Clinical trial results:
Multicentric Single Arm Phase II Clinical Trial, to Evaluate Safety and Efficacy of the Combination of Olaparib and PLD for Platinum Resistant Ovarian Primary Peritoneal Carcinoma, and Fallopian Tube Cancer Patients.

Summary

EudraCT number	2016-004850-14
Trial protocol	ES
Global end of trial date	27 September 2022

Results information

Result version number	v1 (current)
This version publication date	31 October 2023
First version publication date	31 October 2023

Trial information

Trial identification

Sponsor protocol code	GEICO-1601

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03161132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Investigación en Cáncer de Ovario (GEICO)
Sponsor organisation address	C/ Santa Engracia 151, Planta 5ª oficina 2, Madrid, Spain, 28003
Public contact	Contact point designated by the Sponsor, MFAR Clinical Research, investigacion@mfar.net
Scientific contact	Contact point designated by the Sponsor, MFAR Clinical Research, 0034 93 434 44 12, investigacion@mfar.net

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	27 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2022
Global end of trial reached?	Yes
Global end of trial date	27 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of the addition of Olaparib to PLD in platinum resistant advanced ovarian cancer patients plus maintenance with Olaparib. The primary endpoint is 6 months progression-free survival rate (PFS6m).

Protection of trial subjects:

The trial already safety measures to ensure protection of enrolled patients

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 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: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

3 screening failures
1 died before receiving the study treatment

Period 1

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

Blinding implementation details:

Single arm, non-randomized, non blided phase II clinical trial

Arms

Arm title	Experimental arm

Arm description:

Pegylated liposomal doxorubicin (PLD) was administered as an intravenous infusion at 30 mg/m2 iv for up to 6 cycles (every 28 days).
Olaparib was administered orally at 300 mg two-times per day until objective disease progression if in the Investigator’s opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Pegylated liposomal doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pegylated liposomal doxorubicin (PLD) was administered as an intravenous infusion at 30 mg/m2 iv for up to 6 cycles (every 28 days).

Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Olaparib was administered orally at 300 mg two-times per day until objective disease progression if in the Investigator’s opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

Number of subjects in period 1	Experimental arm
Started	31
Completed	31

Baseline characteristics

Reporting groups	
Reporting group title	Experimental arm
Reporting group description:	
Pegylated liposomal doxorubicin (PLD) was administered as an intravenous infusion at 30 mg/m2 iv for up to 6 cycles (every 28 days). Olaparib was administered orally at 300 mg two-times per day until objective disease progression if in the Investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.	

Reporting group values	Experimental arm	Total	
Number of subjects	31	31	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	58		
standard deviation	± 10	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	0	0	
ECOG PS			
Measure Description: Describes a patients's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working...). The scale ranges from 0 (Fully active, able to carry on all predisease performance without restriction) to 5 (Dead)			
Units: Subjects			
ECOG PS 0	10	10	
ECOG PS 1	21	21	
Histological subtype			
Measure Description: Describes the histology subtype of tumor, the type of cells from which the tumor has arisen.			
Units: Subjects			
Serous	27	27	
Endometrioid	3	3	
Mixed	1	1	
BRCA status			
Measure Description: BRCA1 and BRCA2 are two tumor suppressor genes. Mutations in BRCA genes have been correlated with sensitization to treatments such as olaparib.			

Units: Subjects			
Native	26	26	
Mutant	5	5	
Previous bevacizumab			
Measure Description: Bevacizumab is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian. Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.			
Units: Subjects			
Yes	19	19	
No	12	12	
Cancer antigen 125 (CA-125)			
Measure Description: CA-125 is a blood biomarker that is used to monitor certain cancers during and after treatment. The CA-125 blood levels are used to evaluate response to treatment. Increasing values may indicate worsening of the disease.			
Units: Subjects			
Basal lower than 2 upper limit normal (ULN)	7	7	
Basal higher than 2 upper limit normal (ULN)	24	24	
Neutrophil to lymphocyte ratio (NLR)			
Measure Description: NLR in blood is an indirect measure of the immune system condition and elevated values may indicate pathological processess such as cancer, atherosclerosis, infection, inflammation or others. Patients with cancer and an NLR above the defined cutoff have consistently been found to have worse outcomes than patients with a lower NLR across cancer types. High NLR values have been previously correlated with poor prognosis in platinum-sensitive ovarian cancer			
Units: Subjects			
< 2	11	11	
≥ 2	20	20	
lymphocyte to monocyte ratio (LMR)			
Measure Description: LMR in blood can indicate systemic inflammatory responses and have proved to be related with the survival of cancer patients.			
Units: Subjects			
< 4	20	20	
≥ 4	11	11	
Platelet to lymphocytes ratio			
Measure Description: PLR in blood can indicate systemic inflammatory responses and have proved to be related with the survival of cancer patients			
Units: Subjects			
< 125	13	13	
≥ 125	18	18	
Initial dose of PLD			
Measure Description: The study treatment scheduled was modified after inclusion of a first set of patients. PLD dose was reduced from 40 mg/m2 to 30 mg/m2.			
Units: Subjects			
40 mg/m2	17	17	
30 mg/m2	14	14	
Total previous lines			
Measure Description: Number of previous treatment lines received for ovarian cancer for each patient.			
Units: Number of previous lines			

median	2		
full range (min-max)	1 to 5	-	
Previous platinum lines			
] Measure Description: Number of previous treatment lines containing platinum chemotherapeutics received for ovarian cancer for each patient			
Units: Number of previous platinum lines			
median	2		
full range (min-max)	1 to 4	-	

End points

End points reporting groups

Reporting group title	Experimental arm

Reporting group description:

Pegylated liposomal doxorubicin (PLD) was administered as an intravenous infusion at 30 mg/m2 iv for up to 6 cycles (every 28 days).
Olaparib was administered orally at 300 mg two-times per day until objective disease progression if in the Investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

Subject analysis set title	Experimental arm
Subject analysis set type	Full analysis

Subject analysis set description:

Pegylated liposomal doxorubicin (PLD) was administered as an intravenous infusion at 30 mg/m2 iv for up to 6 cycles (every 28 days).
Olaparib was administered orally at 300 mg two-times per day until objective disease progression if in the Investigator's opinion they were benefiting from treatment and they did not meet any other discontinuation criteria.

Primary: Progression-free Survival

End point title	Progression-free Survival[1]

End point description:

Proportion of pacients with no progression of disease at 6 months after start of treatment with Olaparib plus PLD

End point type	Primary

End point timeframe:

6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Single arm study, no compaison apply. The comparison is established indirectly with the state of the art and previous clinical trials.

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Percentage of patients free of event				
number (confidence interval 95%)	47 (32 to 69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Proportion of patients with tumor size reduction. Response duration is measured from the time of initial response until documented tumor progression. The Objective Response Rate (ORR) is defined as the sum of partial responses plus complete responses according to RECIST 1.1.

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Patients				
Partial response (PR)	9			
Stable disease (SD)	15			
Progressive disease (PD)	6			
Not evaluable (NE)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Proportion of patients who have achieved complete response, partial response and stable disease of 8 or more months according to RECIST 1.1

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Patients				
Yes	10			
No	20			
NE	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Response to Treatment Rate According CA-125 Levels

End point title	Response to Treatment Rate According CA-125 Levels

End point description:

Proportion of patients who have achieved a response according to CA-125: and it has occurred if there is at least a 50% reduction in CA-125 levels from a pretreatment sample.

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Patients				
Responders	10			
Non responders	14			
NE	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Time from the date of the first dose of study treatment to the date of objective disease progression or death (in the absence of progression) regardless of whether the subject withdraws from study treatment or receives another anticancer therapy prior to progression.

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Months				
median (confidence interval 95%)				
Overall study, intention to treat (ITT)	5.8 (4.4 to 9.7)			
PLD 30 mg/m2	5.8 (4.4 to 100000)			
PLD 40 mg/m2	5.4 (4 to 13.2)			
BRCA native	5.4 (4 to 12)			
BRCA mutated	6.5 (5.3 to 100000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Time from inclusion until death of any cause.

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Months				
median (confidence interval 95%)				
Overall study, intention to treat (ITT)	14.5 (9.9 to 100000)			
BRCA wt	12.2 (10.6 to 100000)			
BRCA mutated	21.3 (12.5 to 100000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life

End point title	Health Related Quality of Life

End point description:

Change in patient's quality of life during the study, using the self-reported European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) (EORTC QLQ-C30) and the EORTC ovarian cancer module (EORTC-OV-28). Both scores will be combined to report a final outcome.
Values range from 0 to 100. higher values indicate better performance status.

End point type	Secondary

End point timeframe:

20 months

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Arbitrary units				
median (full range (min-max))				
Baseline	58.3 (16.7 to 100)			
Week 32	66.7 (16.7 to 83.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0

End point title	Number of Participants With Treatment-related Adverse Events as Assessed by CTCAE v4.0
End point description:	
Frequency, nature and number of patients developing adverse events throughout follow up	
End point type	Secondary
End point timeframe:	
20 months	

End point values	Experimental arm			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: Patients				
Had at least one treatment-related adverse event	30			
Had no treatment-related adverse event	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Throughout the study period, approximately 5 years.	
Assessment type	Systematic

Dictionary used	
Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Experimental arm

Reporting group description:

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Serious adverse events	Experimental arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 31 (35.48%)		
number of deaths (all causes)	25		
number of deaths resulting from adverse events	0		
Vascular disorders			
Thromboembolic event - G3			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia - G3			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia - G4			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased - G3			

subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction - G3				
subjects affected / exposed	4 / 31 (12.90%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intestinal obstruction - G2				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction - G5				
subjects affected / exposed	2 / 31 (6.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Mucositis oral - G3				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucositis oral - G4				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural effusion - G3				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Pyelonephritis- G3				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Renal insufficiency- G2			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory infection - G2			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Experimental arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	17		
Neutrophil count decrease			
subjects affected / exposed	15 / 31 (48.39%)		
occurrences (all)	15		
Platelet count decrease			
subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	7		
Lymphocyte count decrease			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	6		
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	21 / 31 (67.74%)		
occurrences (all)	21		
Headache			

subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 31 (38.71%)		
occurrences (all)	12		
Diarrhoea			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	11		
Intestinal obstruction			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Mucositis oral			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	8		
Nausea			
subjects affected / exposed	22 / 31 (70.97%)		
occurrences (all)	22		
Vomits			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	17		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2019	- Update of inclusion criteria. - Update of information related to the treatment of toxicities associated with the investigational product.
25 February 2020	Safety modifications in the IB V16 of January 29, 2019. Necessary modification of protocol V3.1 (19DEC19) and HIP-CI V4.0 (19SEP19).
13 July 2020	Safety modifications in the IB V18 of January 29, 2020. Necessary modification of protocol V4.0 (18MAR2020) and HIP-CI V5.0 (18MAR2020).
08 January 2021	Safety modifications in IB V19 of August 6, 2020. Necessary modification of protocol V5.0 (8NOV20) and HIP-CI V6.0 (8NOV2020). Change IP H. Dr. Negrin
15 July 2021	Update of the olaparib investigator's manual (version 20 of January 21, 2021) that includes new information on the safety of patients treated with this medication. HIP-CI _7.0_08 April 2021. IB-olaparib-edition-20.pdf

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.

the sample size was small, and toxicity led to dose reuction in a proportion of patients.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/84468