talazoparib, NCT01945775) trial showed that among patients with advanced breast cancer and a germline BRCA1/2 mutation, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival[62]. OlympiAD (olaparib, NCT02000622) trial compared treatment with olaparib tablets to physician's choice of a standard of care chemotherapy in the treatment of patients with HER2-negative metastatic breast cancer harboring germline *BRCA1* or *BRCA2* mutations and have shown that patients treated with olaparib showed a statistically-significant and clinically-meaningful improvement in PFS compared with those who received chemotherapy (capecitabine, vinorelbine or eribulin)[63].

Finally, BROCADE3 study (NCT02163694)[64] will test the efficacy of veliparib versus placebo in combination with carboplatin and paclitaxel in HER2-negative metastatic or locally advanced, unresectable, *BRCA*-associated breast cancer.

1.4. Overview of Olaparib

Investigators should be familiar with the current olaparib (AZD2281, KU-0059436) Investigator Brochure (IB). The approved tradename for olaparib is LYNPARZA™.

Olaparib 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 the more serious 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 (HRR). Tumours with HR deficiencies (HRD), such as ovarian cancers in patients with *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.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo[65,66] and in the clinic[55]. The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair[67,68]. Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR 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* knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

1.4.1. Preclinical Data

The preclinical experience is fully described in the current version of the olaparib Investigator's Brochure (IB).

Olaparib was developed as a PARP inhibitor from a targeted screening programme of pharmacophores, with the aim of enhancing the killing actions of certain existing cancer chemotherapies such as the topoisomerase I inhibitors and alkylating agents. Development has yielded a compound that has the potential for stand-alone cancer therapy as well as use in combination cancer treatments[69].

Olaparib activity against PARP-1, PARP-2, PARP-3 and another PARP family member, Tankyrase-1 is shown in Table 1.

Table 1. Activity of olaparib against purified PARP enzyme

Enzyme	IC_{50} (nM)
PARP-1	5
PARP-2	1
PARP-3	4
Tankyrase-1	1500

IC_{50} Concentration for 50% inhibition; PARP Polyadenosine 5'diphosphoribose polymerase; PARP-1 Polyadenosine 5'diphosphoribose polymerase-1; PARP-2 Polyadenosine 5'diphosphoribose polymerase-2; PARP-3 Polyadenosine 5'diphosphoribose polymerase-3.

1.4.2. Toxicology and safety pharmacology summary

Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test.

Secondary pharmacodynamics and safety pharmacology studies were conducted with olaparib to assess for potential off-target activity and effects on the cardiovascular, respiratory as well as central nervous systems, respectively.

- Olaparib showed no significant off-target activity at concentrations 6-fold the human mean free Cmax at the clinical dose of 300 mg bd (3.65 μM) when screened in vitro against a diverse panel of molecular targets including enzymes, receptors, transporters and ion channels.
- Olaparib inhibited the hERG encoded potassium channel expressed in vitro, with an IC_{50} of 226 μM, which was 60-fold greater than the human mean free Cmax (3.65 μM) at the clinical dose of 300 mg bd.
- Olaparib showed no significant effects in vivo in dog cardiovascular/respiratory and rat Irwin (behavioural) tests.

The nonclinical safety evaluation of olaparib is based on data from a variety of single and repeat dose toxicology studies in rats and dogs, reproductive toxicology studies in rats and an in vitro and in vivo assessment of genotoxic potential. In addition, studies investigating single and repeat dose combinations of olaparib with topotecan or temozolomide (TMZ) were conducted in rats. Key findings are summarised below:

- The principal target organ for toxicity was the bone marrow in repeat dose toxicity and tolerability studies in rats and dogs, all changes showed full or partial recovery following withdrawal of treatment or a 28 day recovery period.
- Olaparib was not mutagenic in an Ames bacterial mutation test, but was clastogenic in a Chinese Hamster Ovary (CHO) chromosome aberration test in vitro. These findings are consistent with genomic instability resulting from the primary pharmacology of olaparib.
- In reproductive toxicology studies in rats, olaparib produced no adverse effects on male fertility, while on female rats, although conception rates were unaffected, embryofoetal survival was decreased. Administration of olaparib during organogenesis caused reductions in early embryofoetal survival and foetal weights as well as increases in the incidence of abnormalities at dose levels that were not maternally toxic.
- Combination studies in rats suggested potential for olaparib to exacerbate the effects of TMZ or topotecan, although combination of olaparib with these anti-cancer agents did not induce any additional target organ toxicities to those seen with single agent administration.

There were relatively few findings of concern in the non-clinical toxicology studies, although exposures in these studies were generally below those achieved at the clinical dose of olaparib (300 mg b.i.d. tablet). In conclusion, the non-clinical safety evaluation studies conducted with olaparib support the use of olaparib for the treatment of cancer patients.

Further information can be found in the current version of the olaparib Investigator's Brochure.

1.4.3. Pharmacokinetics and Drug Metabolism in Humans

The initially developed capsule formulation of olaparib consists of 50 mg dosing units with a monotherapy dosing schedule of 400 mg b.i.d. The tablet formulation consists of dosing units up to 150 mg olaparib with a monotherapy dosing schedule of 300 mg b.i.d. Given the different drug delivery technologies in the capsule and tablet, the formulations cannot be considered bioequivalent.

As of 15 December 2017, pharmacokinetics (PK) data are available from 11 clinical studies: Studies D081BC000001 (Japanese Phase I monotherapy), D081BC00002 (Chinese Phase I monotherapy and interaction with paclitaxel), D0816C00004 (food interaction and QT), D0816C00007 (CYP3A4 inhibition and QT), D0816C00008 (CYP3A4 induction) and D0810C00024 (relative bioavailability for the capsule and tablet formulations) D0816C00005 (hepatic impairment), D0816C00006 (renal impairment) and D081CC00001

(interaction with anti-hormonal agents), D0816C00002 (SOLO2) and D0819C00003 (OlympiAD) The tablet formulation is under study in the majority of the on-going and future olaparib studies. Based on the totality of the efficacy, safety/tolerability profile and the patient convenience of a b.i.d. dosing schedule, the 300 mg b.i.d. tablet dose was chosen as the recommended Phase III monotherapy dose (Study D0810C00024).

1.4.3.1. Pharmacokinetics following single and multiple dosing of the olaparib monotherapy tablet formulation

Single dose final PK data (using intensive PK sampling and non-compartmental analysis) are available following oral dosing of olaparib at dose levels ranging from 25 mg to 450 mg in Western patients with normal renal and hepatic function. Single dose PK data for 56, 56, 22, 13 and 12 patients are available from Studies D0816C00004 (300 mg), D0816C00007 (100 mg) and D0816C00008 (300 mg), D0816C00005 (300 mg) and D0816C00006 (300 mg), respectively. Multiple dose final data (using intensive PK sampling) following oral dosing of olaparib to Western patients are available from Studies D0816C00004 (300 mg b.i.d.), D0816C00007 (300 mg b.i.d.), D0810C00024 (Group 8, 400 mg o.d.) and D081CC00001 (300 mg b.i.d) for 49, 45, 12 and 27 patients, respectively. Additional multiple dose data are available based on sparse PK sampling in Study D0810C00024 and Study D0816C00002 (SOLO2), and PK parameters were derived using nonlinear mixed effects PK modeling.

Following single oral dosing to cancer patients using the tablet formulation, olaparib was rapidly absorbed with peak plasma concentrations typically observed at 1.5 hours. Following time to maximum plasma concentration (tmax), plasma concentrations of olaparib declined in a biphasic manner with an average terminal elimination t1/2 of 14.9 hours (SD 8.2 hours). The mean apparent oral plasma clearance was approximately 7.4 L/h (SD 3.9 L/h). The mean volume of distribution was greater than total body water indicating that olaparib was distributed into the tissues; 158 L (SD 136 L). The observed interindividual variability in exposure was moderate to high, the Gmean %CV for AUC and Cmax following 300 mg single dose olaparib were 58.9 % and 34.3% respectively.

In Studies D0816C00004, D081BC00001 and D081BC00002, as anticipated based on t1/2 values following single dose, systemic plasma exposure to olaparib (Cmax and AUC0-τ) following multiple dosing (100 mg to 300 mg tablet b.i.d.), was higher than after single dose administration. However, the observed mean accumulation ratio for AUC (RAUC = 1.4-1.9) was more than expected as the temporal change parameter (TCP, AUC0-τ at steady state/AUC single dose) was more than unity, indicating that the PK of olaparib was time-dependent. As olaparib is a substrate as well as a time dependent inhibitor of CYP3A, the mechanism of the time dependent change in olaparib PK is believed to be related to the above properties.

In Study D0816C00007, the single dose PK was for 100 mg olaparib tablet, whereas the multiple dose PK was for 300 mg b.i.d.; therefore, a direct comparison of the single and multiple dose PK within each patient was not possible. However, following multiple daily

b.i.d. dosing of olaparib (300 mg tablet), exposures (C_{max} and $AUC_{0-\tau}$) were consistent with steady state exposures observed following multiple administration of the tablet (300 mg b.i.d.) under fasting conditions in Part B of the food effect study (D0816C00004). Similarly, steady state exposures (Cmax and $AUC_{0-\tau}$) in Study D081CC00001 (300 mg tablet) were also in the same range as those observed in Studies D0816C00007 and D0816C00004.

In the Phase III study SOLO2 (D0816C00002) with sparse PK samples, steady state olaparib exposure parameters (area under the plasma concentration-time curve at steady state [AUC_{ss}], $C_{max\ ss}$ and $C_{min\ ss}$) in ovarian cancer patients when dosed with tablet formulation at 300 mg b.i.d. were found to be in the same range as those in patients dosed with capsule formulation at 400 mg b.i.d. and were lower when compared with those in patients dosed with 300 mg b.i.d. tablet formulation in Phase I studies. There was a large variability in individual exposures among the studies and the low exposure observed in SOLO2 and OlympiAD may be a manifestation of a large between study variability. Although the mean exposure to olaparib in SOLO2 and OlympiAD studies was lower than the Phase I studies, there was a large overlap in individual patient exposures.

The AUC for olaparib tablet across the clinical programme appears to increase approximately proportionally with dose.

1.4.3.2. Metabolism and Excretion of Olaparib

The metabolism and excretion of olaparib were investigated in 6 female patients (aged 34 years to 72 years) following oral administration of a single 100 mg (~120 μCi) dose of olaparib in Study D0810C00010. Although 6 patients were dosed in total, only 5 received the intended 100 mg dose of olaparib (1 patient received only the 50 mg radiolabelled capsule). Recovery data were determined for all 6 patients but PK parameters were only reported for the 5 who received the full olaparib dose.

Olaparib was the major component present in plasma and accounted for approximately 70% of the radioactivity present. Three other metabolites, M12, M15 and M18, each represented approximately 10% of the material (9.3%, 10.3% and 13.7%, respectively). These metabolites were identified as products of hydroxylation and opening of the cyclopropyl ring (M12), monooxygenation of the fluorophenyl ring (M15) and dehydrogenation of the piperazine ring (M18). The major drug derived components in plasma were M12 (ring-open piperazin-3-ol), M15 (4-fluorophenol (hydroxy)methyl) and M18 (piperazin 3-ol); each accounted for 9-14% of the plasma radioactivity. Drug-related material was eliminated in the urine (approximately 44% of the dose) and in the faeces (approximately 42% of the dose).

In the urine, olaparib was the most abundant component, accounting for between 10% and 19% of the dosed material. Up to 37 further drug-related components were observed. At least 20 components were observed in the pooled faecal samples with 6 components accounting for >1% of the dose and the remaining metabolites detectable only by

HPLC/MS. The major components present were unchanged olaparib (0.6 to 14% of the dose) and M15 (0.9 to 8% of the dose). Four further metabolites (M9, M12, M23 and M25) were also prominent each accounting for ≤6% of the dose.

1.4.3.3. Effect of Intrinsic Factors on the PK of Olaparib

Following administration of oral doses to patients in the Japanese or Chinese tablet PK studies (D081BC00001 and D081BC00002, respectively) the Gmean C_{max} and AUC observed in Japanese or Chinese patients were within the range observed for Western patients when given the same dose, 300 mg olaparib tablet.

In the tablet population PK analysis, age, body weight and gender covariates were not found to be predictors of olaparib plasma exposure and therefore dose adjustment on the basis of age, body weight or gender is not required.

The data obtained from the human mass balance study using the capsule formulation (Study D0810C00010) showed that both renal and metabolic routes were involved in the elimination of olaparib.

A formal study to evaluate the impact of mild and moderate renal impairment on single dose olaparib tablet PK has been completed (D0816C00006). AUC increased by 24% and Cmax by 15% in patients with mild renal impairment (creatinine determined by Cockcroft Gault of 51 ml/min to 80 mL/min) and no olaparib tablet dose adjustment is required in this group. AUC and Cmax for olaparib were 44% and 26% higher in patients with moderate renal impairment, and a dose adjustment is recommended. Hence, it is recommended that patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥51 mL/min to be included in a clinical trial. If a patient develops moderate renal impairment whilst on treatment the recommended olaparib tablet dose is 200 mg b.d. (400 mg total daily dose). It is not recommended that olaparib is dosed to patients with severely impaired renal function (creatinine clearance <30 ml/min) as data are not available in these patients.

A formal study to evaluate the impact of hepatic impairment on olaparib tablet PK has been completed (Study D0816C00005). D0816C00005 is a 2-part study in patients with advanced solid tumours in which the PK of a single oral 300 mg tablet dose of olaparib is investigated in Part A and continued access to multiple dose olaparib (300 mg b.d.) is provided in Part B to obtain additional safety data. When olaparib (300 mg) was administered as a single dose to patients with mild hepatic impairment, there was a 13% increase in Geometric least squares (GLS) mean Cmax and a 15% increase in GLS mean AUC compared to those observed in patients with normal hepatic function. For patients with moderate hepatic impairment, there was a 13% decrease in GLS mean Cmax and an 8% increase in GLS mean AUC compared to patients with normal hepatic function. The changes in AUC and Cmax in patients with mild and moderate hepatic impairment were small (15% or less) and were considered not clinically significant. There were also no

obvious relationships for any of the PK parameters with any parameters associated with liver function, including serum bilirubin, albumin and prothrombin time.

Olaparib is not recommended for use in patients with severe hepatic impairment as the safety and PK of olaparib has not been studied in these patients.

The impact of previous gastric surgery on olaparib exposure when administered at 100 mg in combination with paclitaxel dosed weekly 80 mg/m^2 was assessed in a subgroup of olaparib-treated dosed with advanced gastric cancer in Study D081BC00004. Exposure to olaparib in combination with paclitaxel appeared to be lower in patients with gastric surgery.

1.4.3.4. Effect of Extrinsic Factors on the PK of Olaparib

The effect of food on olaparib tablet has been investigated. Study D0816C00004 has formally evaluated the effect of food (a high fat meal) on the PK of olaparib following dosing of the tablet formulation to man. The point estimates for the treatment ratio for AUC and AUC from time zero to the last measurable concentration (AUC0-t) indicated a small (8%) increase in olaparib exposure when administered following a high fat meal which was of borderline statistical significance (treatment ratio: 1.08; 90% CI: 1.01-1.16). However, both the point estimate and 90% CI for the treatment ratios for AUC lay entirely within the 0.80 to 1.25 bounds, indicating that there was no effect of food on olaparib AUC. In contrast, there was a statistically significant 21% decrease in C_{max} following a high fat meal (treatment ratio: 0.79; 90% CI: 0.72-0.86). Co-administration with food slowed the rate of absorption (tmax delayed by 2.5 hours and Cmax reduced by 21%), however food did not significantly affect the extent of absorption (AUC), therefore olaparib tablet can be given without regard to food.

Regarding drug-drug interactions:

- CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib. All clinical studies conducted to date have excluded co-administration of known strong inhibitors or inducers of CYP3A4/5. The data in Study D0816C00007 indicated the presence of a marked interaction with a known strong inhibitor of CYP3A and P-glycoprotein (P-gp), itraconazole while the study D0816C00008 indicated the presence of marked interaction with a known strong inducer of CYP3A and Pgp, rifampicin. It is therefore recommended that known strong inhibitors or inducers of CYP3A4/5 isozymes should be avoided with olaparib.

  Physiologically-based pharmacokinetic (PBPK) modeling has shown that moderate inhibitors will alter the clearance of olaparib and therefore concomitant use of moderate CYP3A inhibitors is not recommended with olaparib. It is also not recommended to consume grapefruit juice while on olaparib therapy.

  If a strong or moderate CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 100 mg b.i.d. (equivalent to a total daily dose of 200 mg) with a strong CYP3A inhibitor or 150 mg b.i.d. (equivalent to a total daily dose of 300 mg) with a moderate CYP3A inhibitor.

PBPK modelling has shown that moderate CYP3A inducers will decrease olaparib AUC by approximately 50% and therefore concomitant use of moderate CYP3A inducers such as, but not limited to bosentan, efavirenz, etravirine, modafinil and nafcillin is not recommended with olaparib. If a moderate CYP3A inducer must be coadministered, the prescriber should be aware of a potential for decreased efficacy of olaparib.

- In vitro olaparib is a substrate for the efflux transporter P-gp. Clinical studies to evaluate the impact of specific P-gp inhibitors and inducers have not been conducted; however based on the physical and absorption, distribution, metabolism and excretion properties of olaparib, there is low risk that P-gp modulator could significantly alter systemic exposure to olaparib.
- A clinical study was conducted to evaluate the drug-drug interaction between olaparib and anti-hormonal agents. There was no drug-drug interaction between olaparib and letrozole or anastrozole. Tamoxifen (20 mg o.d.) decreased mean exposure to olaparib at steady state (by 20% for Cmax and by 27% for AUC0-12). In addition, olaparib had a small impact on exposure to tamoxifen (mean increase by 13% for Cmax and 16% for AUC0-12). These were not considered to be clinically significant. Considering the small PK drug-drug interaction effects, the observed safety and tolerability profiles of olaparib when combined with anti-hormonal agents in this study, the known inter-patient variability for olaparib and the lack of relationship between olaparib plasma exposure and safety or efficacy, AstraZeneca recommend that olaparib can be given in combination with anti-hormonal agents without dose adjustment.
- Substrates of UGT1A1 should also be given with caution in combination with olaparib (e.g., irinotecan, nintedanib, ezetimibe, raltegravir or buprenorphine).
- Induction of CYP1A2, 2B6 and 3A4 has been shown in vitro, with CYP2B6 being most likely to be induced to a clinically relevant extent. The potential for olaparib to induce CYP2C9, CYP2C19 and P-gp is unknown. It cannot be excluded that olaparib upon co-administration may reduce the exposure to substrates of these metabolic enzymes.Based on evaluation using enzyme activity, olaparib was not considered an inducer of CYP2C9 and 2C19.
- In vitro, olaparib has been shown to be an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K and is a weak inhibitor of BRCP. PBPK modelling predicts olaparib would have no effect on digoxin, a probe P-gp substrate. It cannot be excluded that olaparib may increase the exposure to substrates of OATP1B1 (e.g., bosentan, glibenclamide, repaglinide, statins and valsartan), OCT1 (e.g., metformin), OCT2 (e.g., serum creatinine), OAT3, MATE1 and MATE2K. In particular, caution should be exercised if olaparib is administered in combination with any statin.

- Olaparib is predicted by PBPK modeling to be a weak inhibitor of CYP3A in vivo. Co-administration with olaparib is predicted to increase the AUC of CYP3A substrates such as midazolam and simvastatin by 60% or less. This prediction is consistent with results from Study D081CC00001, in which olaparib was found to have only a small effect on the exposure of CYP3A substrates such as tamoxifen, anastrozole and letrozole. Based on in vitro data and PBPK modelling, caution is recommended when administering olaparib with sensitive CYP3A substrates or substrates with a narrow therapeutic margin (e.g. simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine).
- In reference to interactions with chemotherapeutic agents PK sampling has been included in a number of studies evaluating the safety and tolerability of olaparib capsule when dosed in combination with a number of chemotherapeutic agents. The data available from these studies are summarised below.

Table 2. Drug-drug interactions with chemotherapeutic agents

Combinations (study codes)	Results of the interaction analysis
Olaparib capsule plus DTIC (Study D0810C00003)	- Co-administration of DTIC had little or no effect on olaparib exposure and *vice-versa*.
Olaparib capsule plus carboplatin, paclitaxel or carboplatin and paclitaxel (Studies D0810C00004 and D0810C00041)	- Although co-administration of carboplatin and paclitaxel has little or no effect on single dose exposure to olaparib, co-administration with paclitaxel does appear to reduce steady state exposure by up to 45%. - Co-administration with a single dose of olaparib appears to have had no effect on exposure to free carboplatin; - Co-administration with a single dose of olaparib appears to have had no effect on exposure to paclitaxel.
Olaparib capsule + gemcitabine (Study D0810C00005)	- Co-administration of gemcitabine had no effect on steady state exposure to olaparib - Co-administration of olaparib had no effect on exposure to either gemcitabine or gemcitabine and 2',2'-difluorodeoxyuridine
Olaparib capsule + topotecan (Study D0810C00006)	- Olaparib steady state exposure was reduced when olaparib was dosed in combination with topotecan. The average reduction in exposure was approximately 20%. Due to bioanalytical difficulties, the impact of olaparib on exposure to topotecan could not be determined.
Olaparib capsule + cisplatin (Study D0810C00021)	- Co-administration of cisplatin had little/no effect on steady state exposure to olaparib
Olaparib capsule + bevacizumab (Study D0810C00022)	- Co-administration of bevacizumab did not affect steady state exposure to olaparib

Olaparib + liposomal doxorubicin (Study D0810L00001)	- A within patient comparison of the exposures achieved when olaparib was given in combination with liposomal doxorubicin showed that average olaparib Cmax and AUC from zero to 10 h was increased by approximately 30% and 40%, respectively. When further PK data, obtained only when dosed in combination with liposomal doxorubicin, were compared to data obtained following olaparib monotherapy in other studies, there was no clear difference in the olaparib exposures achieved. Based on comparison with literature values, there was no evidence that olaparib (at doses between 50 mg bd and 400 mg bd) altered the PK of liposomal doxorubicin.

1.4.4. Effect of Olaparib on Cardiac Repolarisation

Olaparib was active in the hERG assay at high concentrations but showed no evidence of effects on ECG intervals in anaesthetised dogs. The hERG assay IC_{50} (226 μM) was 60-fold higher than the average steady state maximum free plasma concentration following a 300 mg b.i.d. tablet dose in man (3.65 μM) suggesting that an effect of olaparib on QT interval in man is unlikely.

The effect of olaparib on cardiac re-polarisation has been studied in Studies D0816C00004 and D0816C00007. Triplicate, time matched digital ECGs were collected after both single and multiple dosing of olaparib in these studies and analysed by an independent cardiologist. The resulting data were subjected to statistical analysis. The primary aim of this analysis was to assess the effect of multiple doses of olaparib on the corrected QT interval using Fridericia's formula (QTcF interval), by calculating the difference in Least Square (LS) means (olaparib QTcF interval LS mean at time t minus control QTcF interval LS mean at time t) and two-sided 90% CI. An analysis of covariance (ANCOVA) model was fitted to the pooled Part B data from Studies D0816C00004 and D0816C00007. In addition, supportive analysis was performed to investigate the effect of single dosing of olaparib on QTc.

From this analysis of the pooled multiple dose data from Studies D0816C00004 and D0816C00007, the upper confidence limit of the two-sided 90% CI around the mean treatment effect was <10 ms for the contrast of multiple dose olaparib versus control for every time point, suggesting a lack of clinically relevant effect on cardiac repolarisation. The supportive single dose analysis also showed no effect of olaparib on cardiac polarisation. Olaparib had no clinically relevant effect on partial response (PR) and QRS interval or heart rate.

In conclusion, these data have provided no indication of a clinically relevant effect on cardiac repolarisation (as detected by QT prolongation) following multiple doses of 300 mg b.i.d. of olaparib (tablet formulation) or following single doses of olaparib (tablet formulation).

1.4.5. Clinical Experience

Clinical experience with olaparib is fully described in the current version of the olaparib Investigator's Brochure.

The clinical development programme for olaparib continues to assess the effect of olaparib (as a single agent or in combination) in the treatment of patients with tumours enriched for HRD, including *BRCA* mutated cancers (germline and tumour).

Olaparib has demonstrated anti-tumour activity in non-comparative studies in patients with gBRCA mutated cancers including ovarian, breast, pancreas and prostate.

The capsule formulation of olaparib was registered for use in the European Union (EU) and United States (US) in December 2014 and has been approved in 28 other markets globally. The tablet formulation has subsequently been registered in the US in August 2017 and Japan in January 2018. The recommended olaparib monotherapy capsule dose is 400 mg b.i.d. Post marketing patient exposure for olaparib is estimated to be >6700 patient-years (6470 patient-years for capsules and 230 patient-years for tablets) up to 30 November 2017. The majority of completed studies have been performed with the capsule formulation of olaparib but, since 2012/2013 most new studies, including the Phase III registration studies, are being performed with the tablet formulation which delivers the therapeutic dose of olaparib in fewer dose units than the capsule.. The recommended olaparib monotherapy tablet dose is 300 mg b.i.d.

Olaparib monotherapy (tablet formulation) is currently in Phase III investigation in patients with ovarian cancer and *BRCA* mutations, in patients with *gBRCA* mutated advanced breast cancer, in patients with *gBRCA* mutated breast cancer in the adjuvant treatment setting, in patients with *gBRCA* mutated advanced pancreatic cancer and in a combination treatment setting with paclitaxel in patients with advanced gastric cancer. Additionally, Phase I, II or III studies include investigation of cancers driven by other DNA homologous recombination repair deficiencies beyond *BRCA* mutations.

As of 15 December 2017, approximately 8319 patients are estimated to have received olaparib in the clinical programme of Olaparib. Olaparib monotherapy is generally well tolerated at monotherapy doses up to 400 mg b.i.d. (capsule formulation) and 300 mg b.i.d. (tablet formulation) in patients with solid tumours. Adverse Event (AE) reports considered to be associated with administration of olaparib are generally mild or moderate (NCI-CTCAE Grade 1 or 2) haematological effects (anaemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, mean corpuscular volume [MCV] elevation and increase in blood creatinine), decreased appetite, nausea, vomiting, diarrhoea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), headache dizziness and cough. Generally these AEs didn't require treatment discontinuation.

In a relatively small number of patients, pneumonitis, myelodysplastic syndrome (MDS) /acute myeloid leukaemia (AML) and new primary malignancies have been reported, however totality of data from the whole development programme does not support a

conclusion that there is a causal relationship between olaparib and these events. These important potential risks for olaparib are being kept under close surveillance.

The safety and efficacy data presented in this section consist of final report data. Only blinded serious adverse event (SAE) data are presented for the Phase III programme in ovarian cancer, breast cancer and gastric cancer as the studies are ongoing.

In the majority of the completed studies providing efficacy and safety data to date, olaparib has been administered to patients via a Gelucire™ capsule formulation.

1.4.5.1. Olaparib Monotherapy Efficacy Data

Data from three completed non-comparative Phase II studies provided efficacy data for olaparib (capsule) as a monotherapy in breast cancer and other solid tumours. Recently one completed, open label, controlled Phase III study has provided efficacy data for olaparib (tablet) as a monotherapy in breast cancer Descriptions of the study design and patient disposition/demography for each of these studies are provided in this section, followed by side by side presentations of Response Evaluation Criteria in Solid Tumours (RECIST) response and PFS data for the Phase II capsule studies, with special focus on data from breast cancer patients enrolled on those studies.

- **Study D0810C00002 (KU36-92): advanced solid tumours**

This was a first time in man (FTIM), Phase I, PK and biological evaluation of olaparib (capsule formulation) in patients with advanced tumours. The primary objective was to determine the safety, tolerability, dose-limiting toxicity (DLT), PARP inhibitory dose range and maximum tolerated dose (MTD) of olaparib in patients with advanced solid tumours. After the MTD was identified (400 mg b.i.d.), an expansion phase at 200 mg b.i.d. was opened in ovarian, breast and prostate cancer patients who had hereditary *BRCA* mutations.

Overall, 98 patients were recruited and treated in the study. The main tumours by type were ovarian (54 [55.1%]), breast, (13 [13.3%]); large intestine (5 [5.1%]), prostate (4 [4.1%]) and skin cancers (4 [4.1%]).

- **Study D0810C00008 (KU36-44): *gBRCA* mutated breast cancer**

This was a Phase II, open-label, non-comparative, international, multicentre study to assess the efficacy and safety of olaparib (capsule formulation) given orally b.i.d. in patients with advanced *gBRCA1* or *gBRCA2* breast cancer. The primary objective was to assess the efficacy of the capsule formulation at 2 different doses of olaparib in terms of objective response rate (ORR) using RECIST in patients with advanced *BRCA1* or *BRCA2* related breast cancer. Patients received olaparib at a dose of 400 mg b.i.d. or 100 mg b.i.d. continuously in 28-day cycles, for multiple cycles until no further clinical benefit was apparent or the patient was withdrawn from the study.

- **Study D0810C00020: *BRCA* mutated or serous ovarian cancer, *BRCA* mutated or triple negative breast cancer (TNBC)**

This was a Phase II, open label, non-randomised correlative study to determine the ORR of single agent olaparib (400 mg b.i.d. capsule formulation) in patients with recurrent breast and ovarian cancer. The study enrolled both *BRCA* inherited mutation carriers and non-carriers. Twenty-six patients with breast cancer were allocated to receive study treatment and all received at least one dose. The majority (69.2%) of patients with breast cancer were White with a mean age of 48.2 years (range 24 years to 80 years).

- **Study D0810C00042: advanced solid tumours in patients with a *gBRCA* mutation – non-ovarian cancer cohorts**

This was a Phase II, open-label, non-randomised, non-comparative, multicentre study to assess the efficacy and safety of olaparib (400 mg capsules) given orally b.i.d. in patients with advanced cancers who had a confirmed genetic *BRCA1* and/or *BRCA2* mutation.

A total of 298 patients received treatment: 193 patients had ovarian cancer, 62 patients had breast cancer, 23 patients had pancreatic cancer, 8 patients had prostate cancer, and 12 patients had other cancers. The mean age of the patients was 55.3 years (range 29 years to 79 years). The majority of patients were White (283 [95%]) and female (272 [91.3%]).

A summary of overall response (RECIST) in the non-ovarian cancer groups of studies D0810C00008, D0810C00020 and D0810C00042 is presented in Table 3 and median PFS, OS and response duration (RD) in the non-ovarian cancer groups of Studies D0810C00008, D0810C00020 and D0810C00042 is presented in Table 3.

Table 3. Summary of overall response (RECIST) in Studies D0810C00008, D0810C00020 and D0810C00042 (non-ovarian cancer).

	Number (%) patients						
	D0810C00008 (*gBRCA* breast)[a]		D0810C00020 (breast)[b]	D0810C00042 (advanced *gBRCA* cancers)[c]			
	Olaparib 100 mg b.i.d	Olaparib 400 mg b.i.d	Olaparib 400 mg b.i.d	Olaparib 400 mg b.i.d			
	N=27	N=27	N=26	Breast N=62	Pancreas N=23	Prostate N=8	Others N=12
Objective response (CR + PR)	6 (22.2)	11 (40.7)	0	8 (12.9)	5 (21.7)	4 (50.0)	1 (8.3)
CR	0	1 (3.7)	0	0	1 (4.3)	0	0
PR	6 (22.2)	10 (37.0)	0	8 (12.9)	4 (17.4)	4 (50.0)	1 (8.3)
SD	12 (44.4)	12 (44.4)	10 (38.5)	29 (46.8)	8 (34.8)	2 (25.0)	7 (58.3)
PD	9 (33.3)	4 (14.8)	15 (57.5)	23 (37.1)	9 (39.1)	2 (25.0)	3 (25.0)
Not evaluable	0	0	1 (3.8)	2 (3.2)	1 (4.3)	0	0

a Data were based on the ITT population consisting of all enrolled patients who received at least one dose of olaparib irrespective of whether they completed the trial schedule and the study regime or not.

b Data were based on the safety analysis set consisting of all patients who received at least one dose of olaparib.

c Data were based on the full analysis set.

b.i.d. Twice daily; CR Complete response; *gBRCA* Germline *BRCA*; ITT Intention-to-treat; PD Progressive disease; PR Partial response; RECIST Response Evaluation Criteria in Solid Tumours; SD Stable disease.

Table 4. Summary of median PFS, OS and DoR in Studies D0810C00008, D0810C00020 and D0810C00042 (non-ovarian cancer).

	D0810C00008 (*gBRCA* breast)[a]		D0810C00020 (breast)[b]	D0810C00042 (advanced *gBRCA* cancers)[c]		
	Olaparib 100 mg b.i.d	Olaparib 400 mg b.i.d	Olaparib 400 mg b.i.d	Olaparib 400 mg b.i.d		
	N=27	N=27	N=26	Breast N=62	Pancreas N=23	Prostate N=8
Median DoR (days)	NR	NR	NC	204.0	134.0	326.5
Median PFS (95% CI)	115.0 days (58-167)	173.0 days (140-226)	54.0 days (51-106)	3.68 months (2.69-5.42)	4.55 months (1.84-7.72)	7.15 months (1.71-17.45)
Median OS (months)	NR	NR	NR	11.01	9.81	18.38

a Data were based on the ITT population consisting of all enrolled patients who received at least one dose of olaparib irrespective of whether they completed the trial schedule and the study regime or not.

b Data were based on the safety analysis set consisting of all patients who received at least one dose of olaparib.

c Data were based on the full analysis set.

b.i.d. Twice daily; CI Confidence interval; DoR Duration of response (from onset of response); gBRCA Germline *BRCA*; ITT Intention-to-treat; NC Not calculable; NR Not reported; OS Overall survival; PFS Progression-free survival.

- **Study D0819C00003 (OlympiAD): gBRCA mutated breast cancer**

This was an open label, randomised study of olaparib versus standard Chemotherapy of Physician's Choice (TPC) as treatment of MBC. Study patients harboured a deleterious germline mutation of *BRCA1/2* (gBRCAm), were previously treated with an anthracycline and a taxane, and had received no more than 2 prior chemotherapy regimens for metastatic disease. Of the 302 patients who underwent randomisation, 205 were assigned to receive olaparib tablets 300 mg b.i.d. and 97 to receive TPC.

Olaparib tablet monotherapy provided a statistically significant and clinically meaningful improvement in PFS compared with TPC. At 77% maturity, PFS by blinded independent central review was significantly longer in patients treated with olaparib versus TPC (HR 0.58; 95% CI 0.43-0.80; p=0.0009; 7.0 *vs*. 4.2 months, respectively). Objective response rate was 59.9% and 28.8% in the olaparib and TPC arms, respectively. Final analysis of OS at 64% maturity revealed no evidence of a detriment to survival in patients given olaparib compared to those given TPC, with a small non-significant numerical trend favouring olaparib.

1.4.5.2. Olaparib 400 mg b.i.d. Monotherapy (capsule formulation) Pooled Safety Data

This section presents a pooled analysis of olaparib 400 mg b.i.d. (capsule formulation) monotherapy safety data from Study D0810C00019 plus 11 additional studies. A total of 766 patients with advanced solid tumours are included in this analysis.

In the olaparib 400 mg b.i.d. capsule pooled dataset, the contributing studies have differing patient populations. The majority of patients in the pooled dataset (522/766) had ovarian cancer. Patients with other advanced solid tumours, including breast (n=145), colorectal (n=42), pancreas (n=24) or prostate (n=8) cancers were also treated in these studies. With the exception of Study D0810C00019, where olaparib was administered in the maintenance setting to responding patients, the treatment setting was as a late line of therapy to patients with relapsed, progressive disease.

The number of patients in the 400 mg b.i.d monotherapy pooled dataset who had at least 1 AE in any category during the course of the study is 749 (97.8 %), any AE causally related to study treatment 666 (86.9 %), any AE of CTCAE grade 3 or higher 347 (45.3 %), and any AE leading to discontinuation of study treatment 45 (5.9%). Fatigue and anaemia were the most common CTCAE Grade 3/4 AEs in the capsule pool dataset: CTCAE Grade 3/4 fatigue was reported by 6.9% of patients and CTCAE Grade 3/4 anaemia was reported by 11.5% of patients.

1.4.5.2. Olaparib 300 mg b.i.d. monotherapy (tablet formulation) pooled dataset

This section presents a pooled analysis of olaparib 300 mg b.i.d. (tablet formulation) monotherapy safety data from Study D0816C00002 (including the China cohort) plus 10 additional studies: D0819C00003 (OlympiAD), D0810C00024, D0816C00004, D0816C00007, D0816C00008, D081BC00001, D081CC00001, D0816C00006, D0816C00005 and D081BC00002. A total of 759 patients with advanced solid tumours are included in this analysis.

In the olaparib 300 mg b.i.d. tablet pool dataset, the contributing studies have differing patient populations. The majority of patients in the pooled dataset had either ovarian fallopian tube or primary peritoneal cancer (335/759) or breast cancer (268/759). Patients with other solid tumours including colon/colorectal (n=23), pancreas (n=12) or prostate (n=11) were also treated. Patients were generally heavily pre-treated with anticancer therapies.

The number of patients in the 300 mg b.i.d. monotherapy tablet pool dataset who had at least 1 AE in any category during the course of the study is 741 (97.6 %), any AE causally related to study drug 654 (86.2 %), any AE of CTCAE Grade 3 or higher 278 (36. 6 %), and any AE leading to discontinuation of study treatment 50 (6.6%).

Haematological toxicity was reported at an increased frequency with the tablet formulation, compared with the capsule formulation; however, anaemia and neutropenia remained manageable by interrupting or reducing the olaparib dose or giving blood transfusions or colony stimulating factor, when indicated; treatment discontinuation was rarely required. Reports of thrombocytopenia remained at low frequency with the tablet formulation; these events were primarily low grade and rarely required treatment discontinuation.

Anaemia, neutropenia and fatigue were the most common CTCAE Grade 3/4 AEs in the tablet pool dataset: CTCAE Grade 3/4 anaemia was reported by 14.6% of patients, CTCAE

Grade 3/4 neutropenia was reported by 3.8% of patients and CTCAE Grade 3/4 fatigue was reported by 3.2% of patients.

AEs leading to discontinuation of olaparib occurred infrequently and were reported at a similar frequency in the tablet and capsule pooled datasets. Anaemia, leading to discontinuation was reported in a slightly higher proportion of patients in the tablet pool (7 patients [1.5%]) compared with patients in the capsule pool (3 patients [0.4%]). The majority of deaths were reported as due to the disease under investigation, and for deaths unrelated to disease under study, there were no major differences between the capsule and tablet pooled datasets.

1.4.5.3. Emerging Safety Profile

This section lists those adverse drug reactions that are currently regarded as expected for regulatory reporting purposes.

A full description of the emerging safety profile for olaparib, with guidance for Investigators, is provided in Section "Emerging Safety Profile" of the current version of the olaparib's Investigator Brochure.

Administration of olaparib monotherapy has been associated with adverse reactions (Table 5), generally of mild or moderate severity (NCI-CTCAE Grade 1 or 2) and generally not requiring treatment discontinuation. The emerging safety profile for olaparib supports further studies in cancer patients.

The safety profile is based on pooled data from 1248 patients treated with olaparib monotherapy in clinical trials in the therapeutic indication at the recommended dose.

The following adverse reactions have been identified in completed clinical trials with patients receiving olaparib monotherapy where patient exposure is known. Adverse Drug Reactions are listed by Medical Dictionary for Regulatory Activities (MedDRA) SOC and then by MedDRA preferred term. Within each SOC, preferred terms are arranged bydecreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); and very rare (<1/10,000); not known (cannot be estimated from available data)..

Table 5. Adverse Drug Reactions from Completed Clinical Studies

	Adverse reactions	
MedDRA System Organ Class	**Frequency of all CTCAE grades**	**Frequency[a] of CTCAE grade 3 and above**
Blood and lymphatic system disorders	**Very common** Anaemia[a] **Common**	**Very common** Anaemia[a] **Common**

	Neutropenia[a] Thrombocytopenia[a] Leukopenia[a] **Uncommon** Lymphopenia	Neutropenia[a] Thrombocytopenia[a] Leukopenia[a] **Uncommon** Lymphopenia
Immune system disorders	**Common** Rash[a] **Uncommon** Hypersensitivity[a], Dermatitis[a]	-
Metabolism and nutrition disorders	**Very common** Decreased appetite	**Uncommon** Decreased appetite
Nervous system disorders	**Very common** Dizziness Headache Dysgeusia	**Uncommon** Dizziness Headache
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a]	**Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia **Common** Stomatitis Upper abdominal pain	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis Upper abdominal pain
General disorders and administration site conditions	**Very common** Fatigue (including asthenia)	**Common** Fatigue (including asthenia)
Investigations	**Common** Increase in creatinine **Uncommon** Mean corpuscular volume elevation[b]	**Uncommon** Increase in creatinine

[a] Anaemia includes preferred terms (PTs) of anaemia, haemoglobin decreased, red blood cell count decreased, erythropenia and haematocrit decreased; Neutropenia includes PTs of neutropenia, granulocytopenia, granulocyte count decreased and neutrophil count decreased, febrile neutropenia, neutropenic infection and neutropenic sepsis; Thrombocytopenia includes PTs of thrombocytopenia, platelet count decreased, platelet production decreased and plateletcrit decreased; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalised erythema; Hypersensitivity includes PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative.

[b] Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.

CIOMS Council for International Organizations of Medical Sciences; CTCAE Common Terminology Criteria for Adverse Events v.3.0; MedDRA Medical Dictionary for Regulatory Activities; SOC System organ class.

A description of selected adverse reactions is included below:

Haematological toxicity: Anaemia and other haematological toxicities are generally low grade (CTCAE Grade 1 or 2), however, there are reports of CTCAE Grade 3 and higher events. Anaemia was the most common CTCAE Grade ≥3 adverse reaction reported in clinical studies. Median time to first onset of anaemia was approximately 4 weeks (approximately 7 weeks for CTCAE Grade ≥3 events). Anaemia was managed with dose interruptions and dose reductions, and where appropriate with blood transfusions. In clinical studies the incidences of dose interruptions, reductions and discontinuations for anaemia were 8.3%, 5.0% and 0.8%, respectively. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with olaparib, the incidence of CTCAE Grade ≥2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils 15%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate). The incidence of elevations in MCV from low to normal at baseline to above the upper limit of normal was approximately 55%. Levels appeared to return to normal after treatment discontinuation and did not appear to have any clinical consequences.

Baseline testing, followed by monthly monitoring of complete blood counts is recommended for the first 12 months of treatment with olaparib, and periodically after this time to monitor for clinically significant changes in any parameter during treatment which may require dose interruption or reduction and/or further treatment.

Other laboratory findings: In clinical studies with olaparib the incidence of CTCAE Grade ≥2 shifts (elevations) from baseline in blood creatinine was approximately 15%. Data from a double-blind placebo controlled study showed median increase up to 23% from baseline remaining consistent over time and returning to baseline after treatment discontinuation, with no apparent clinical sequelae; 90% of patients had creatinine values of CTCAE Grade 0 at baseline and 10% were CTCAE Grade 1 at baseline.

Nausea and vomiting: Nausea was generally reported very early, with first onset within the first month of olaparib treatment in the majority of patients. Vomiting was reported early, with first onset within the first two months of olaparib treatment in the majority of patients. Both nausea and vomiting were reported to be intermittent for the majority of patients and can be managed by dose interruption, dose reduction and/or antiemetic therapy. Antiemetic prophylaxis is not required.

Important potential risks of MDS/AML, pneumonitis and new primary malignancies are discussed in section 1.6.1.

1.5. Study Rationale

Approximately 15% of ovarian cancer patients and 5% of breast, pancreatic and prostate cancer patients have inherited mutations of *BRCA1* or *BRCA2*. In addition to genetic loss of *BRCA* function, it has been suggested that a further ~20% of tumours display so-called "*BRCAness*"[70,71] phenotype. Furthermore, reduced function of other key proteins in the homologous recombination pathway similarly results in increased sensitivity to PARP inhibition and enhancement of chemotherapy and radiotherapy treatments. For these reasons, PARP inhibition represents a novel approach to anti-tumour therapy and may address an unmet need in patients with *BRCA* associated cancer.

1.6. Benefit/risk and ethical assessment

As of 15 December 2016, approximately 6558patients with ovarian, breast, gastric, pancreatic, and a variety of other solid tumours are estimated to have received treatment with olaparib in AstraZeneca-sponsored, investigator-sponsored, and collaborative group studies and a Managed Access Programme. In the AstraZeneca-sponsored studies, olaparib has been given as either monotherapy (an estimated 2618patients) or in combination with chemotherapy or other anti- cancer agents (eg, capecitabine, vinorelbine, eribulin, abiraterone, topotecan, gemcitabine, carboplatin and paclitaxel, paclitaxel or liposomal doxorubicin), including studies where patients received monotherapy and combination therapy sequentially (n=1181)Of the 4475 patients treated with olaparib in AstraZeneca-sponsored, interventional studies and the MAP, 2109 received the capsule formulation, 2341 received the tablet formulation, and 25 received both capsule and tablet. . Approximately 1327patients have received comparator or placebo across the olaparib development programme in AstraZeneca-sponsored studies.

From the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure. An analysis of monotherapy data across 12 AstraZeneca-sponsored monotherapy studies in 766 patients with ovarian cancer and other non-ovarian solid tumours who have been given olaparib capsules estimated that 18.3% (140/766) of patients had been exposed to olaparib capsules for ≥12 months, 9.4% (84/1006) for >18 months,5.4% for >24 months, 3.3% for >36 months and 2.6% for >48

months (as of 08 August 2016) at the time of database closure for the respective studies. Eighteen patients (2.1%) had received ≥60 months of olaparib exposure.

The 300 mg b.i.d. monotherapy tablet regimen has shown an acceptable tolerability profile relative to the 400 mg b.i.d. capsule and has been determined to be the recommended olaparib monotherapy tablet dose for future studies with olaparib using the tablet formulation. Olaparib as monotherapy at doses up to 400 mg b.i.d. (capsule formulation) and 300 mg b.i.d. (tablet formulation) is generally well tolerated, with most common AEs including nausea, fatigue, vomiting, and anaemia, being mainly mild-to-moderate (CTCAE Grade ≤ 2) in severity.

1.6.1. Important Potential Risks

- **Myelodysplastic syndrome (MDS) /acute myeloid leukaemia (AML)**

The incidence of MDS/AML in patients treated in clinical trials with olaparib monotherapy, including long-term survival follow-up, was <1.5 % and the majority of these events have had a fatal outcome. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents. The majority of reports were in germline *BRCA* mutation carriers and some of the patients had a history of previous cancer or of bone marrow dysplasia.

Since bone marrow is known to be a target organ for olaparib toxicity, increased risk of MDS/AML with long-term exposure to olaparib cannot be excluded. However, there is insufficient data at present to evaluate 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 must be considered that there were other potential contributing factors in all cases. The risk is perceived as low and not outweighing the potential benefit of study treatment in the breast cancer patients to be included in the current trial.

Clinical guidelines for managing bone marrow toxicity are indicated in Section 5.4. Special Treatment Considerations. Dose Adjustments of Olaparib.

- **Pneumonitis**

Pneumonitis events have been reported in <1% of patients receiving olaparib monotherapy in clinical studies. The reports of pneumonitis had no consistent clinical pattern and were confounded by a number of pre-disposing factors (cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy). When olaparib was used in clinical studies in combination with other therapies there have been events with a fatal outcome.

Investigation of any new or worsening pulmonary symptoms has been implemented as part of the safety management of the study in Section 5.4.2. Management of Non-Haematological Toxicity.

- **New Primary Malignancies other than MDS/AML**

New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents.

Study team will review emerging data from the trial in order to detect possible risks for the patients.

To ensure robust safety monitoring of these adverse events of special interest (AESIs), patients enrolled on this clinical study will have safety assessments during the first week on study treatment on a monthly basis afterwards until treatment discontinuation for any reason, and in the follow up visit performed approximately 30 days after the last dose of the study treatment. Study monitors will be trained on the safety profile of olaparib and Investigators will be advised to consider a thorough follow up of those patients experiencing any AESI. Procedures for reporting AESIs are indicated in Section 6.2.3. In addition, a continuous data validation will be performed with periodic review of safety data by the GEICAM medical and pharmacovigilance department.

1.6.2. Potential Benefit

A Marketing Authorisation Application was approved in EU/EEA on 16 December 2014 for the indication "LYNPARZA monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed *BRCA*-mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy".

A New Drug Application was approved in the US on 19 December 2014 for the indication "LYNPARZA monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy". The tablet formulation of olaparib was approved in August 2017 US for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy; and for the treatment of adult patients with deleterious or suspected deleterious germline breast cancer susceptibility gene (BRCA)-mutated (gBRCAm) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy.

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 ORR of up to 41%, A phase 3 trial, OlympiAD showed that olaparib provided a significant benefit over standard therapy; median PFS was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.

US approved in January 2018 the tablet formulation for patients with deleterious or suspected deleterious gBRCAm, HER2-negative MBC who have previously been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine treatment. Based on these results and data from the full clinical program to date, it is anticipated that olaparib will have a positive benefit risk profile for the treatment of the small well-defined population of advanced triple negative breast cancer patients with promoter methylation of *BRCA*.

2. Objectives

2.1. Primary Objective

- To analyse the olaparib efficacy in the treatment of patients diagnosed of advanced triple negative breast cancer (TNBC) with *BRCA1* and/or *BRCA2* promoter methylation assessed in somatic DNA.

2.2. Primary End-point

- Objective Response Rate (ORR) defined as Complete Response (CR) plus Partial Response (PR) according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

2.3. Secondary Objectives

- To analyse other efficacy measures.
- To analyse olaparib safety.
- To explore changes in the methylation status of *BRCA1*/*2* promoter in germline DNA prior and after treatment discontinuation for any reason and correlate germline *BRCA1/2* methylation data with efficacy parameters.
- To correlate *BRCA1*/2 methylation between germline and somatic DNA and between primary tumour and metastatic lesions.
- To correlate *BRCA1/2* expression with methylation status of *BRCA1/2* promoter and efficacy parameters.

2.4. Secondary End-points

- Clinical Benefit Rate (CBR), Response Duration (RD), Progression Free Survival (PFS) and Overall Survival (OS).
- Adverse events defined by the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) version 4.0.
- The methylation status of *BRCA* 1 and *2* promoters will be measured in germline DNA from blood cells at the beginning of the study and after disease progression, or at the end of study treatment by other reason, and in paired primary and metastatic lesions. It will be analysed: 1) changes of germline methylation pre and post-treatment; 2) correlation between germline methylation status and efficacy outcome data; 3) correlation between germline and somatic methylation status and 4) correlation between primary and metastatic lesions.

- mRNA levels of *BRCA1* and 2 will be assessed in blood and available tumour samples. Expression data will be correlated with promoter methylation status of *BRCA* and outcome data.

2.5. Exploratory Objectives

- To explore biomarkers of clinical activity in tumour and blood samples.

2.6. Exploratory End-points

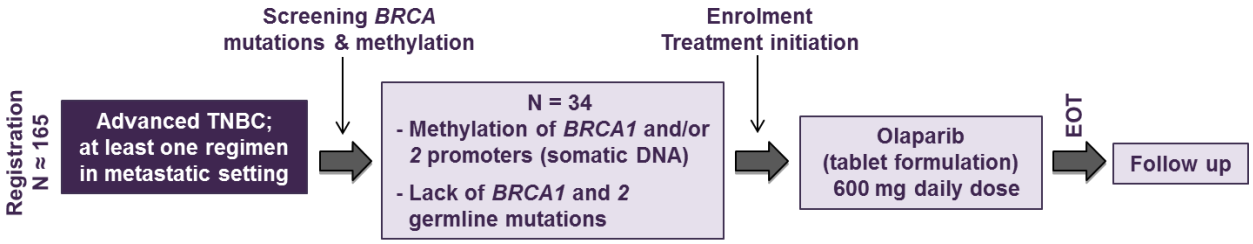
- Biomarker values from the primary or metastatic tumour tissue could be used for assessment of biomarkers related to breast tumour sensitivity and/or resistance to olaparib (e.g. may include but not limited to somatic *BRCA1*/2 mutational status or other genes related to cancer susceptibility or thought to be related to the drug mechanism of action). These samples will be instrumental to explore biomarkers of response or resistance to olaparib.
- DNA and RNA obtained from the blood samples collected during the study may be used for potential pharmacogenomics analyses related to drug response or adverse drug reactions (including but not limited to comparison of germline DNA or RNA patterns of patients who respond well and those who respond poorly to treatment). For example, genes coding drug metabolizing enzymes, drug transport proteins or genes involved in DNA repair pathways, cancer susceptibility or thought to be related to the drug mechanisms of action may be analysed.
- Specific mutations or epigenetic biomarkers identified in pre-therapy tumour specimens as potentially linked to treatment response could be tested in plasma DNA. A targeted NGS panel may be designed to study all the candidate mutations. Plasma DNA has also the potential to be a surrogate of tumour load and may also be instrumental to monitor disease.

3. Investigational Plan

3.1. Study Design

This is a multicenter, non-randomized, phase II clinical trial to assess the efficacy and safety of olaparib in monotherapy in patients diagnosed of advanced triple negative BC with methylation of *BRCA1* and/or *2* promoters (assessed in DNA from metastatic lesions) and absence of *BRCA1* and 2 germline mutations. Patients must have received at least one previous regimen in the advance disease setting.

Figure 1 Study Design



Potential eligible patients will be screened to assess germinal (g) *BRCA* mutational status at Myriad laboratory (unless the *BRCA* mutational status is already known based on a Myriad previous report).

Blood samples for mutational *BRCA* screening could be sent either 1) during the previous line of treatment, once the eligibility criteria have been reviewed and the patient is considered a potential candidate for the study (at least the patient must have measurable and biopsiable disease) or 2) after end of the line of treatment prior to study enrolment (simultaneously to the shipment of the tumour samples for methylation analysis). A specific ICF must be signed for this screening assessment.

Somatic (s) *BRCA* promoter methylation will be assessed also centrally at an external reference central laboratory selected by GEICAM. Tumour samples must proceed from a metastatic lesion, it is strongly recommended to obtain it after the line treatment immediately previous to the study entry.

Patients with a positive methylation status on *BRCA1* and/or *BRCA2* and lacking of known deleterious or suspected deleterious mutations in both genes could be included in the study to receive olaparib tablet formulation at 600 mg daily dose (given in two oral administrations of 300 mg every 12 hours approximately). Blood and tumour samples collected from all registered patients could be used for the secondary and exploratory analysis of the study, including but not limited to the assessment of germline methylation status and gene expression levels of *BRCA1/2*.

Patients will continue to receive their treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Each assessment of tumour response will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy.

According to RECIST v.1.1 in case of patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time every effort should be made to document objective progression, even after discontinuation of treatment. The objective response status of such patients should be determined considering RECIST v.1.1 instructions. In case any efficacy assessment cannot be done, they will be considered not evaluable for response rate analysis and PFS will be censored at the date of the last tumour assessment.

3.1.1. Step 1 analysis of the optimal two stage Simon model

Following the two-stage Simon design, it will review that 4 of the first 12 evaluable patients show tumour response according to RECIST v.1.1, additional patients will be included to get a total of 34 patients.

3.2. Duration of the Study

It is estimated that the patient recruitment will be completed approximately in 24 months.

All patients included will receive study therapy until radiographic or symptomatic progression, unacceptable toxicity or withdraw of the informed consent, whatever occurs first, this is the active treatment phase. Patients discontinuing the study treatment will enter the follow-up phase.

For safety reasons all patients will have a visit 30 (+/-7) days after finishing treatment with the study drugs/medications. This post-treatment visit must be performed before starting with any new anticancer therapy; however, in case the beginning of this new therapy cannot be delayed as per the investigator's judgment, the safety visit may be performed in advance, but always before starting with the new anticancer therapy.

All patients will be followed till death or data cut-off date to evaluate the OS objective.

The start date of study is the date of the first site initiation visit. The data cut-off date will be the date of last patient´s death or withdraw of the informed consent or the date when there is sufficient data to achieve the primary and secondary objectives, whichever comes first. It is estimated that the final analysis could be performed approximately 30 months after the enrolment of the first patient because, considering a median OS of 12 months, it is estimated that more than 50% of death events will have occurred at that time and overall survival analysis could be performed.

The study will be considered complete following the data cut-off date and data-lock for the final analysis. Performing exploratory objectives will be independent of the date of the end of the study.

4. Study Population

4.1. Inclusion Criteria

Patients are eligible to be included in the study only if they **meet all** of the following criteria. Any asterisked* are also applicable as an inclusion criteria prior to perform the BRCA methylation testing via central testing; to perform the *BRCA* methylation test, investigator judgement of patient's potential eligibility to the study should be assessed as per Protocol Attachment 1. Study Schedule and by reviewing the below inclusion criteria):

1. *The patient has signed and dated the informed consent document and it has been obtained before conducting any procedure specifically for the study.
2. Female ≥ 18 years of age on day of signing informed consent.
3. Patient with histological confirmation of breast cancer with evidence of advanced disease not amenable to resection or radiation therapy with curative intent.
4. Documented **triple negative** disease by immunohistochemistry (IHC) and/or *in situ* hybridization based on local testing (preferably assessed on the most recent tumour biopsy available). TN is defined as **negative hormone receptor status** (< 1% of tumour cells with ER and PgR expression) and **HER2-negative status** (defined as IHC score 0/1+ or negative by *in situ* hybridization according to local criteria).
5. Patient must have received at least one previous regimen in the advance disease setting.
6. Absence of deleterious or suspected deleterious germline mutations in *BRCA1* and *BRCA2*. Germinal *BRCA* mutational status will be centrally assessed in Myriad laboratories to check eligibility unless the test has been previously performed at Myriad and absence of mutations has been determined.
7. Availability of a tumour tissue sample from the metastatic lesions (every effort should be done to obtain the sample after the previous therapeutic regimen for advanced disease) for central testing.
8. Documented methylation of *BRCA1* and/or *2* promoters based on central testing by analysis on the most recent tumour from metastatic lesions available.
9. At least one lesion measurable not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have short axis ≥ 15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) or clinical examination and which is suitable for accurate repeated measurements according to RECIST v.1.1.
10. Patients must have normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

- Haemoglobin ≥ 10.0 g/dL with no blood transfusions in the past 28 days
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
- Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase, SGOT) /Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase, SGPT)] ≤ 2.5 x institutional upper limit of normal unless liver metastases are present in which case, they must be ≤ 5 x ULN
- Patients must have creatinine clearance estimated using the Cockcroft-Gault equation of ≥ 51 mL/min:

  Estimated creatinine clearance = $\frac{\text{(140-age [years])} \times \text{weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72}$ (x F)[a]

  [a] where F=0.85 for females.

11. *Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see protocol attachment 2).
12. *Patient must have a life expectancy ≥ 16 weeks.
13. *Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day 1.

    Postmenopausal patient is defined as a woman fulfilling any one of the following criteria (based on the NCCN definition of menopause [National Comprehensive Cancer Network 2008]):

    - Prior bilateral oophorectomy.
    - Age > 60 years.
    - Age ≤ 60 years and with amenorrhea for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle stimulating hormone and estradiol in the postmenopausal range.
14. 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 as listed below. This should be started from the signing of the informed consent and continue throughout period of taking study treatment and for at least 1 month after last dose of study drug or they must totally/truly abstain from any form of sexual intercourse (see below).

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must continue for the total duration of the study treatment and for at least 1 month after one dose. Periodic abstinence (e.g., 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.
- Intrauterine Device (IUD) PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) plus male condom with spermicide. Cerazette is currently the only highly efficacious progesterone based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom.
- Etonogestrel implants (e.g. Implanon or Norplan) PLUS male condom.
- Norelgestromin/ethinyl estradiol (EE) transdermal system PLUS male condom
- Intrauterine system (IUS) device (e.g., levonorgestrel releasing IUS-Mirena®) PLUS male condom.
- Intravaginal device PLUS male condom (e.g. EE and etonogestrel).

14. *Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits, laboratory tests and examinations and other study procedures.

4.2. Exclusion Criteria

Patients will be excluded from the study if they **meet any** of the following criteria. Any asterisked* are also applicable as an exclusion criteria prior to perform the BRCA methylation testing via central testing; to perform the BRCA methylation test, investigator judgement of patient's potential eligibility to the study should be assessed as per Protocol Attachment 1. Study Schedule and by reviewing the below exclusion criteria):

1. Involvement in the planning and/or conduct of the study (applies to the sponsor and/or study site staff).
2. Previous enrolment in the present study.
3. Participation in another clinical study with an investigational product during the last 4 weeks.
4. *Any previous treatment with a PARP inhibitor, including olaparib.

5. *Patients with other malignancy within the last 5 years, except: adequately treated non-melanoma skin cancer (basal cell or squamous cell carcinoma), 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 inclusion. Patients with a history of localised breast cancer with a tumour histology different to TN, with no evidence of disease for ≥ 5 years since they completed their adjuvant treatment.
6. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons), within 3 weeks prior to study treatment (or a longer period depending on the defined characteristics of the agents used).
7. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome.
8. *Concomitant use of known strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting olaparib is 2 weeks. Please refer to section 5.5.2.1 about strong and moderate CYP3A inhibitors.
9. *Concomitant use of known strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil). The required washout period prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents. Please refer to section 5.5.2.2 about strong and moderate CYP3A inducers.
10. *Persistent toxicities (> NCI-CTCAE grade 2) caused by previous cancer therapy (except alopecia or other toxicities not considered a safety risk for the patient at investigator´s discretion).
11. *Patients with myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) or with features suggestive of MDS/AML.
12. *Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required. Patients with brain metastases may be eligible for the study only if more than 4 weeks from treatment completion for these metastases (including radiation and/or surgery), are clinically stable at the time of study entry. The patient can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days.

13. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.
14. *Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.
15. *Breast feeding women.
16. *Immunocompromised patients, e.g. patients who are known to be serologically positive for human immunodeficiency virus (HIV).
17. *Patients with known active hepatitis (i.e. Hepatitis B or C) due to risk of transmitting the infection through blood or other body fluids.
18. *Patients with a known hypersensitivity to olaparib or any of the excipients of the product.
19. *Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, severe hepatic impairment (according to Child-Pugh classification), an extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) or any psychiatric disorder that prohibits obtaining informed consent.
20. *Previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT).
21. *Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, for timing refer to inclusion criteria nº10).

Procedures for withdrawal of incorrectly enrolled subjects see Section 4.4.Discontinuations.

4.3. Restrictions during the Study

It is not recommended to consume grapefruit juice while on olaparib therapy.

Consider information about contraception in section 4.1. Inclusion Criteria.

Consider information about restricted concomitant medication in section 5.5. General Concomitant Medication and Supportive Care Guidelines.

4.4. Discontinuations

4.4.1. Discontinuation of Study Drugs/Medications

The criteria for enrolment must be followed explicitly. If a patient who does not meet enrolment criteria is inadvertently enrolled, that patient should be discontinued from the study drugs/medications, but can be allowed to continue in the study in order to provide the follow-up data needed for the analysis of the entire population. An exception may be granted if the patient, in the opinion of the Investigator, is having benefit from the study drugs/medications. In these rare cases, the investigator must obtain documented approval from GEICAM to allow the patient to continue to receive the study drugs/medications.

Patients can be discontinued from the study therapy in the following circumstances:

- Patient's own request. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Unacceptable toxicity as defined in the protocol.
- Any clinical adverse event (AE), laboratory abnormality or inter-current illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the patient.
- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML)
- Pregnancy:
  - ✓ Instruct to contact the investigator or study staff immediately if they suspect they might be pregnant.
  - ✓ The investigator must immediately notify GEICAM if a study patient becomes pregnant.
- Tumour progression as defined in the protocol.
- Severe non-compliance with the study protocol by the patient
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (e.g. infectious disease) illness.
- Physician's decision, including need of other anti-cancer therapy, not specified in the protocol.
- Termination of the study by GEICAM.

All permanent treatment discontinuation should be recorded by the Investigator in the eCRF when considered as confirmed.

It is important to discriminate between discontinuation of study treatment only and withdrawal from study (study treatment and follow up).

4.4.2. Discontinuation of Study Sites

Study Site participation may be discontinued if GEICAM, the investigator or the Independent Ethics Committee (IEC) of the study site judges it necessary for any reason.

4.4.3. Discontinuation of Study

The study may be discontinued by GEICAM if this is medically reasonable and consistent with applicable regulations of Good Clinical Practice (GCP). Stopping the study for medical reasons may be required if patients experienced adverse reactions under the treatment with the study drug/medication or if new information about the safety or effectiveness of the study drug/medication justifies it.

5. Treatment

5.1. Treatments Administered

Patients will receive the following treatment:

Olaparib as single agent at a continuous daily dose of 600 mg (tablet formulation), given in two oral administrations of 300 mg with a dosing interval of about 12 h with a window interval of 2 hours before and after the scheduled time.

Olaparib is for oral use. Olaparib tablets should be taken with one glass of water and swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

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 (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 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.

The treatment discontinuation criteria are indicated in Sections 3.2 and 4.4.1.

5.2. Materials and Supplies

5.2.1. Doses and treatment regimens

For this study, the term "study drug/medication" (Investigational Medicinal Product [IMP]) refers to olaparib.

The AstraZeneca Pharmaceutical Development R&D Supply Chain will supply olaparib to GEICAM as as round or oval green film-coated tablet containing 100 mg or 150 mg of olaparib.

Table 6. Product Descriptions

IMP	Dosage form and strength
Olaparib	100 mg tablet
Olaparib	150 mg tablet

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

GEICAM will provide the study sites with olaparib for the purpose of this study.

For all centres, olaparib tablets will be packed in high-density polyethylene (HDPE) bottles with child-resistant closures. Each dosing container will contain required sufficient medication for at least 28 days plus overage.

Olaparib will be dispensed to patients prior to initiate cycle 1 and every 28 days (+/- 7 days) thereafter until the patient completes the study, withdraws from the study or closure of the study.

For guidance on dose reductions for management of AEs refer to section 5.4. Special Treatment Considerations. Dose Adjustments of Olaparib.

For guidance on dose reductions when concomitant strong or moderate CYP3A inhibitors cannot be avoided see section 5.5.2. Restricted concomitant medications.

5.2.2. Labelling

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

Each bottle of olaparib will have an investigational product label permanently affixed to the outside stating that the material is for clinical trial/investigational use only and should be kept out of reach and sight of children. The label will include the dosing instructions and a space for the enrolment code (E-code) to be completed at the time of dispensing.

The label will include the following information:

- blank lines for quantity of tablets to be taken
- enrolment code (E-code)
- date of dispensing
- instructions stating that the olaparib tablets should be taken at approximately the same time each morning and evening

5.2.3. Storage

Storage conditions stated in the Study Reference Safety Document may be superseded by the label storage.

Olaparib should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements under appropriate storage conditions. Olaparib should be stored at at the study site at controlled room temperature in their original container. The label on the bottle specifies the appropriate storage.

Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of the investigational product. These include thermometers for the room storage. Any temperature excursions must be reported immediately to GEICAM and documented. Once a deviation is identified, the investigational product MUST be quarantined and not used until GEICAM provides documentation of permission to use the investigational product.

Returned medication should be stored separately from medication that needs to be dispensed.

5.2.4. Accountability

It is the responsibility of the investigator to ensure that a current record of olaparib disposition is maintained at each study site where the study drug is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines.

On a per-patient basis, records must be maintained documenting dates and quantities (ie, pill counts) of provided study treatment dispensed and returned at each study visit. GEICAM will provide forms to facilitate inventory control if the staff at the investigational site does not have an established system that meets these requirements.

During the course of the study, the monitor regularly will review the records of medication stocks and document preservation ensuring it is properly performed according to ICH-GCP.

After each monitoring visit, the study drug and containers returned by the patients and upon completion or termination of the study, all unused and/or partially used study drug will be preferably destroyed at the site per institutional policy, the site must obtain written authorization from the Sponsor before it is destroyed, and this destruction must be documented on the appropriate form. It is the investigator´s responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.3. Method of Assigning a Patient to a Treatment

Patients will be screened by one of the Investigators prior to entry on this study. An explanation of the study and discussion of the expected side effects and presentation of the informed consent document/s will take place. Eligible and consenting patients (entered) will be registered into the study.

To check eligibility, a blood sample must be sent to Myriad laboratory to assess the existence of germinal *BCRA* mutations (unless the *BRCA* mutational status is already known based on a Myriad previous report) and tumour samples must be sent to the central pathology laboratory, where it will be obtained DNA that will be sent to the central epigenetics laboratory for assessment of methylation status of *BRCA1* and *2*. . Patients with a positive methylation status of either *BRCA1* or 2 genes and lacking of *gBRCA* mutations in both genes could be enrolled in the study and receive the Study treatment, although blood and tumour samples collected from all registered patients could be used for the secondary and exploratory objectives of the study. Instructions for timing and procedures to be followed for sample shipment are indicated in section 6.3 and Protocol Attachment1 of the protocol.

No patients can receive protocol treatment until registration and enrolment has been performed. All eligibility criteria must be met at the time of enrolment. There will be no exceptions. Any question should be addressed with GEICAM prior to registration or enrolment. The eligibility checklist must be completed and signed by the Principal Investigator or Sub-Investigator prior to enrolment and it should be filed with the study documentation. Inclusion and exclusion criteria needed to be assessed prior to the shipment of samples for *BRCA* analysis are indicated in section 4. Study Population.

The study personnel at the site will register and enrol the patient through the eCRF and the system will send the unique number of the patient identification to the site.

All eligible patients registered in the study will be entered in a patient screening log maintained by each site and the GEICAM central office. Only after the confirmation of the enrollment by the system, the patient can receive the study treatments. All patients enrolled in the study will be registered in a Patient Enrollment and Identification Log and will be only maintained by the site.

Trial treatment must be administered within 7 days from enrolment.

5.4. Special Treatment Considerations. Dose Adjustments of Olaparib

All dose modifications should be based on the worst preceding toxicity.

Every effort should be made to administer study treatment at the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of olaparib may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dose adjustments may be required for olaparib.

In the event of significant treatment-related toxicity, olaparib dosing may be interrupted and/or reduced. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

All dose modifications/adjustments must be clearly documented in the patient's source notes and the appropriate section of the eCRF.

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the GEICAM study team must be informed. Olaparib 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.

Olaparib recommended dose modifications for treatment related toxicities requiring treatment interruption/reduction or persisting despite optimal medical treatment are described in the following sections.

5.4.1. Management of haematological toxicity

5.4.1.1. Management of Anaemia

Table 7. Management of anaemia

Haemoglobin	Action to be taken
Hb < 10 ***but*** **≥ 8 g/dl (NCI-CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) *or* interrupt dose for a maximum of 4 weeks. If repeat Hb**< 10** ***but*** **≥ 8 g/dl**, dose interrupt (for max of 4 weeks) until Hb ≥ 10 g/dl and upon recovery dose reduction to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step may be considered.
Hb < 8 g/dl (NCI-CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥ 10 g/dl. 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.

Common treatable causes of anaemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases management of anaemia may require blood transfusions. For cases where patients develop prolonged haematological toxicity (≥2 week interruption/delay in study treatment due to NCI-CTCAE grade 3 or worse anaemia and/or development of blood transfusion dependence), refer to Section 5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment.

5.4.1.2. Management of Neutropenia, Leukopenia and Thrombocytopenia

Table 8. Management of neutropenia, leukopenia and thrombocytopenia

Toxicity	Study treatment dose adjustment
NCI-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.
NCI-CTCAE Grade 3-4	Dose interruption until recovered to NCI-CTCAE grade 1 or better for a maximum of 4 weeks. If repeat grade 3-4 occurrence, dose reduce olaparib 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 Section 5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment.

5.4.1.3. 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 grade 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 GEICAM. Olaparib should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

5.4.2. Management of Non-Haematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer than this the study monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further

dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Olaparib can be dose reduced to 250 mg b.i.d. as a first step and to 200 mg b.i.d. as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the investigator considers to be related to administration of study treatment.

5.4.2.1. Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (e.g. dyspnoea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high resolution CT scan) should be performed, to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with GEICAM.

5.4.2.2. 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. These events are generally mild to moderate (NCI-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. Alternatively, olaparib tablets can be taken with a light meal/snack (e.g. 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone.

5.4.2.3. Management of 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 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 b.i.d.

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.

5.4.3. 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 GEICAM.

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 needle 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 9. 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

5.4.4. Medication Errors and Overdose

Medication errors may result in the administration or consumption of the wrong drug, by the wrong patient, at the wrong time or at the wrong dosage strength. If patient taking the lower dosing consciously/deliberately and not by mistake (e.g. if the patient is not

tolerating the full dose very well), then this isn't a medication error. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the eCRFs and on the SAE form when appropriate. In the event of medication dosing error GEICAM should be notified immediately. If an overdose or lower dose on olaparib occurs in the course of the study and it is associated with an AE (serious or not) are to be reported within 24 hours on a SAE form. Overdoses which are not associated with any AE can be reported within 30 days in a SAE form.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an eCRF page (refer to Management, Timing and Assessment of Adverse Events section for further details).

Please refer to section 11.1 for specific management of overdoses.

5.5. General Concomitant Medication and Supportive Care Guidelines

Patients must be instructed not to take any additional medication (over-the-counter or other products) during the study without prior consultation with the Investigator. 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 from 28 days prior to the start of study treatment and up to approximately 30 days following the last dose of investigational product and the reason for their administration must be recorded in the eCRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anaesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anaesthesia" on the concomitant treatment records; it is not necessary to list the specific anaesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

5.5.1. 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 live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.5.2. Restricted concomitant medications

5.5.2.1. Strong or Moderate CYP3A inhibitors

Known strong CYP3A inhibitors or moderate CYP3A inhibitors should not be taken with olaparib. While there is not an exhaustive list of CYP3A inhibitors the table below covers known CYP3A inhibitors.

Table 10. CYP3A inhibitors

CYP Enzymes	**Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in Clearance (CL)**	**Moderate inhibitors ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL**	**Weak inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL**
CYP3A	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, boosted protease inhibitors	Amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice imatinib, verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

If there is no suitable alternative concomitant medication then the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded in the CRF with the reason documented as concomitant CYP3A inhibitor use; the reductions should be made as follows:

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg b.i.d. for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.

- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg b.i.d for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.

- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

In case of doubt about the procedure for concomitant administration of CYP3A inhibitors, the investigator should contact with GEICAM study team in order to avoid protocol deviations.

5.5.2.2. Strong or Moderate CYP3A inducers

Strong and moderate CYP3A inducers of CYP3A should not be taken with olaparib. While there is not an exhaustive list, table 11 covers known CYP3A inducers.

Table 11. CYP3A inducers

CYP Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
CYP3A	Avasimibe, carbamazepine, phenytoin, rifampicin, St. John's wort, rifapentine, rifabutin, phenobarbital, nevirapine, enzalutamide.	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, echinacea, pioglitazone, prednisone, rufinamide

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer or inhibitor then they must be monitored carefully for any change in efficacy of olaparib.

5.5.3. P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (e. g. amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be observed.

5.5.4. Other Concomitant Medications

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP3A4, CYP1A2, 2B6, 2C9, 2C19 and P-gp.

The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

Caution should therefore be observed if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include:

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus and quetiapine
- CYP1A2 – duloxetine, melatonin

- CYP2B6 – bupropion, efavirenz
- CYP2C9 – warfarin
- CYP2C19 - lansoprazole, omeprazole, S-mephenytoin
- P-gp - simvastatin, pravastatin, digoxin, dabigatran, colchicine
- OATP1B1 - bosentan, glibenclamide, repaglinide, statins and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 - serum creatinine
- OAT3 -furosemide, methotrexate

Any medications, with the exceptions noted in Section 5.5., which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the eCRF.

Standard therapies for pre-existing medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrhoeals, antidepressants) may also be used at the Investigator's discretion. All medications should be recorded in the eCRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the eCRF.

Anticoagulant Therapy

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

Anti-emetics/Anti-diarrhoeals

If a patient develops nausea, vomiting and / or diarrhoea, then these symptoms should be reported as AEs (see section 8.2.7. Safety Analyses) and appropriate treatment of the event given.

Palliative Radiotherapy

Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the Investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before the patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

Administration of other Anti-cancer Agents

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

Subsequent therapies for cancer

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

5.6. Treatment Compliance

Patients will be required to return all bottles of olaparib as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on day 1 of every 28-day cycle (+/- 7 days) prior to dispensing drug supply for the next cycle. The number of remaining tablets of olaparib will be documented and recorded. Compliance will be assessed by the tablet count and the information should be recorded in the appropriate section of the eCRF.

The patient number should be recorded on the bottle label at time of assignment to a patient. Site personnel must ensure that patients clearly understand the instructions on how and when to take their study treatment. Patients will self-administer study treatment. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next visit. The remaining tablets will not be returned to the patient, but will be retained by the investigative site, the site must obtain authorization from the Sponsor before destroy it.

Dose adjustments must follow instructions provided in the dose adjustment guidelines section.

6. Efficacy and Safety Evaluations, Sample Collection and Testing (Standard Laboratory Testing) and Appropriateness of Assessments

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule, Protocol Attachment 1.

6.1. Efficacy Assessments

All assessments to be performed at baseline and during the study are specified in the Study Schedule, Protocol Attachment 1.

According to RECIST v.1.1 in case of patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time every effort should be made to document objective progression, even after discontinuation of treatment. The objective response status of such patients should be determined considering RECIST v.1.1 instructions, regarding situations where not all basal lesions can be evaluated. In case any efficacy assessment can be done they will be considered not evaluable for those efficacy endpoints applicable.

6.1.1. Primary Efficacy Assessments

The primary efficacy variable is Objective Response Rate (ORR).

Tumour response will be assessed using RECIST v.1.1. Tumour assessment will be performed at baseline; the same method of measurement used at baseline will be used for further assessments, which will be conducted every 8 weeks (+/- 1 week). Responses should be confirmed according to RECIST v.1.1 after at least 28 days.

The best response across treatment will be recorded. ORR is defined as the percentage of patients with a complete or partial response out of the total of patients in the considered study population (refer to section 8.2.1. Patient Populations).

6.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments are PFS, CBR, RD, and OS:

- ✓ Progression Free Survival (PFS): is defined as the time from study enrolment to the first documented progressive disease, using RECIST version 1.1., or death from any cause, whichever occurs first.
- ✓ Clinical Benefit Rate (CBR): is defined as complete response (CR), partial response (PR), or stable disease (SD) ≥ 24 weeks according to the RECIST version 1.1.
- ✓ Response Duration (RD): is defined as the time from the first documentation of objective tumour response (CR or PR) to the first documented progressive disease using RECIST version 1.1, or to death due to any cause, whichever occurs first.
- ✓ Overall Survival (OS): is defined as the time from the date of study enrolment to the date of death from any cause.

6.2. Safety Assessments

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting GEICAM of any event that seems unusual.

The Investigator is responsible for appropriate medical care of patients during the study.

The Investigator remains responsible for following, through an appropriate health-care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

During the course of the study, all patients entering the trial must be evaluated according to the schedule outlined in the flow charts and described below. The results of the evaluation will be recorded in the eCRF pages until the patients are not followed anymore.

6.2.1. Timing of Assessments

All assessments to be performed at baseline and during the study are specified in the Study Schedule, Protocol Attachment 1.

Physical examination will include vital signs assessments (**blood pressure, pulse and body temperature)** and **performance status** evaluation. Clinical signs and symptoms of disease recurrence should be further investigated as appropriate.

Resting 12-lead ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. 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.

The following **safety laboratory assessments** will be performed by the local laboratories, at the times specified in the Study Schedule:

- **Haematology:** Full haematology assessments for safety (haemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell haemoglobin concentration [MCHC], mean cell haemoglobin [MCH], white blood cells [WBC], absolute differential white cell count [neutrophils, lymphocytes, monocytes, eosinophils and basophils] and absolute neutrophil count or segmented neutrophil count and band forms) should be performed at each visit and when clinically

indicated. If absolute differentials are not available % differentials should be provided. Study visits for safety assessments will be scheduled on baseline visit and day 8 (+/- 3 days) of cycle 1 and in subsequent cycles every 28 days (+/- 7 days). This analysis should be performed also in the 30-day post-discontinuation follow-up evaluation performed 30 days (+/- 7 days) following the discontinuation of study treatment. In case the beginning of this new therapy cannot be delayed as per the investigator's judgment, the safety visit may be performed in advance, but always before starting with the new anticancer therapy.

If treatment is discontinued close to the theoretical date for the next cycle and it is not planned to perform in advance the post-treatment visit due to the initiation of a new anticancer therapy, a new haematology analysis should be performed at the moment of the study treatment discontinuation.

- **Coagulation testing:** Activated partial thromboplastin time (aPTT) and international normalised ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and aPTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.
- **Blood Chemistry:** sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, gamma glutamyltransferase (GGT), alkaline phosphatase (AP), aspartate transaminase (AST), alanine transaminase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin and lactic dehydrogenase (LDH) should be performed.

  In case a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x ULN please refer to Appendix 5 "Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law", for further instructions.
- Similar to haematology test, blood chemistry analysis should be performed on baseline visit, day 8 (+/- 3 days) of cycle 1 and in subsequent cycles every 28 days (+/- 7 days) and if clinically indicated. This analysis should be performed also in the 30-day post-discontinuation follow-up evaluation performed 30 days (+/- 7 days) following the discontinuation of study treatment. In case the beginning of this new therapy cannot be delayed as per the investigator's judgment, the safety visit may be performed in advance, but always before starting with the new anticancer therapy.

  If treatment is discontinued close to the theoretical date for the next cycle and it is not planned to perform in advance the post-treatment visit due to the initiation of a new anticancer therapy, a new haematology analysis should be performed at the moment of the study treatment discontinuation.

- **Urinary testing:** Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.
- **Serum or urine pregnancy test:** Two pregnancy tests on blood or urine samples must be performed for pre-menopausal women of childbearing potential, one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.
- **Bone marrow or blood cytogenetic analysis** may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment. 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. If findings are consistent with MDS/AML, study drug should be discontinued and a full description of findings should be submitted with an SAE report by the Investigator to GEICAM for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database.
- Additional analyses may be performed if clinically indicated. All AEs (and their relatedness to the study drugs/medications) occurring during the study will be repeated as clinically indicated and documented in the eCRF. AEs will be graded according to NCI-CTCAE version 4.0.

6.2.2. Definitions

The safety definitions are described in the table 12.

Table 12. Safety definitions

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

	investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs. Laboratory abnormalities should be reported as AE only in case they lead to an action on study treatment or if they are serious.
Adverse Reaction (AR)	All untoward and unintended responses to a medicinal product related to any dose administered. All expected ARs are listed in the Investigator's Brochure (IB) in case of not authorized investigational product or Summary of Product Characteristics [SmPC] in case of an authorized investigational product. If the nature or the severity of an adverse reaction is not consistent with the applicable product information, the AR is defined as unexpected. The basis for the decision is the current version of the corresponding reference document that has been submitted and approved by the competent authority and the ethics committees. **Accountability criteria** The sponsor will classify the adverse event, based in their causation relation with the investigational product, following the Karch and Lasagna algorithm (1977)[72], as: • Final: there is reasonable temporal sequence between the drug administration and the existence of the adverse event. This event matches with the adverse reaction described for the investigational product, improves with the omission and reappears after its re-administration and can't be explained by other causes. • Probable: there is reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event matches with the adverse reaction described for the drug, improves with the omission and can't be explained by other causes. • Possible: there is reasonable temporal sequence between the investigational product administration and the

	appearance of the adverse event. This event matches with the adverse reaction described for the drug but can be explained by other causes. • Conditional or improbable: there is reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event does not matches with the adverse reaction described for the drug and can be explained by other causes. • Not related: there is no reasonable temporal sequence between the investigational product administration and the appearance of the adverse event. This event does not matches with the adverse reaction described for the drug and can be explained by other causes. For expedited reporting purposes it is considered as related the categories: final, probable and possible from Karch and Lasagna algorithm (1977) and as not related the category conditional or improbable of that algorithm. The determination of the possible relation with the study treatment is responsibility of the Principal Investigator of the site or the person designated by him.
Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)	A serious adverse event is an AE occurring during any study phase (e.g., screening, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria: • Results in death • Is immediately life-threatening • Requires in-patient hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability or incapacity • Is a congenital abnormality or birth defect • Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the Investigator(s) and communicated to Pharmacovigilance Department of GEICAM.

	The following events will be considered as AEs of Special Interest (AESIs) and they have to be documented as a SAE and notified to the Pharmacovigilance Department of GEICAM immediately: Development of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis. Overdose and medication errors should be reported as indicated in section 5.4.4. and 11.1. Any temporary increase in the severity of a symptom or previous sickness that happens after the baseline of the study is considered also as an adverse event.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any serious adverse reaction whose nature, intensity or consequences do not correspond with the reference information for the investigational product (example, Investigator Brochure [IB] in case of not authorized investigational product or Summary of Product Characteristics [SmPC] in case of an authorized investigational product). The unexpected nature of an adverse reaction is based in the fact of not being observed previously and not in what could be advanced based on the pharmacological properties of the drug.

6.2.3. Management, Timing and Assessment of Adverse Events

AE Classification	Adverse events should be classified following version 4.0 of the NCI-CTCAE. A copy can be downloaded in the NCI web site: http://evs.nci.nih.gov/ftp1/CTCAE. The Investigators team must have access to the NCI-CTCAE version 4.0. The AE not included in the CTCAE will be classified as described on Protocol Attachment 3. The causal relationship between the investigational product and the AE will be assessed by the Investigator using the Karch and Lasagna (1977) algorithm.
Procedure to notify an AE to GEICAM	The site must notify to GEICAM, through eCRF, the following events: • All adverse events that occur after signed any of the study Informed Consent Forms.

	• Pre-existing conditions that get worse during the study. • The evaluation of the possible relationship of each adverse event to the study drugs/medications or protocol procedure. • The circumstances and data that causes the suspension of the treatment of a patient due to an adverse event. • The events leading to the clinical outcome of death from disease progression will be included in the efficacy analysis and are not recorded as adverse events, unless the Investigator believes they could have been caused by the study drugs/medications or if the cause is not clearly due to disease progression.
Recording of adverse events	The following variables will be collected 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 IMP (yes or no). • Action taken with regard to IMP. • Outcome. • Changes in NCI-CTCAE grade and the maximum CTC grade attained. 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 hospitalization. • Date of discharge. • Probable cause of death. • Date of death. • Autopsy performed. • Description of AE. • Causality assessment in relation to Study procedure(s). • Causality assessment in relation to other medication. It is important to distinguish between serious and severe AEs. Severity is a measure of intensity (minor/mild/severe) whereas seriousness is defined by the criteria in 6.2.2. Definitions. 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. **Adverse Events based on signs and symptoms** When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately. **Adverse Events based on examinations and tests** Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for dose modification or discontinuation of treatment with olaparib. 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 (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s). Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE. **N.B.** Cases where a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x ULN may need to be reported as SAEs, please, refer to Appendix 5 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions. **Disease progression** Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the

	investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study. **New cancers** The development of a new primary cancer (including skin cancer) should be regarded as an AE of special interest and will generally meet at least one of the serious criteria (see Section 6.2.4 for reporting instructions). New primary malignancies 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 breast cancer, 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: please, refer to Section 6.2.4.**
Timing and assessment of AE (see Protocol Attachment 4)	The site staff will report on the eCRF the information of the AE in the following periods: • **Baseline (after ICD and before study drug/medications):** study site personnel will note the occurrence and nature of each patient´s medical condition(s) and pre-existing conditions in the appropriate section of the eCRF. If a patient never receives study drug/medications but experiences an adverse event after the ICD is signed, ONLY events the Investigator believes may have been caused by a protocol procedure will be reported to GEICAM via eCRF.

	• **During treatment with the study drug:** during the study, site personnel will record any change in the condition(s) and the occurrence and nature of any adverse events. A CTCAE grade rating will be assigned before each cycle for any adverse event experienced during the previous cycle. • **30-day post- treatment follow-up period:** each patient will have a 30-day post-discontinuation follow-up evaluation approximately 30 days following the discontinuation of study treatment. Patients should be closely followed for study treatment adverse events in order to detect delayed toxicity. If drug-related toxicity is present beyond 30 days post-discontinuation, patients must be followed until the toxicity resolves or improved to baseline, the relationship is reassessed as unrelated, the Investigator confirms that no further improvement can be expected, another therapy is initiated, or death. • **Long-Term Follow-up Period (after the 30-day post-discontinuation):** For Pharmacovigilance purposes and characterization, any case of MDS/AML or new primary malignancy occurring after the 30 day follow up period should be reported to GEICAM whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality. Investigators will be asked during the regular follow up for overall survival if the patient has developed MDS/AML or a new primary malignancy and prompted to report any such cases. 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 or protocol procedure, the investigator should notify GEICAM. If patients who are gaining clinical benefit are allowed to continue study treatment post data cut off and/or post study completion then all SAEs must continue to be collected and reported to Patient Safety within the usual timeframe. Other new and ongoing SAEs thought to be related to study drug/medications or protocol procedures should be

	documented on the eCRF and immediately reported to GEICAM via the designated transmission method, even if the study has been closed. 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).

6.2.4. Management, Timing and Assessment of SAEs

Timing of SAEs (see Protocol Attachment 4)	All the SAEs (either spontaneously or during the trial visits) will be collected since the patient signs the Informed Consent Document (ICD). All the SAEs must be documented in the medical record of the patient and in the eCRF. All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.
Pregnancies	If a patient becomes pregnant while enrolled on a GEICAM study, it must be reported in the Pregnancy Form and sent to the GEICAM pharmacovigilance department within 24 hours of becoming aware of it.
SAEs which do not need to be notified to the Pharmacovigilance Department of GEICAM	The following events are not considered SAEs: • A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event). • Elective surgery planned before signing consent. • Hospitalization which is due solely to a planned study visit and without prolongation. • Routine health assessment requiring admission for baseline/trending of health status (e.g. routine colonoscopy). • Medical/surgical admission for purpose other than

	remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative). • Progression of the malignancy during study (including signs and symptoms of progression), unless the outcome is fatal and death occurred before end of treatment. Thereafter death due to disease progression has not to be reported as SAE. • Hospitalization due to signs and symptoms of disease progression. • An overnight stay in the hospital that is only due to transportation, organization or accommodation problems and without medical background. They will be reported in the eCRF and in the patient record. The rest of SAEs must be notified as described as follows.
Procedure to notify a SAE to the Pharmacovigilance Department of GEICAM	The SAEs must be notified to the Pharmacovigilance Department of GEICAM. A member of the Investigator team must complete and sign the GEICAM SAE notification form which will be sent by fax/mail, immediately and always during the 24 hours following knowledge of the SAE: **Pharmacovigilance Department of GEICAM** Fax: +34 917 371 619 farmacovigilancia@geicam.org GEICAM will review the received form and, if necessary, will ask more information to the Investigator. When additional information is obtained about the SAEs, or this is solved or is improbable it will change, a follow-up report must be also completed and sent by fax/mail, immediately and always during the following the 24 hours to the Pharmacovigilance Department of GEICAM. If GEICAM suspects that the SAE could be a SUSAR, the Investigator should give the follow up information requested.

	All SAEs/AESIs from the time the patient have the first dose of the study drug/medications through 30 days following the last administration of study drug/medications must be reported according to the procedure described below. All SAE regardless of timing must be reported, if considered related to study drug/medication. Likewise, progression of a patient's underlying condition leading to one of the above should also not be reported as a SAE, but documented as primary study endpoint. GEICAM will report all SAEs and AESIs immediately to the Chief Investigator. All SAEs and AESIs will be followed-up by the Investigator until satisfactory resolution. Annually all SARs will be reported as the DSUR to the competent authorities and the leading ethics committee, including all SUSARs. Withdrawal from further treatment shall be at the discretion of the Investigator.
Adverse Events of Special Interest (AESIs)	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 GEICAM. An AESI may be serious or non-serious. Adverse Events of Special Interest for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis. **ANY event of MDS/AML, new primary malignancy, or pneumonitis** should be reported to GEICAM immediately (within 24 hours following knowledge of the event), as per the SAE notification instructions whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality. A questionnaire will be sent to any investigator reporting these AESIs, 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 characterize the event and gain a better understanding regarding the relationship between the event and study treatment. For information about overdose and medication errors please refers to sections 5.4.4. and 11.1. Overdose.

AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN	**Cases where a subject shows an AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN** could need to be reported as SAEs, please, refer to Attachment 5 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.
Death on Study	**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: • Where death clearly is the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE unless they occurred before end of treatment. • 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**. 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 GEICAM (within the usual timeframes). • Deaths after the end of study which are considered to be related to study treatment have to be reported as SAEs. To the extent feasible sufficient information including relevant laboratory values, ECG, scan, biopsy or autopsy results must be provided by the Investigator in the SAE narrative (even if Investigator determines the SAE is not related) so as to permit an independent causality assessment by a Competent Authority.

6.2.5. Management, Timing and Assessment of SUSARs

Expedited Notification of SUSAR to the Competent Authorities	The Pharmacovigilance Department of GEICAM is responsible to notify to each of the competent authorities of the participating countries, all the SUSARs collected in the study, following the procedures shown in the current legislation.
Timing of notification	The deadline for reporting a SUSAR shall be 15 calendar days from when GEICAM becomes aware of it. When suspected SUSAR caused the death of the patient or endangered her life, GEICAM will send the information within 7 calendar days from the date on which it becomes aware. This information must be completed, if possible, in the next 8 days. This information must also be sent to AstraZeneca at the same time as it is sent to the Regulatory Authorities.
Expedited reporting of other relevant safety information	GEICAM will also notify, expeditiously, all the information that could modify the balance benefit/risk of the investigational product, or determine changes in its administration pattern or in the study performance, such as: • A qualitative change or an increase in the percentage of occurrence of the SAR expected, which are considered clinically significant. • The SUSAR occurring after completion of the study and are reported by the Investigator to the sponsor. • New events related to the conduct of a trial or the development of an IMP likely to affect the safety of patients, such as: ✓ SAE that could be related with the study procedure and could modify the conduct of the trial. ✓ A significant risk to patients such as lack of efficacy in a drug used to treat a life-threatening illness. ✓ A major safety finding from a newly completed animal study (such as carcinogenicity). ✓ A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country and if this information is known by GEICAM. ✓ Any recommendation of the IDMC that is relevant to the safety of patients (if applicable). This relevant information shall be notified as soon as possible

	and no later than 15 days after GEICAM becomes aware of it. Additional information will also be notified as quickly as possible.
Development Safety Update Report (DSUR)	The DSUR that includes the SAEs and SUSARs collected during the study will be sent by GEICAM to the Competent Authorities and EC/IRB at the time established by the current legislation.
Notification to Investigators	GEICAM will communicate to the Investigators any safety information that may affect the safety of trial patients, as soon as possible. Information on SUSAR occurred during the study will be sent quarterly, in aggregate, in a list along with a brief analysis of the data provided. They will be informed also, throughout the entire study, of any safety aspect that impacts the performance on the clinical trial or in the product development, including the interruption or modification in the development program of the protocol safety-related.

6.3. Biological sampling procedures

6.3.1. Biological Samples

Detailed instructions for the collection, handling and shipment of biological samples are outlined in the Sample Management Manual (SMM). The following table summarizes all samples required during study conduction.

Table 13. Biological Samples

Sample type	Visits	Requirements
Whole blood sample for *gBRCA* mutational testing.	**Blood sample could be sent either**: **1) During the line of treatment previous to study entry**, if the patient is considered a potential candidate for the study (at least the patient must have measurable and biopsiable disease). or **2) During screening, after ending the previous line of treatment**, (simultaneously to the shipment of the tumour samples for	**Mandatory for eligibility of all registered patients**, (unless *BRCA* mutational status is already known based on a Myriad previous report).

	methylation analysis). A specific ICF must be signed for this assessment.	
Metastatic tumour sample (FFPE) for prospective sBRCA methylation testing (strongly recommended to be obtained after previous therapy regimen) Remaining tissue to be used for secondary and exploratory objectives.	- **Screening**	**Mandatory for eligibility**
Whole blood for *BRCA* retrospective methylation and expression analysis and/or perform other biomarker analysis	- **Screening** In case it is not obtained at screening it should be obtained prior to start the study treatment (enrolled patients) or the next therapy (screening failure patients).	Required for all registered patients
	- **At the end of treatment** (prior to next therapy regimen). If a patient ends treatment due to other cause different to disease progression, one additional sample should be collected once progression is documented, if feasible.	Required for all enrolled patients
Plasma samples for biomarker analysis	- **Screening:** In case it is not obtained at screening it should be obtained prior to start study treatment (enrolled patients) or the next therapy (screening failure patients).	Required for all registered patients
	- **Between 4 to 6 weeks of treatment**	Required for all enrolled patients
	- **At the end of treatment** (prior to next therapy regimen). If a patient ends treatment due to other cause different to disease progression, one additional sample should be collected once progression is documented, if feasible.	

Archival primary tumour sample (if available)	- To be collected during the study	Required for all registered patients, if available
Biopsy from **metastatic tumour sample at disease progression (if available)**	- **At disease progression** If the patient ends the study due to disease progression**,** it must be collected prior to next therapy regimen. If the patient ends treatment due to other cause different to disease progression, collect this sample once progression is documented.	Required for all enrolled patients, if available

The samples and data from this research will be coded and not identified with any personal details. Each sample will be identified with the study and patient number. In this way biomarker data may be correlated with clinical data, samples destroyed or returned in the event of withdrawal of consent and regulatory audit enabled. Access to the link between the biomarker sample and the individual patient are restricted to the Investigator and his collaborators, IEC, health authorities, monitors and auditors of the sponsor or its authorized agents, who are bound to secrecy inherent to their profession, when they are required to check the data and study procedures to ensure that the study is being done correctly and the data is accurate, but always maintaining the confidentiality of the same in accordance with current legislation.

6.3.2. BRCA1 and BRCA2 Promoter Methylation Testing in Somatic DNA

At least one paraffin sample from metastatic lesions is mandatory to perform methylation test and determine patient eligibility. Every effort should be done to obtain the sample after last treatment for metastatic disease, prior to the study entry. Surgery blocks or core biopsies would be acceptable, minimal amount of tumour tissue will be specified in the SMM.

Tumour samples for methylation screening analysis must be sent to the epigenetic central laboratory following shipment instructions in the SMM. Results from both analyses will be provided to Investigator within 8 working days after the day the samples are received in the central laboratory, unless extra-time is needed for justified reasons.

The sBRCA methylation status result from the central laboratory assessment will be provided to the Investigator in order to determine subject eligibility. Investigator must explain to the patient that this assessment has unknown clinical significance in this moment and that the results of this trial will test the olaparib efficacy in patients with methylated sBRCA promoter, helping to elucidate if a relation between the methylation status and the response to olaparib may exist. If so, subsequent studies should be needed to confirm it.

DNA from paraffin-embedded tumour samples will be obtained in a central pathology laboratory and sent to the central epigenetics laboratory for methylation assessment. There, DNA will be treated with sodium bisulphite which will induce the deamination of cytosine

to uracil while 5-metilcytosine will remain as cytosine. *BRCA1* and *2* CpG island methylation status will be established using pyrosequencing, a semi-quantitative method that will give a methylation value of each of the CpG dinucleotides included in the sequence to be analyse. Samples will be processed per triplicate, computing for each promoter CpG island (*BRCA1 & BRCA2*), average methylation values of CpG sites, considering as unmethylated whenever the value is lower than 25% ($\beta \leq 0.25$), while methylated status will be consider when methylation value is higher than 25% ($\beta > 0.25$). If a modification of the cut-off value is deemed necessary it will be established in laboratory manual.

Analysis will be performed using validated methods with defined acceptance criteria including the circumstances that require repeating analysis; positive and negative controls will be included in each analysis.

6.3.3. Germline BRCA1 and BRCA2 Mutational Testing

All patients must lack of deleterious or suspected deleterious germline BRCA mutation to be eligible; this will be assessed via central testing by Myriad unless test have been done previously at Myriad.

Central *BRCA* assessment will require the shipment of one blood sample (9-10 ml) collected in EDTA tubes.

Blood samples for mutational *BRCA* screening analysis must be sent to the central laboratory following shipment instructions in the SMM, once signed the specific ICF for this mutational analysis. Signature of ICF and shipment of blood samples could be performed either simultaneously to the shipment of the tumour samples for methylation analysis or before, in previous lines of treatment, once inclusion/exclusion criteria have been reviewed and the patient is considered a potential candidate to the study (at least the patient must have measurable disease and biopsiable disease).

Results of *BRCA* mutation analysis will be provided to investigator within 10 working days after the day the samples are received in the central laboratory, unless extra-time is needed for justified reasons (e.g. in case of finding a variant of uncertain significance).

The analysis will be performed in Myriad Genetics laboratories Inc. at Salt Lake City (Utah, USA), using the *BRACAnalysis CE test*, which counts with the EU certificate about compliance of the directive 98/79/EC on in vitro diagnostic medical devices.

The gBRCA mutational status result from the Myriad assessment will be provided to the Investigator and will be collected as part of the patient's demography and medical history details.

6.3.4. Other Biomarker Assessments

The following samples will be collected to achieve secondary objectives and exploratory work.

Blood specimens: Blood samples will be collected prior and after treatment to assess germinal methylation status and mRNA levels of *BRCA 1* and *2*. Methylation data will be used to assess correlation of germinal methylation status with outcome data and evaluate correlation between germinal and somatic methylation status. *BRCA* expression results will be correlated with the methylation status and outcome data. Changes of *BRCA* methylation and expression levels during the study and after progression will be explored.

Blood samples will be also retained for exploratory biomarker analyses related to drug response or adverse drug reactions. Genomic, epigenetic, metabolomic and proteomic variation may help to explain some of the variability in response seen among different individuals. Comparing the DNA, RNA, protein, and metabolite patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes thought to be related to the mechanism of drug action may be examined. As indicated in table 13 blood samples prior to treatment will be collected for all registered patients, after treatment only from enrolled patients.

Plasma Samples: blood samples collected at time-points showed in table 12 from all enrolled patients will be processed to obtain plasma in study sites. Plasma samples will be collected for exploratory analyses of circulating free DNA or RNA or other biomarkers and their relationship to resistance or sensitivity to treatment with olaparib. Plasma samples may also be analyzed to explore the pharmacodynamic (PD) treatment effects on the expression of specific biomarkers.

Tumour Tissue: FFPE samples from primary and metastatic tumour will be collected as indicated in Table 13 in order to address correlation between primary and metastatic lesions.

Retrospective, exploratory tumour tissue biomarkers, including DNA, RNA and protein analytes, could be analysed to investigate possible associations with resistance/sensitivity to treatment with olaparib. Examples of such biomarkers may include but not limited to somatic *BRCA1*/2 mutational status or other genes related to cancer susceptibility and though to be related to the drug mechanism of action. These samples will be instrumental to explore biomarkers of response and biomarkers of primary resistance to olaparib.

The relationship between centrally assessed biomarkers and resistance/sensitivity to treatment with olaparib will be reported in an exploratory fashion.

Blood and tumour samples for secondary and exploratory objectives will be sent to the central pathology laboratory where they will be kept until analysis is performed in analysis laboratories appointed by GEICAM.

7. Data Quality Assurance

To ensure accurate, complete and reliable data, GEICAM will do the following:

- Provide instructional material to the study sites, as appropriate
- Sponsor a start-up training session to instruct the Investigators and study coordinators. This session will give instructions on the protocol, the completion of the eCRFs, and study procedures
- Make periodic visits to the study site to review study progress, Investigator and patient compliance with the clinical trial protocol requirements and any emergent problems.
- Be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- Review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- Conduct a quality review of the database
- Verify the quality of the data

To ensure the safety of participants in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the Investigator will provide GEICAM, applicable regulatory agencies, and applicable ethical review boards with direct access to original source documents.

7.1. Data Management and Registries File

Data for this study will be recorded via an electronic data capture system using eCRFs. Data will be transcribed by the site from the paper source documents onto the eCRF. In no case the eCRF is to be considered as source data for this trial. The eCRFs must be completed in an electronic Data Base. That electronic Data Base carries out with the regulatory authorities requirements. It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by GEICAM to record (according to GEICAM instructions) all observations and other data pertinent to the clinical investigation. All eCRFs should be completed in their entirety in a neat, to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to GEICAM as soon as they are entered in the eCRF.

The computerized handling of the data by GEICAM when available in the eCRF may generate additional requests to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

8.1.1. Sample Size Determination

We have set the null hypothesis (H0) that ORR will be 30% (ORR achieved by TN patients treated with gemcitabine plus carboplatin[1]) versus the alternative hypothesis (H1) that ORR will be 54% (ORR showed by TN *BRCA* mutated patients treated with olaparib[2]). Using an optimal two-stage Simon model and considering an alpha error of 0.05 and a statistical power of 80%, it will be required to include 31 evaluable patients. Twelve evaluable patients will be enrolled in the first stage, and if at least 4 patients of them have response, additional patients will be recruited to get a total of 31 evaluable patients. Assuming a 10% dropout rate, the total number of patients to be enrolled is 34. Considering, these data the number of responders needed at the end of stage 2 to reject the null hypothesis is at least 14 responders.

8.2. Statistical and Analytical Plans

8.2.1. General Considerations

Statistical analysis of this study will be the responsibility of GEICAM. The interpretation of study results will be the responsibility of the Chief Investigator of the study.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by GEICAM. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

All analysis will be performed using the SAS Enterprise Guide 5.1 version.

8.2.1. Patient Populations

Intent to treat population (ITT): The ITT population will include all patients who are enrolled in the study.

Efficacy population: a subset of the ITT population that have received at least one dose of study medication and has performed at least one tumour response assessment according to RECIST v.1.1 (unless a progression, death or unacceptable toxicity is seen before the first tumour response assessment) and without major protocol deviations according to the protocol deviation manual.

The **efficacy** population will be the primary population for the efficacy analysis.

It will be performed a sensitivity analysis using the ITT population.

Safety population: will include all patients enrolled in the study who received at least one dose of treatment. This population is for the safety analysis.

Population for Biomarker Analysis: a subset of enrolled patients with evaluable blood and/or tumour samples required for achievement of the secondary and exploratory objectives of the study.

8.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include:

- Summary of patients entered and by site.
- Total number of patients entered.
- Total number of patients enrolled.
- Summary of reasons for patients entered, but not enrolled.
- Total number of patients treated.
- Summary of reasons for patients enrolled, but not treated.

A detailed summary of reasons for patient discontinuation from study treatment will be provided.

A summary of all identified important protocol violations will be provided.

8.2.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics.
- Baseline disease characteristics.
- Pre-existing conditions/secondary conditions.
- Prior therapy.

Other patient characteristics will be summarized as deemed appropriate.

Standard descriptive statistics, such as the mean, median, range and proportion, will be used to summarize the patient sample and to estimate parameters of interest. Ninety-five percent confidence intervals will be provided for estimates of interest where possible.

8.2.4. Concomitant Therapy

A summary of concomitant therapies will be generated in the safety population.

8.2.5. Treatment Compliance

Treatment information will be collected at each dose administration. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual dose administered per week} \times 100}{\text{Dose expected to be administered per week}}$$

No minimal level of compliance will be defined for patient inclusion in final efficacy analysis. In the step 1 analysis it will be necessary that the twelve included patients have received at least 80% of the planned dosis. Exploratory analysis of the impact of compliance on selected efficacy endpoints may be performed if deemed necessary.

8.2.6. Efficacy Analyses

All efficacy definitions are described in section 6.1.

All efficacy analysis will be based on the Efficacy population. Additional efficacy analyses will be performed on the ITT population.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumour burden (ORR, CBR, RD, PFS, etc.) will be derived using the local radiologist's/investigator's assessment.

8.2.6.1. Analyses of Primary Endpoint

The primary endpoint is ORR

Objective Response Rate (ORR): A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the ORR analysis. ORR will be estimated by dividing the number of patients with objective response (CR or PR) by the Efficacy population ("response rate").

$$\text{Objective Response Rate} = \frac{\text{Number of CRs + PRs}}{\text{Efficacy population}}$$

The ORR will be reported, including a 95% confidence interval.

These analyses will be conducted at a two-sided 0.05 level of significance.

The number of responders needed at the end of stage 2 to reject the null hypothesis is at least 14 responders.

Additional sensitivity analyses will be outlined in the SAP. For the analysis in the ITT population, patients with inadequate data for tumour assessment (e.g., no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

In addition, the best objective response for each patient will be summarized.

8.2.6.2. Analysis of Secondary Endpoints

The secondary efficacy endpoints are:

Clinical Benefit Rate (CBR): A patient will be considered to have CB if the patient has a sustained complete response (CR) or partial response (PR), or stable disease (SD) ≥ 24

weeks according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as not achieving CB in the CBR analysis.

CBR will be estimated by dividing the number of patients with CR, PR, or SD ≥ 24 weeks by the efficacy population by treatment arm.

$$\text{Clinical Benefit Rate} = \frac{\text{Number of CRs + PRs + SD} \geq 24 \text{ weeks}}{\text{Efficacy population}}$$

The CBR will be reported, including a 95% confidence interval.

For the CBR analysis in the ITT population, patients with inadequate data for tumour assessment (e.g., no baseline assessment or no follow-up assessments) will be considered as not achieving CB in the CBR analysis.

Response Duration (RD): RD data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who have not died due to any cause while on study. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy.

RD will only be calculated for the subgroup of patients with an objective response.

Progression-Free survival (PFS): PFS data will be censored on the date of the last tumour assessment on study for patients who do not have objective tumour progression and who have not died due to any cause while on study. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumour assessment prior to the start of the new therapy.

The analyses of PFS will be performed in the ITT and Efficacy populations. PFS time will be summarized for the ITT population using the Life tables and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles of the event free time will be reported.

Overall Survival (OS): OS data will be censored on the last date the patient is known to be alive.

OS will be analysed in the ITT and Efficacy population. The median event times and 95% CIs will be estimated.

All of the above secondary analyses will be conducted at a two-sided 0.05 level of significance.

The secondary time-to-event endpoints (RD, PFS, OS) will be summarised using a Kaplan-Meier analysis and associated curves.

Additional sensitivity analyses will be outlined in the SAP.

8.2.7. Safety Analyses

The toxicity and tolerability of study drugs/medications will be evaluated in the safety population. Safety analyses will include summaries of the incidence of adverse events by maximum NCI-CTCAE grade (v4.0; NCI 2010) that occur during the study treatment period or within 30 days of the last dose of study treatment, regardless of causality and according to the relationship to study drug/medication as assessed by the Investigator. Additionally, the following safety-related outcomes will be summarized:

- Study treatment discontinuations due to adverse events.
- Deaths.
- SAEs and AESIs
- Hospitalizations and transfusions.
- Use of key concomitant medications or growth factors.

Analyses for data with discrete dates, for example, deaths, transfusions, and concomitant medications, will be done through 30 days after each patient's last dose of study treatment. Adverse events will also be analysed in this timeframe; that is, if an event starts within 30 days of discontinuation from study treatment, but after 30 days after the last dose of study treatment, it will not be included.

Adverse events data and serious adverse events will be presented in frequency tables by grade. Haematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. The safety analysis will be performed in the safety population.

8.2.7.1. Other significant adverse events (OAE)

During the evaluation of the AE data, GEICAM qualified experts will review the list of AEs that were neither reported as SAEs nor AESIs. Based on the expert's judgment, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such.

A similar review of laboratory, vital signs or 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.

There are currently no identified OAEs for olaparib

8.2.8. BRCA1/2 Methylation and expression analysis

To explore changes in the methylation status of *BRCA1/2* promoter in germline DNA prior and after treatment discontinuation.

The methylation status of the *BRCA1* and *2* promoters will be measured in germline DNA from blood cells at the beginning of the study and after disease progression or at the end of

study treatment for other cause, and in paired primary and metastatic lesions. Methylation status will be provided as a continuous (the methylation value will be obtained from the average of the CpG dinucleotides included in the sequence analysed) and also as a binomial variable (status methylated or not methylated).

If methylation status is a continuous variable, to compare the value of methylation between prior and after treatment, the difference of these values will be used and will be used statistical t (student-Fisher) or Wilcoxon test depending if it must be used a parametric or non-parametric test.

If methylation status is a binomial variable, to compare the value of methylation between prior and after treatment it will be used the McNemar test or exact binomial test.

To correlate germline *BRCA1/2* methylation data with efficacy parameters:

To evaluate the effect of methylation status with time to event variables (e.g. PFS, OS) it will be used a univariate Cox Regresion model.

To evaluate the effect of methylation status with efficacy rate parameters it will be used chi-square test if both of them are quantitative, and will be used an ANOVA analysis if one variable is quantitative and the other one is qualitative.

To correlate *BRCA1*/2 methylation between germline and somatic DNA:

To compare the continuous values of germline and somatic DNA methylation, the difference of these values will be used and it will be used statistical t (student-Fisher) or Wilcoxon test depending if it must be used a parametric or non-parametric test.

To correlate *BRCA1*/2 methylation between primary tumour and metastatic lesions:

If *BRCA1*/2 in metastatic lesions is a continuous variable, to compare the value of *BRCA1*/2 between primary tumour and metastatic lesions, the difference of these values will be used and it will be used statistical t (student-Fisher) or Wilcoxon test depending if it must be used a parametric or non-parametric test.

To correlate *BRCA1*/2 expression with efficacy parameters:

mRNA levels of *BRCA1* and 2 will be assessed in blood and available tumour samples. Expression data will be given as a continuous or as a binomial variable.

To evaluate the effect of *BRCA1*/2 expression with time to event variables (PFS, OS) it will be used a univariate Cox Regresion model.

To evaluate the effect of *BRCA1*/2 expression with efficacy rate parameters it will be used chi-square test if both of them are quantitative, and will be used an ANOVA analysis if one variable is quantitative and the other one are qualitative.

To correlate *BRCA1*/2 expression with *BRCA1*/2 promoter methylation status:

We will compare *BRCA1/2* expression and *BRCA1/2* promoter methylation status when they are binary data using chi-square test.

If methylation status and expression data are given as continuous variables, they will be compared using statistical t (student-Fisher) or Wilcoxon test depending if it must be used a parametric or non-parametric test.

If appropriate, additional analysis on all these biomarkers may be performed. More detail of all the Analysis of Secondary Endpoints will be described in the SAP.

8.2.9. Other Analysis

8.2.9.1. Other Biomarker Analysis

For baseline continuous endpoint data, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided.

For baseline categorical data, the number and percentage of patients in each category will be provided.

Appropriate statistical methods will be used to investigate any possible relationship of biomarker levels with olaparib anti-tumour efficacy. If appropriate, additional exploratory analysis on biomarkers may be performed.

8.2.9.2. Subgroup Analyses

Exploratory subgroup analysis may be performed if deemed appropriate.

8.2.10. Interim Analysis

There is no planned any interim analysis.

The optimal two stage Simon Model is carried out in two steps. The purposes of the step 1 analysis is to allow early stopping of the study for futility.

Following the two-stage Simon design, it will be reviewed whether 4 of the first 12 evaluable patients show tumour response according to RECIST v.1.1, and if this occurs, additional patients will be included to get a total of 34 patients.. If 3 or less than 3 patients of the first 12 evaluable patients show an OR, recruitment will be stopped.

8.2.11. Criteria for End of Study

This study will be considered complete following the data cut-off date and datalock for the final analysis. The data cut-off date for the final analysis will occur after all enrolled patients have died or withdraw of the informed consent or there is sufficient data to achieve the primary and secondary objectives, whatever occurs first. It is estimated that the final analysis could be performed approximately 30 months after the enrolment of the first patient because, considering a median OS of 12 months, it is estimated that more than 50% of death events will have occurred at that time and overall survival analysis could be performed. If further data are collected that are not included as part of the final locked

database, the post-lock data will eventually be combined with the locked database and stored in a data library separate from the locked database.

Performing exploratory objectives will be independent of the date of the end of the study.

9. Informed Consent, Confidentiality, Responsibility Insurance and Regulatory Considerations

9.1. Informed Consent

The Investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing any new information that may be relevant to the patient's willingness to continue his or her participation in the trial in a timely manner.

The informed consent documents will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The Investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug/medication.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

9.2. Respect of Confidentiality

The Investigator will be responsible for preserving the suitable information about each patient (for example, name, address, telephone number, social security number and study identification) so that the competent authorities can have access to said information if necessary. These records must be confidentially preserved for the time indicated by the legislation.

The Investigators and GEICAM will maintain the confidentiality of all patients participating in the study, according to Good Clinical Practice (GCP) and local legislation.

The patient data and biological samples collected for the study will be identified through a code which will not contain any personal identification and only the study doctor/collaborators will be able to link this data with the patient medical history. Access to the link between the code and the individual patient will be restricted to IEC, health authorities, monitors and auditors of the sponsor or its authorized agents, who are bound to secrecy inherent to their profession, when they are required to check the data and study procedures to ensure that the study is being done correctly and the data is accurate, but always maintaining the confidentiality of the same in accordance with current legislation.

The patient identity will not be revealed to anyone else except in cases of medical emergency or if legally required

This clinical trial will be held in accordance and in compliance with local current legislation. Any treatment of personal data that is held within the clinical trial, for Sponsor, Principal Investigator, center and/or any other participant in the clinical trial, especially as far as informed consent, shall conform to the provisions of Organic Law 15/1999, of December 13, Protection of Personal Data and Royal Decree 1720/2007 of 21 December, approving the Regulations implementing the approved law 15/1999, , Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 and any other rules in the matter.

9.3. Responsibility Insurance

GEICAM has signed an insurance policy to cover the responsibilities of the investigator and those of other parties participating in the study in accordance with the current Spanish legislation (RD 1090/2015) which regulates clinical trials with medicines in Spain.

9.4. Regulatory Considerations

This study will be conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki and with good clinical practices and the applicable laws and regulations. The Investigator, head of the medical institution, or designee will promptly submit the protocol to applicable ethics committee(s).

9.4.1. Investigator Information

Physicians with a specialty in medical oncology will participate as Principal Investigators in this clinical trial.

If investigators are added after the study has been approved by GEICAM, an IEC, or a regulatory agency, these additions will not be considered changes to the protocol.

9.4.2. Protocol Signatures

After reading the protocol, each Principal Investigator will sign the protocol signature page and send a copy of the signed page to GEICAM.

10. Practical Considerations

10.1. Monitoring, Audit and Inspections

Onsite or remote monitoring visits to the study site will be made periodically during the study and according to the Monitoring Plan Document to ensure that all aspects of the protocol are followed. During the visits to the site, the monitor will review the original records of the patients, the records of medication stocks and document preservation. The monitor must also evaluate the study procedures and discuss the possible problems with the Investigator. During the course of the study, audit visits can be carried out in the participating sites. The Investigator will allow direct access to the source documents/data for the tasks of monitoring, audit, reviewed by the IEC and the inspection by the Competent Authorities.

10.2. Preservation of Study Documentation

The copies of all the relevant information will be preserved by the Investigator for a period of at least 25 years after the end of the study according to current legislation.

10.3. Protocol Modification

Once it has been authorized by the IEC and the competent authority any protocol modification must be documented by writing, in the form of an amendment.

The amendments must be duly identified, by its chronological order number, dated and signed by GEICAM and the Chief Investigator.

All the protocol substantial amendments must be notified to the IEC involved in the trial, the authorization of the involved IEC and/or the competent authority will be necessary before their application.

After reading the protocol amendment, each Principal Investigator will sign the protocol amendment signature page and send a copy of the signed page to GEICAM.

10.4. Study Resources, Use of the Information and Publication

All the information concerning the study treatment provided by GEICAM in relation to this study, and not previously published, is considered to be confidential information with property right of GEICAM. This information comprises the basic information about the product, the clinical protocol, the work forms where appropriate, the e-CRFs, the assessment methods, the technical methodology and the basic scientific data. This confidential information will be the property of GEICAM, it must not be disclosed to third parties without the prior written consent of GEICAM and it must not be used other than for the purposes of the study.

The information developed during the practice of this clinical study is also considered to be confidential. This information can be disclosed to the extent considered necessary by GEICAM.

To allow the use of the information derived from this study and to ensure the compliance with the current rules, the Investigator is obliged to provide GEICAM with all the results of examinations and all the data developed in this study. Except in that required by law, the information obtained during the study can only be provided to the doctors and to the competent authorities by GEICAM.

GEICAM commits to comply with current legislation relating to studies, which establishes the obligation to publish the results, both positive and negative, in conferences and journals, with reference to IEC that approved the study, and its funding source. The list of authors will be developed in accordance with the GEICAM SOPs (standard operating procedures). The different disclosures will be decided by the Chief Investigator. By signing this protocol, the Chief Investigator and Principal Investigators accept the terms of the GEICAM´s publications policy and commit to respect them.

GEICAM, as sponsor of the study, will assume the funding of the project according to the guidelines of this protocol. GEICAM has the support of the company Astrazeneca Farmaceutica Spain, S.A. to cover this cost; this support will be independent of the results of the study. Additionally, this project will have the support from Centro de Investigación Biomédica en Red in the thematic area of Breast Oncology (CIBERONC Breast), of the Instituto de Salud Carlos III (ISCIII), in the conduction of the study.

10.5. Ethics Committee

The protocol and the informed consent document will be reviewed by the involved IEC. The single decision of the IEC referring to the development of the study will be provided in writing to GEICAM.

GEICAM will submit the required reports of the progress of the study to the IEC. At the end of the study, GEICAM must inform the IEC of trial closure.

11. Important medical procedures to be followed by the investigator

11.1. Overdose

There is currently no specific treatment in the event of overdose with 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 b.i.d. (tablet formulation).

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose CRF information.
- An overdose without associated symptoms is only reported on the Overdose CRF information.

If an overdose on olaparib occurs in the course of the study and it is associated with an AE (serious or not), then Investigators or other site personnel inform appropriate GEICAM representatives **within one day**, i.e., immediately but no later than **the end of the next business day** of when he or she becomes aware of it, using the SAE form. Overdoses which are not associated with any AE, can be reported within 30 days. The designated GEICAM representative will work with the Investigator to ensure that all relevant information is provided.

When GEICAM has information on overdose, this should also be notified to AstraZeneca.

11.2. Pregnancy

All outcomes of pregnancy should be reported to GEICAM.

11.3. Maternal exposure

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

The outcome of any conception occurring from the date of the first dose until 1 month after the last dose should be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that olaparib may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic

pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel must inform appropriate GEICAM representatives **within one day** i.e., immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated GEICAM representative works with the Investigator to ensure that all relevant information is provided within 1 day for SAEs, see Section 6.2.4. and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

When GEICAM has information on pregnancies and maternal exposure, this should also be notified to AstraZeneca.

12. References

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Protocol Attachment 1. Study Schedule

Study Schedule of Events and Timelines. Protocol GEICAM/2015-06 (COMETA-Breast)

Study Schedule of Events and Timelines. GEICAM/2015-06 (COMETA-Breast)			**During Study Treatment. During first month: Visits on day 1 and day 8 (+/-3 days); in subsequent cycles: every 28 days (+/- 7 days),**			**Post-treatment 30 days (±7 days) from the last olaparib dose** (before starting a new anticancer therapy[Z])	**After study treatment termination**	
Cycle	**Baseline**		**Cycle 1**	**Cycle 2**	**Subsequent Cycles**			
Day of cycle		ENROLMENT	**1, 8**	**1**	**1**		**PFS Follow-up Period (+/- 7 days)**	**OS Follow-up Period**
Procedure/Laboratory/ Diagnostic Test	**Within 28 days[b]**							
ICD for Entry (before any study specific tests)[a]	**X**							
Inclusion/Exclusion Criteria[b]	**X**							
Medical and surgical history and demographics[bc]	**X** (prior to sample shipment)							
Physical examination[d]	**X**		**X**	**X**	**X**	**X**		
ECOG PS[b]	**X** (prior to sample shipment)		**X**	**X**	**X**	**X**		
Serum or urine pregnancy test[b,e]	**X** (prior to sample shipment)		**X** (day 1 pre-dose)	In the event of a suspected pregnancy				
Haematology[f]	**X**		**X[g]**	**X**	**X**	**X**		
Coagulation testing[h]	**X**		If clinically indicated; unless patient is taking warfarin then it is recommended that INR and aPTT be monitored at least once per week for the first month, then monthly if the INR is stable[h]					
Blood Chemistry[i]	**X**		**X[g]**	**X**	**X**	**X**		
Urinary testing[j]	**X**		If clinically indicated					
Resting 12-lead ECG[k]	**X**		If clinically indicated					

Concomitant medications[b]	**X** (prior to sample shipment)		**X**					
AEs and SAEs[l]	**X**		**X**					
Olaparib dosing[ll]			**X**	**X**	**X**			
Tumour Assessment	**X**[m]		Every 8 weeks (+/-1 week) from the start of treatment. Responses should be confirmed after 4 weeks[m]. Patients with bone lesions identified at baseline will repeat the bone scans if indicated[n]**.**				**X**[r]	
Date of death								**X**[s]
Biological Samples								
Metastatic tissue for central determination of *BRCA* methylation and other biomarker analysis [b,t]	**X**							
Whole blood for central determination of *BRCA* mutations [b,u]	**X**							
Whole blood for *BRCA* methylation and expression analysis and other biomarker analysis [b,v]	**X**					**X**	**X**	
Plasma samples for exploratory biomarker analysis[w]	**X**			**X** (between week 4-6)		**X**	**X**	
Primary and after progression tumour tissue for biomarker analysis[y]	**X**					**X** (if available)	**X** (if available)	

Study Schedule of Events and Timelines. Protocol GEICAM/2015-06 (COMETA-Breast)

a	Signed, written informed consent (approved by IEC) obtained prior to any study specific procedure.
b	Some inclusion/exclusion criteria must be checked before sending the tumour and blood samples for *BRCA* analysis. Refer to Section 4 of the protocol for details. To verify these criteria medical history, concomitant medication, ECOG assessment and pregnancy test must be done prior to the shipment of the samples to check these inclusion/exclusion criteria
c	Includes among others, local laboratory ER/PgR/HER2 expression levels and methods used to assess them, previous treatments, race and age.
d	Physical examination includes measurements of blood pressure, pulse rate and body temperature.
e	**Serum or urine pregnancy test:** for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. In the event of a suspected pregnancy during the study, the test should be repeated.
f	**Haematology:** Full haematology assessments for safety (haemoglobin, red blood cells, platelets, mean cell volume, mean cell haemoglobin concentration, mean cell haemoglobin [MCH], white blood cells, absolute differential white cell count [neutrophils, lymphocytes, monocytes, eosinophils and basophils] and absolute neutrophil count or segmented neutrophil count and band forms) at indicated visits and when clinically indicated. If treatment is discontinued close to the theoretical date for the next cycle and it is not planned to perform in advance the post-treatment visit due to the initiation of a new anticancer therapy, a new haematology analysis should be performed at the moment of the study treatment discontinuation. **Bone marrow or blood cytogenetic analysis** may be performed according to standard haematological practice for patients with prolonged haematological toxicities as defined in Section 5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment 5.4.1.3. Management of Prolonged Haematological Toxicities while on Study Treatment.
g	Not on day 1 of cycle 1, if the assessments were performed within the 7 days previous day 1 of treatment. The initiation of the treatment will be within 7 days after enrolment
h	**Coagulation testing:** Activated partial thromboplastin time (aPTT) and international normalised ratio (INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and aPTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.
i	**Blood Chemistry:** sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, GGT, AP, AST, ALT, urea or blood urea nitrogen (BUN), total protein, albumin and lactic dehydrogenase (LDH) should be performed at indicated visits and when clinically indicated. In case a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x ULN please refer to Attachment 5 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions. If treatment is discontinued close to the theoretical date for the next cycle and it is not planned to perform in advance the post-treatment visit due to the initiation of a new anticancer therapy, a new biochemistry analysis should be performed at the moment of the study treatment discontinuation.
j	**Urinary testing:** Urinalysis by dipstick should be performed at baseline and then only if clinically indicated. Microscopic analysis should be performed by the hospital's local laboratory if required.
k	**Resting 12-lead ECGs** are required within 7 days prior to starting study treatment and when clinically indicated after starting study treatment.
l	After informed consent form signature, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. Adverse events to be monitored continuously during the treatment period. All AEs occurring during the study and until the treatment discontinuation visit 30 days after the last study medication to be recorded with grading according to NCI-CTCAE, thereafter all study drug/medication-related SAEs should continue to be collected.

ll	**Olaparib will be taken orally as a continuous dose every 12h.**
m	**Disease assessment** for all patients at baseline will include: • CT or MRI scan of the chest, abdomen and pelvis (CAP). • Bone scans will be mandatory if the patient has bone disease or if there is any suspicious of bone metastases. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline will follow the same assessment schedule as for measurable lesions. • Brain CT or MRI scan is mandatory if the patient has CNS metastases or if there is any suspicious of CNS metastases. • CT or MRI scan of any other sites of disease as clinically indicated. • Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the eCRF. Tumour response will be assessed using RECIST v.1.1. every 8 weeks (+/- 1 week).
n	**Bone scans** (if applicable) will be repeated if indicated when complete response is identified in target disease or when progression in bone is suspected. Responses should be confirmed according to RECIST v.1.1 after at least 28 days.
r	Only to be performed post-study treatment if disease progression has not yet been confirmed and patients have not begun a new therapy, the tumour assessment will be performed every 8 weeks from the last tumour assessment.
s	The patients will be followed for survival until death, loss to follow-up, withdrawal of consent or study termination by GEICAM. After progression or patient is receiving other therapy, the tumour assessment will be performed according to the standard medical practice. The date of death and all treatments received by the patient after progression (according to the standard medical practice) will be collected in the eCRF.
t	**At least one paraffin sample from a metastatic lesion** must be sent to the sponsor-designated central laboratory to perform methylation testing and other biomarker analysis related to secondary and exploratory objectives. It is strongly recommended that the metastatic sample has been obtained after previous therapy regimen. Surgery blocks or core biopsies would be acceptable, minimal amount of tumour tissue will be specified in the SMM.
u	**One blood sample (EDTA) to analyse *BRCA* mutational status** must be sent to Myriad laboratories, unless test have been done previously at Myriad and absence of mutations has been already determined. It could be sent once signed the ICD 1) in the previous line of treatment, once inclusion/exclusion criteria have been reviewed and the patient is considered a potential candidate to the study or 2) after ending the previous line of treatment, during screening procedure (see section 6.3 for further instructions).
v	**Whole blood samples** (EDTA and tubes optimized for RNA isolation) will be collected at screening and at the end of treatment **to assess germline methylation status and/or expression levels of *BRCA* genes as well as to perform other exploratory analyses**. Sample after treatment must be taken at the end of study treatment prior to initiation of next therapy regimen. If a patient end the treatment due to other cause different to disease progression, collect other sample once progression is documented (although initiated other treatment), if available.
w	**Plasma samples** will be obtained at screening (solicited to all screened patients) and during treatment (one sample taken between 4 to 6 week of treatment, preferable prior to receive the treatment) and at the end of study treatment prior to initiation of next therapy regimen (only enrolled patients). If a patient end the treatment due to other cause different to disease progression, collect other sample once progression is documented (although initiated other treatment), if available.
y	**Tumour Tissue for Biomarker Assessments**: If available, tumour tissue (FFPE) from primary tumour (solicited to all screened patients) and metastatic lesions at disease progression (only enrolled patients) will be collected for retrospective biomarker assessments. Samples will be sent to the sponsor-designated central laboratories. If a patient end the treatment due to other cause different to disease progression, collect this once progression is documented (although initiated other treatment), if available.

z	This post-treatment visit must be performed before starting with any new anticancer therapy; however, in case the beginning of this new therapy cannot be delayed as per the investigator's judgment, the safety visit may be performed in advance, but always before starting with the new anticancer therapy.

Protocol Attachment 2. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. 1982. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5(6):649-65.

Protocol Attachment 3. Adverse event (AE) non defined in NCI-CTCAE

CTC Grade	Equivalent to:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life-threatening / disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death.

Protocol Attachment 4. Adverse Events / Serious Adverse Events Assessment Guide

Time	After ICD Before Drug	During Therapy	30-Day Post-treatment Follow-up Period	Long-Term Follow-up Period
Events to Collect	AE/SAEs Related to Procedures	New/Ongoing AE/SAEs Regardless of Relatedness to Study Treatment or Procedures		New/Ongoing SAEs, including sudden death of unknown cause, that the investigators considers there is a reasonable possibility that the event is causally related to the investigational product or protocol procedure, even if the study has been closed Any case of MDS/AML or new primary malignancy whether it is considered a non-serious AE [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality

Abbreviations: AE = adverse event, ICD = informed consent document, SAE = serious adverse event.

Protocol Attachment 5. Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law

TABLE OF CONTENTS

1. INTRODUCTION

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

The Investigator participates, together with GEICAM 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 Product (IMP).

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

2. DEFINITIONS

Potential Hy's Law (PHL)

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

Hy's Law (HL)

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

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

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

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

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

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the GEICAM representative who will then inform the central Study Team.
- GEICAM project representatives contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:
- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available.

- If at any time (in consultation with the GEICAM project representatives) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the GEICAM standard processes.

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

- Report an SAE (report term 'Hy's Law') according to GEICAM standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply.
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to

determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

6. ACTIONS REQUIRED WHEN POTENTIAL HY'S LAW CRITERIA ARE MET BEFORE AND AFTER STARTING STUDY TREATMENT (NOT APPLICABLE)

7. ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met chronic or progressing malignant disease?

If No: Follow the process described in Section 4.2 of this Appendix.

If Yes: Determine if there has been a significant change in the patient's condition* compared with when PHL criteria were previously met.

- If there is no significant change no action is required.
- If there is a significant change follow the process described in Section 4.2 of this Appendix.

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

8. REFERENCES

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

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

Protocol Attachment 6. Patient Diary

In a separate document.