Statistical Analysis Plan (SAP)

GEICAM/2015-06

A Phase II Clinical Trial to analyse Olaparib Response in patients with *BRCA1* and/or *2* Promoter Methylation Diagnosed of Advanced Breast Cancer *"COMETA-Breast study"*

Sponsor: GEICAM (Spanish Breast Cancer Research Group Foundation)

Chief Investigator: Dr. Juan R. de la Haba-Rodríguez,
Instituto Maimónides de Investigación Biomédica (IMIBIC)
Hospital Universitario Reina Sofía; Córdoba, Spain

Author: María José Escudero

Version: 1.0

Date: 22 September 2020

Protocol No.: GEICAM/2015-06

Protocol title: A Phase II Clinical Trial to analyse Olaparib Response in patients with *BRCA1* and/or *2* Promoter Methylation Diagnosed of Advanced Breast Cancer". "COMETA-Breast study.

Protocol Version: 3.0 10 June 2019

Sponsor: *GEICAM*

This Statistical Analysis Plan was created according the ICH Good Clinical Practice (1) (2), GEICAM policies and Standard Operating Procedures (SOP); and is consistent with the study protocol (3).

Version Date: : 22-Sep-20

Version No.: 1

Previous Version: NA

Prepared by Statistician:		
María José Escudero		
Name	Signature	Date
Reviewed by:		
Statistician		
Juan José Miralles		
Name	Signature	Date

Project Manager **NA** Name	Signature	Date
Translational Project Manager **Nuria Martín** Name (project manager until March 2018 and current PM back up)	Signature	Date

Approved by: **Medical Monitor** **Susana Bezares** Name	Signature	Date
Chief Investigator **Dr. Juan R. de la Haba-Rodríguez** Name	Signature	Date

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
AML	Acute Myeloid Leukaemia
BC	Breast Cancer
BRCA1	Breast Cancer type 1
BRCA2	Breast Cancer type 2
CB	Clinical Benefit
CBR	Clinical Benefit Rate
CI	Confidence Interval
CpG	5'—C—phosphate—G—3'
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
ECG	Electrocardiography
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.
GCP	Good Clinical Practice
GEICAM	Spanish Breast Cancer Group
ICF	Informed Consent Form
IDMC	Interim Data Monitoring Committee
IEC	Independent Ethics Committee
ITT	Intent To Treat
MDS	Myelodysplastic Syndrome
MDS/AML	Myelodysplastic Syndrome/Acute Myeloid Leukaemia
NCI	National Cancer Institute
NGS panel	Next Generation Sequencing panel
OAE	Other significant Adverse Events
OR	Objective Response
ORR	Objective Response Rate

OS	Overall Survival
PARP	Enzyme Poly ADP Ribose Polymerase
PD	Progressive Disease or Programmed Death depending on the context
PFS	Progression-Free Survival
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
TLFs	Tables, Listings and Figures
TN	Triple-Negative
TNBC	Triple-Negative Breast Cancer

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to give a detailed description of the statistical analyses to be performed to generate the final report for GEICAM/2015-06 study (COMETA-Breast).

Based on published data included in the protocol and data from the full clinical program to date, it is anticipated that olaparib, an orally active inhibitor of the enzyme poly ADP ribose polymerase (PARPi), will have a positive benefit risk profile for the treatment of the minority well-defined population of advanced triple-negative breast cancer (TNBC) patients with the promoter methylation of *BRCA genes*.

The statistical analyses of this study will be the responsibility of GEICAM. The interpretation of these results will be the responsibility of the Chief Investigator of the study.

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 analyses will be performed using the SAS Enterprise Guide 5.1 version.

2. STUDY OBJECTIVES

2.1 Main Objective

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

2.2 Secondary Objectives

- To analyse other efficacy measures.
    - Clinical Benefit Rate (CBR).
    - Duration of Response (DoR).
    - Progression Free Survival (PFS).
    - Overall Survival (OS).
- 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.

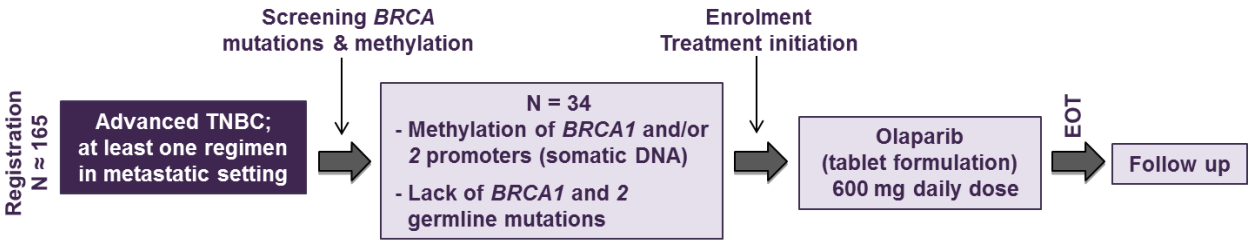
2.3 Exploratory Objectives

- Explore biomarkers of clinical activity in tumour and blood samples.

3. STUDY DESIGN

This is a multicenter, non-randomised, phase II clinical trial to assess the efficacy and safety of olaparib in monotherapy 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.

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 Informed Consent Form (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 analyses 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 Sample Size

We have set the null hypothesis (H0) that ORR will be 30% (ORR achieved by TN patients treated with gemcitabine plus carboplatin[i]) versus the alternative hypothesis (H1) that ORR will be 54% (ORR showed by TN BRCA mutated patients treated with olaparib[ii]). 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.

3.2 Randomization

Not applicable.

4. STUDY POPULATION

4.1 ITT Population

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

4.2 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 version 1.1 (unless PD, death or unacceptable toxicity is observed before the first tumour response assessment) and without major protocol deviations according to the protocol deviation manual.

4.3 Safety population

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

4.4 Biomarker population

A subset of enrolled patients with evaluable blood and/or tumour samples required for achievement of the secondary and exploratory objectives of the study.

4.5 Discontinuations

4.5.1 Discontinuation of Study Drug/Medication

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).

4.5.2 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.

4.5.3 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. STUDY VARIABLES

5.1 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 and by site.
- Summary of reasons for patients entered, but not enrolled. This summary will include:
    - Nº of patients not included due to having *BRCA1/2* germline mutations
    - Nº of patients not having methylated *BRCA1and/or BRCA2* promoters
    - Nº of patients not having tumor available
    - Nº of patients in which the methylation or germline mutation analysis was not assessable.
- Total number of patients treated and by site.
- 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 major violations will be provided.

5.2 Patient Characteristics

Patient characteristics will include a summary of the following:

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

- Prior anti-cancer 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.

5.3 Concomitant Therapy

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

5.4 Treatment Compliance

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

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

No minimal level of compliance will be defined for patient inclusion in efficacy analyses. To be considered compliant patients should have received at least 80% of the planned number of doses. Exploratory analysis of the impact of compliance on selected efficacy endpoints may be performed if deemed necessary.

6. ENDPOINTS

6.1 Efficacy Endpoints

6.1.1 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.

6.1.2 Secondary End-points

The following secondary end-points will be studied:

- Clinical Benefit Rate (CBR), Duration of Response (DoR), 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 PD, 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.

6.2 Exploratory End-points

The following exploratory end-points could be studied:

- 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.

7. DATA SCREENING AND ACCEPTANCE.

7.1 Missing data

The frequency of missing data will be examined and reported for each variable in the analysis. We will not perform data imputation for missing data.

7.1.1 Missing date

If the day of the month is missing for any date used in a calculation, the 15th of the month will be used to replace the missing date unless the calculation results in a negative time duration (e.g., date of onset cannot be prior to day one date). In this case, the date resulting in 1 day duration will be used. If the day of the month and the month are missing for any date used in a calculation, the date will be considered missing.

7.2 Statistical software

The statistical analysis will be developed in SAS Enterprise Guide v7.1.

7.3 Database lock

The first database lock will be carried out when enough data have been obtained to perform the step 1 analysis of the optimal two stage Simon model.

The database lock for efficacy analysis will be carried out when there will be sufficient data to achieve the primary and secondary objectives or at the date of last patient´s death or withdraw of the informed consent, whichever comes first. As the study design is two Stage Simon design, if in step 1 we do not obtain the enough responses the data base will be closed and perform the primary analysis.

8. 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 are to allow early stopping of the study for futility.

Following the two-stage Simon design, it will be reviewed whether if at least 4 of the first 12 evaluable patients show tumour response according to RECIST version 1.1, and if this occurs,

additional patients will be included to get a total of 34 patients. If 3 or less patients of the first 12 evaluable patients show an OR, recruitment will be stopped.

In case of recruitment is stopped after the step 1, it will be reviewed the feasibility and interest of performing some of the described secondary and exploratory analysis based on the available number of patients and samples.

8.1 Purpose of interim analysis

Not applicable.

8.2 IDMC (Interim Data Monitoring Committee)

Not applicable.

9. STATISTICAL METHODS ANNALYSES

9.1 Statistical Methods

For descriptive analyses, frequencies, percentages and ninety-five percent confidence intervals of interest will be calculated for categorical variables wherever possible. For continuous variables, standard descriptive statistics, such as total number of observations, number of available data, mean, standard deviation, minimum, percentile 25, median, percentile 75 and maximum will be calculated.

For efficacy analyses the 2-sided 95% confidence interval will be presented wherever possible. A bilateral (2-sided) 5% significance level will be used to assess the statistical significance.

Chi-square χ^2 test or Fisher exact test will be used to explore the relationship between two qualitative variables. Mann-Whitney-Wilcoxon test will be used to compare a quantitative variable in two independent groups.

Logistic regression models will be used to test the association of co-variables with a binary variable (ORR, CBR) and to estimate odds ratios and their 95% confidence intervals.

Kaplan-Meier Method will be used to estimate the survival function, survival median and probabilities of occurrence of event at a certain point of time.

Cox Proportional Hazards Regression Model will be used to estimate the hazard ratio and assess the association between several risk factors, considered simultaneously, and survival time (PFS, RD, OS).

9.2 Statistical analyses

An exploratory and descriptive analysis will be developed for each variable in the study. All continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, maximum and minimum and confidence interval (CI) will be performed when this information is considered relevant to describe a unique variable. The frequency and percentages of observed levels will be reported for all categorical measures. Ninety-five percent confidence intervals will be provided for estimates of interest wherever possible.

All statistical tests will be performed with a significance level of 5%, unless otherwise specified. For qualitative comparison of independent samples the Chi-squared test (or Fisher's exact test for 2x2 tables) will be used, while for the quantitative samples Mann-Whitney-U will be used. Logistic regression models will be used to test the association of covariables with objective response (yes/no) and clinical benefit (yes/no), and to estimate odds ratios and their 95% confidence intervals. The Kaplan-Meier limit-product method will be used to estimate PFS and OS. The Kaplan-Meier survival curve will be presented graphically. Median PFS and OS with the 95% confidence interval will be reported. Cox regression models will be used to estimate hazard ratios and its 95% confidence interval. The Wald test will be used to establish the prognostic importance of each covariable.

All efficacy analyses 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 tumor burden (PFS, ORR, CBR and RD) will be derived using the local radiologist's/investigator's assessment.

9.2.1.1 Analyses of Primary Endpoint

The primary endpoint is ORR.

Objective Response Rate (ORR): A patient will be considered to have achieved an objective response (OR) if the patient has a complete response (CR) or partial response (PR) according to RECIST version 1.1 (4) definitions. Otherwise, the patient will be considered as non-responder 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").

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

The ORR will be reported, including a 95% confidence interval using the Clopper-Pearson method (5).

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 done with the ITT population. 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 ORR analysis.

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

9.2.1.2 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 version 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.

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

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.

Duration of Response (DoR): DoR is defined as the time from the first documentation of objective tumour response (CR or PR) to the first documented PD using RECIST version 1.1, or to death due to any cause, whichever occurs first. DoR data will be censored on the date of the last tumour assessment on study for patients who do not have objective PD 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 is defined as the time from study enrolment to the first documented PD, using RECIST version 1.1, or death from any cause, whichever occurs first. PFS data will be censored on the date of the last tumour assessment on study for patients who do not have objective PD 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 is defined as the time from the date of study enrolment to the date of death from any cause. 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.

9.2.2 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 (AEs) 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 AEs.
- 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 and SAEs data will be presented in frequency tables by grade. Haematological and clinical biochemistry toxicities will be assessed from laboratory test parameters. The safety analyses will be performed in the safety population.

9.2.2.1 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 AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician of AstraZeneca, 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.

9.2.3 *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 collected 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.

9.2.4 Other Analyses

9.2.4.1 Biomarker Exploratory Analyses

The biomarker analyses of the present study will be exploratory and primarily make use of descriptive statistical methods. For continuous variables, descriptive statistics including the mean, standard deviation, median, minimum and maximum values will be provided. Categorical variables will be summarized by numbers and proportions (if possible, the 95% confidence intervals will be calculated).

Appropriate statistical methods will be used to investigate any possible relationship of biological subtypes/profiles and biomarker levels with the efficacy end-points and outcome, and to compare with data from healthy volunteers (if available). Any exploratory biomarker analyses, including additional sensitivity analyses, will be outlined in the specific statistical analysis plan/summary.

9.2.5 Other Subgroup Analyses

Other exploratory subgroup analyses may be performed if deemed appropriate.

9.2.6 Second Course Phase Analyses

Exploratory second course phase analyses may be performed if deemed appropriate.

10. TABLES Y FIGURES

Table/Figure No.		Title of Table/Figure
1.	**BASELINE**	
1.1.	**Study Information**	
	1.1.1.	Study Information
1.2.	**Disposition of Patients**	
	1.2.1	Screen Failures
	1.2.2	Number of Subjects Randomized by Site
	1.2.3	Disposition of subjects
	1.2.4	Analysis Sets
1.3.	**Consort Study Flowchart**	
	Fig .1.3.1	Consort Flowchart
1.4.	**Baseline characteristics**	
	1.4.1	Demographic Characteristics
	1.4.2	Clinical-Pathological Characteristics
	1.4.3	Local Laboratory Biomarkers
	1.4.4	Baseline Lesions
	1.4.5	Stratification Factors

1.5.	**Medical History**	
	1.5.1	Medical History by Prefered Term
	1.5.2	Most common (at least 5%) Medical and Surgical History by Preferred Term ITT Population
1.6.	**Concomitant Treatments**	
	1.6.1	Concomitant Medications by Standardized Medication Name Safety Population
	1.6.2	Most common concomitant medications (at least 10% overall) by Standardized Medication Name Safety Population
1.7.	**Previous Treatments**	
	1.7.1	Prior Therapies for BC
	1.7.2	Previous Treatment for Early BC.
	1.7.2	Previous Treatment for MTX BC.
1.8.	**Study Drug Exposure**	
	1.8.1	Summary of Study Drug Exposure
	1.8.2	Summary of Dose Modifications
1.9.	**Subsequent Therapies**	
	1.9.1	Subsequent Therapies for BC
	1.9.2	Subsequent Chemotherapy for BC
	1.9.3	Subsequent Hormone therapy for BC
	1.9.4	Subsequent Targeted therapy for BC
2.	**EFFICACY**	
2.1.	**Overall Response Rate**	
	2.1.1	Summary of Overall Response Rate Efficacy population

	2.1.2	Summary of Overall Response Rate ITT population
2.2.	**Progression-free Survival**	
	2.2.1	Progression-free Survival Efficacy population
	Fig . 2.2.1	Progression-free Survival Efficacy population
	2.2.2	Progression-free Survival ITT population
	Fig . 2.2.2	Progression-free Survival ITT population
2.3.	**Overall Survival**	
	2.3.1	Overall Survival Efficacy population
	Fig . 2.3.1	Overall Survival Efficacy population
	2.3.2	Overall Survival ITT population
	Fig . 2.3.2	Overall Survival ITT population
3.	**SAFETY**	
3.1.	**Treatment Emergent Adverse Event**	
	3.1.1	Overview of Treatment-Emergent Adverse Events
	3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
	3.1.3	Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
	3.1.4	Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
	3.1.5	Grade 3 or Higher Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
	3.1.6	Most common (at least 10% in any treatment arm) Treatment-Emergent Adverse Events by Preferred Term
	3.1.7	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Population

	3.1.8	Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Safety Population
	3.1.9	Treatment-Emergent Adverse Events by Grade
	3.1.10	Drug-Related Treatment-Emergent Adverse Events by Grade
	3.1.11	Serious Treatment-Emergent Adverse Events by Grade
	3.1.12	Adverse Events from Laboratory according NCI CTC v4.03 by System Organ Class and Preferred Term
3.1.	**Deaths**	
	3.2.1	All-Cause Mortality Safety Population
4	**OTHER ENDPOINTS**	
	4.1	Changes of germline methylation pre and post treatment
	4.2	Correlation between germline methylation status and efficacy outcome data
	4.3	Correlation between germline methylation status and somatic methylation status
	4.4	Correlation of methylation between primary and metastatic lesions
	4.5	Correlation between expression data and promoter methylation status of *BRCA1/2* and outcome data
5	**EXPLORATORY OBJECTIVES (if performed)**	
	5.1	Exploratory biomarkers of response or resistance to Olaparib
	5.2	Review potential pharmacogenomics analyses related to drug response or adverse drug reactions
	5.3	Specific mutations or epigenetic biomarkers identified in pre-therapy tumour specimens as potentially linked to treatment response

The numbers of tables and figures do not have to match exactly with those of the statistical report. The feasibility and interest of performing some of the described tables and figures based on the available number of patients, data and biological samples.

Please see Shells Tables, Listings and Figures.

11. APPENDIX (if applicable)

See attachment “Shell TLFs GEICAM 2015-06 (COMETA-Breast Study).docx”

12. BIBLIOGRAFHY /REFERENCES

1. *GEICAM, Protocol GEICAM/2015-06 Version 3.0 10 June 2019.*
2. *ICH E9, Statistical Principles for Clinical Trials.*
3. *ICH E3, Structure and Content of Clinical Study Reports.*
4. O’Shaughnessy J, Schwartzberg Lee, Danso MA, et al. Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol 2014;32(34):3840-3847.
5. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010 Jul 24;376(9737):235-44.

13. SUMMARY OF CHANGES FROM PREVIOUS VERSION

Version No.	Effective Date	Modified section	Description of changes
1		*NA*	*Creation of document*

[i] O'Shaughnessy J, Schwartzberg Lee, Danso MA, et al. Phase III Study of Iniparib Plus Gemcitabine and Carboplatin Versus Gemcitabine and Carboplatin in Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol 2014;32(34):3840-3847.

[ii] Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010 Jul 24;376(9737):235-44.