Clinical trial results:
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).

Summary

EudraCT number	2016-001407-23
Trial protocol	ES
Global end of trial date	08 March 2022

Results information

Result version number	v1 (current)
This version publication date	11 November 2023
First version publication date	11 November 2023

Trial information

Trial identification

Sponsor protocol code	GEICAM/2015-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03205761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEICAM (FUNDACIÓN GRUPO ESPAÑOL DE INVESTIGACIÓN EN CÁNCER DE MAMA)
Sponsor organisation address	Avenida de los Pirineos 7, San Sebastián de los Reyes / Madrid, Spain, 28703
Public contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), +34 916592870, inicio_ensayos@geicam.org
Scientific contact	Clinical Operations Department, GEICAM (Fundación Grupo Español de Investigación en Cáncer de Mama), +34 916592870, inicio_ensayos@geicam.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2022
Global end of trial reached?	Yes
Global end of trial date	08 March 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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.

Protection of trial subjects:

Not applicable. It was not necessary to applied extra measures for protection of the subjects out of the good clinical practice environment.

Background therapy:

Epigenetic silencing by aberrant BRCA1/2 promoters' methylation can be responsible for a dysfunctional BRCA protein. BRCA1/2 promoters' methylation occurs in 15-57% of triple negative breast cancer patients. BRCA1/2 promoters' methylation breast cancer display pathologic features and genetic profiles like germline BRCA1/2-mutated (gBRCA1/2m) carriers. Olaparib is a PARP inhibitor approved for treating gBRCAm HER2-negative advanced breast cancer patients. These are the results of a phase II study assessing the Olaparib efficacy in advanced triple negative breast cancer patients with BRCA1/2 promoters' methylation.

Evidence for comparator: -

Actual start date of recruitment	23 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eleven patients were registered in eight Spanish sites.

Pre-assignment

Screening details:

Eleven patients were registered in eight Spanish sites.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Olaparib

Arm description:

Patients with a positive methylation status on at least one of the two genes 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 total daily dose (given in two oral administrations of 300 mg every 12 hours approximately). Patients will continue to receive their treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	Lynparza
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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.

Number of subjects in period 1	Olaparib
Started	11
Completed	0
Not completed	11
Consent withdrawn by subject	1
Progressive Disease	10

Baseline characteristics

Reporting groups	
Reporting group title	Olaparib
Reporting group description:	
Patients with a positive methylation status on at least one of the two genes 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 total daily dose (given in two oral administrations of 300 mg every 12 hours approximately). Patients will continue to receive their treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first.	

Reporting group values	Olaparib	Total	
Number of subjects	11	11	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	51		
full range (min-max)	37 to 64	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	0	0	
Race Units: Subjects			
White	11	11	
Region of Enrollment Units: Subjects			
Spain	11	11	
Menopause Status Units: Subjects			
Postmenopausal	8	8	
Premenopausal	3	3	
Eastern Cooperative Oncology Group (ECOG) status			
ECOG score runs from 0 to 5, with 0 denoting perfect health and 5 death. 0 - Asymptomatic 1 - Symptomatic but completely ambulatory 2 - Symptomatic, <50% in bed during the day 3 - Symptomatic, >50% in bed, but not bedbound 4 - Bedbound 5 - Death			
Units: Subjects			
ECOG 0	6	6	
ECOG 1	5	5	
Histopathologic type Units: Subjects			
Ductal	8	8	

Not Available / Not Done	1	1	
Adenoid Cystic Carcinoma	1	1	
Lobular	1	1	
Histologic grade			
Cancer cells are given a Grade (G) when they are removed from the breast and checked under a microscope. The G is based on how much the cancer cells look like normal cells. G1 or well differentiated (score 3, 4, or 5): cells are slower-growing, and look more like normal breast tissue. G2 or moderately differentiated (score 6, 7): cells are growing at a speed of and look like cells somewhere between G1 and 3. G3 or poorly differentiated (score 8, 9): cells look very different from normal and will probably grow and spread faster			
Units: Subjects			
Grade 1	1	1	
Grade 2	3	3	
Grade 3	7	7	
Status at Initial Diagnosis Units: Subjects			
Without metastasis	7	7	
With metastasis	4	4	

End points

End points reporting groups

Reporting group title	Olaparib

Reporting group description:

Patients with a positive methylation status on at least one of the two genes 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 total daily dose (given in two oral administrations of 300 mg every 12 hours approximately). Patients will continue to receive their treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurs first.

Subject analysis set title	Arm to report statistical analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Arm to report statistical analysis for the ORR endpoint definition section in a single arm trial.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the percentage of patients with a Complete Response (CR) or Partial Response (PR) out of the patients from the efficacy population. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions. Tumor response will be assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). Efficacy population is a subset of the intend to treat population that has received at least one dose of study medication and has performed at least one tumor response assessment according to RECIST v.1.1 (unless a progression, death or unacceptable toxicity is seen before the first tumor response assessment).

End point type	Primary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib	Arm to report statistical analysis		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	1[1]		
Units: participants	1	0		

Notes:

[1] - Arm to report statistical analysis for the ORR endpoint definition section in a single arm trial.

Statistical analyses

Statistical analysis title	ORR analysis

Statistical analysis description:

ORR will be estimated by dividing the number of patients with objective response (CR or PR) by the Efficacy population (“response rate”).

Comparison groups	Olaparib v Arm to report statistical analysis

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Percentage
Point estimate	9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	41.3

Notes:

[2] - The rate of OR and confidence interval.

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. CBR was defined as the percentage of patients with a Complete Response (CR) or Partial Response (PR) plus stable disease (SD) ≥ 24 weeks out of the efficacy population. Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; SD is defined as a failure to meet criteria for CR or PR in the absence of progressive disease. Overall Response (OR) = CR + PR.
Efficacy population is a subset of the intend to treat population that has received at least one dose of study medication and has performed at least one tumor response assessment according to RECIST v.1.1 (unless a progression, death or unacceptable toxicity is seen before the first tumor response assessment).

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: participants	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1). PFS is defined as the time from enrollment to the first documented progression disease (PD), or death from any cause, whichever occurs first. PD is defined using RECIST, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: month				
median (confidence interval 95%)	1.8 (1.2 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) defined as the time from the date of study enrollment to the date of death from any cause.

End point type	Secondary

End point timeframe:

Up to 14 months

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: month				
median (confidence interval 95%)	8.9 (1.2 to 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Value Between BRCA1 Methylation Status and Efficacy Outcome Data

End point title	Correlation Value Between BRCA1 Methylation Status and Efficacy Outcome Data

End point description:

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

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	4[3]			
Units: participants				
BRCA1: 28% methylation	1			
BRCA1: 40.3% methylation	1			
BRCA1: 50.6% methylation	1			
BRCA1: >40% methylation	1			

Notes:

[3] - Only 4 patients with Partial Response or Stable Disease

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Value Between BRCA2 Methylation Status and Efficacy Outcome Data

End point title	Correlation Value Between BRCA2 Methylation Status and Efficacy Outcome Data

End point description:

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

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	4[4]			
Units: participants				
BRCA2: 10.7% methylation	1			
BRCA2: 2.5% methylation	1			
BRCA2: 6.4% methylation	1			
BRCA2: <5% methylation	1			

Notes:

[4] - Only 4 patients with Partial Response or Stable Disease

Statistical analyses

No statistical analyses for this end point

Secondary: Response Duration (RD)

End point title	Response Duration (RD)

End point description:

Tumor response was assessed using Response Evaluation Criteria In Solid Tumors Criteria (RECIST 1.1) criteria. RD was defined as the time from the first documentation of objective tumor response (complete response (CR) or partial response (PR)) to the first documented progressive disease (PD), or to death due to any cause, whichever occurs first.
Per RECIST, CR is defined as the disappearance of all target lesions; PR is defined as an >=30% decrease in the sum of the longest diameter of target lesions; PD is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.

End point type	Secondary

End point timeframe:

Through study treatment, and average of 8 weeks

End point values	Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	1[5]			
Units: months	18			

Notes:

[5] - There was only 1 Partial Response.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE were reported after Informed Consent Document (ICD) and before study drugs until approximately 30 days following the discontinuation of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Olaparib

Reporting group description:

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Serious adverse events	Olaparib		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 11 (36.36%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Progression Disease			
subjects affected / exposed	4 / 11 (36.36%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Olaparib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 11 (72.73%)		
Investigations			
Haemoglobin			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all) Lymphoedema subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 5 1 / 11 (9.09%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3 2 / 11 (18.18%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Nausea	2 / 11 (18.18%) 2 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1		

subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Orthopnoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2017	INTRODUCTION: Pharmacokinetics and safety information has been updated according to the most recent version of the Investigator Brochure (IB) (V.14 March 10, 2017). PROCEDURES FOR PATIENT SELECTION: It is emphasized that every effort should be made to obtain the sample for methylation analysis after the last treatment. It is specified that the analysis of germline BRCA1/2 mutations in blood can be carried out in the prior treatment line in those patients who are future candidates for inclusion in the trial. A specific HIP-ICF has been generated for this analysis. The timeframe for methylation analysis is changed from 10 to 8 working days, unless justified. It has been specified that plasma samples are required for all registered patients who send sample for methylation analysis. MANAGEMENT OF ADVERSE EVENTS AND CONCOMITANT MEDICATION: Olaparib dose adjustment instructions after anemia grade 3 have been updated (Section 5.4.1 Management of haematological toxicity). The instructions for concomitant medication are updated if 1) co-administration of moderate inhibitors of CYP3A is required, the olaparib dose should be reduced to 150 mg twice daily for the duration of treatment with the inhibitor and continue for 3 half-lives; 2) concomitant anticoagulant treatments it is updated that the administration of low molecular weight heparin is allowed and that if the patient is being treated with warfarin is should be follow-up the parameter APTT (5.5 "General Concomitant Medication and supportive care” REPORTING OF ADVERSE EVENTS AND PREGNANCIES The fax number for SAE and pregnancy reporting has been updated.
10 June 2019	INTRODUCTION: Pharmacokinetics and safety information has been updated according to the most recent versions of the Investigator Brochure (IB) ((ver. 15 _08 March 2016, ver.16 _29 Jan 2019 and ver. 17_ 02 May 2019). Investigational Plan: Early efficacy review was changed by Step 1 analysis of the optimal two-stage Simon model.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In this proof-of-concept study, Olaparib did not show clinically nor statistically significant antitumor activity.
The statistical assumptions for the first Simon’s model stage were not met so the recruitment did not proceed onto the second stage

Notes: