Clinical trial results:
Phase (window) preoperative study of olaparib with cisplatin or with durvalumab (MEDI4736) or alone or no treatment in patients with histologically proven squamous cell carcinoma of the head and neck who are candidates for surgery

Summary

EudraCT number	2015-005268-41
Trial protocol	GR
Global end of trial date	10 January 2020

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021

Trial information

Trial identification

Sponsor protocol code	HE5A/15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02882308
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	18 Hatzikonstandi, Athens, Greece, 11524
Public contact	Clincal Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clincal Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr

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	16 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the difference in change in the tumour Ki-67 before and after treatment with the combination of olaparib + cisplatin or olaparib monotherapy.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines and the local regulatory requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2016
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	Greece: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	23
From 65 to 84 years	15
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study from 20 October 2016 until 10 October 2019 in 3 sites

Pre-assignment

Screening details:

Patients were screened for eligibility before entering the study and signed the informed consent form which was obtained before any study procedure

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cisplatin / Olaparib

Arm description:

cisplatin 60 mg/m2 day1 followed by olaparib tabl 75mg daily for 5 days

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

Dosage and administration details:

olaparib tabl 75mg daily for 5

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

One cycle of combined treatment with cisplatin 60 mg/m2 day 1. Cisplatin infusion was administered according to the local treatment guidelines with adequate pre- and post-hydration and antiemetic treatment.

Arm title	Olaparib only

Arm description:

Olaparib tabl 600mg daily for 21-28 days depending on the day of surgery. When surgery was delayed, olaparib was continued until the day before surgery.

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

Dosage and administration details:

One cycle of olaparib tabl monotherapy 600 mg daily (2 tabl 150 mg morning – 2 tabl 150 mg the evening) day1-day21. No routine prophylactic
anti-emetic treatment is required at the start of study treatment. If surgery is delayed, olaparib will be

continued until the day before surgery

Arm title	No treatment
Arm description:	
No treatment was administered until the date of surgery or 2nd biopsy	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Durvalumab/Olaparib
Arm description:	
Durvalumab 1500 mg day1 followed by olaparib tabl 600mg daily for 21-28 days	
Arm type	Experimental
Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Olaparib tabl 600mg daily (2 tabl 150 mg morning – 2 tabl 150 mg evening) day1-day21. Olaparib treatment was started immediately after the completion of durvalumab infusion.	
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
One cycle of combined treatment with durvalumab 1500mg day1. The durvalumab solution should not be infused through an IV line in which other solutions or medications were being administered.	

Number of subjects in period 1	Cisplatin / Olaparib	Olaparib only	No treatment
Started	12	12	5
Completed	12	10	5
Not completed	0	2	0
Disease progression	-	-	-
Adverse event, non-fatal	-	-	-
Patient did not present for follow-up	-	-	-
Protocol deviation	-	2	-

Number of subjects in period 1	Durvalumab/Olaparib
Started	12
Completed	9
Not completed	3
Disease progression	1

Adverse event, non-fatal	1
Patient did not present for follow-up	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Cisplatin / Olaparib
Reporting group description:	
cisplatin 60 mg/m2 day1 followed by olaparib tabl 75mg daily for 5 days	
Reporting group title	Olaparib only
Reporting group description:	
Olaparib tabl 600mg daily for 21-28 days depending on the day of surgery. When surgery was delayed, olaparib was continued until the day before surgery.	
Reporting group title	No treatment
Reporting group description:	
No treatment was administered until the date of surgery or 2nd biopsy	
Reporting group title	Durvalumab/Olaparib
Reporting group description:	
Durvalumab 1500 mg day1 followed by olaparib tabl 600mg daily for 21-28 days	

Reporting group values	Cisplatin / Olaparib	Olaparib only	No treatment
Number of subjects	12	12	5
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	64.7	61.3	56.3
full range (min-max)	51.7 to 70.5	47.8 to 84.8	54 to 67
Gender categorical Units: Subjects			
Female	1	3	1
Male	11	9	4

Reporting group values	Durvalumab/Olaparib	Total	
Number of subjects	12	41	
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			
median	68.7		
full range (min-max)	48.6 to 85.9	-	
Gender categorical			
Units: Subjects			
Female	3	8	
Male	9	33	

Subject analysis sets

Subject analysis set title	Eligible patients
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Subgroup of patients that satisfied the entry criteria of the trial. Two patients were excluded.

Reporting group values	Eligible patients		
Number of subjects	39		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
median	61.5		
full range (min-max)	47.8 to 85.9		
Gender categorical			
Units: Subjects			
Female	8		
Male	31		

End points

End points reporting groups

Reporting group title	Cisplatin / Olaparib
Reporting group description:	
cisplatin 60 mg/m2 day1 followed by olaparib tabl 75mg daily for 5 days	
Reporting group title	Olaparib only
Reporting group description:	
Olaparib tabl 600mg daily for 21-28 days depending on the day of surgery. When surgery was delayed, olaparib was continued until the day before surgery.	
Reporting group title	No treatment
Reporting group description:	
No treatment was administered until the date of surgery or 2nd biopsy	
Reporting group title	Durvalumab/Olaparib
Reporting group description:	
Durvalumab 1500 mg day1 followed by olaparib tabl 600mg daily for 21-28 days	
Subject analysis set title	Eligible patients
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Subgroup of patients that satisfied the entry criteria of the trial. Two patients were excluded.	

Primary: Change in the tumour Ki-67

End point title	Change in the tumour Ki-67[1]
End point description:	
To investigate the change in the tumour Ki-67 after treatment (ΔKi67) with the combination of olaparib + durvalumab or olaparib + cisplatin or olaparib monotherapy.	
End point type	Primary
End point timeframe:	
At baseline and at the day of the surgery or 2nd biopsy (at days 23-29 days).	

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: Since the primary endpoint of the study was the assessment of the percentage of patients with ΔKi67>=25%, we have provided the corresponding statistics for each treatment group separately. The study was not designed to be comparative and therefore no statistical comparisons were performed among treatment/study groups.

End point values	Cisplatin / Olaparib	Olaparib only	No treatment	Durvalumab/Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	9[2]	4[3]	8[4]
Units: percentage of patients with ΔKi67>=25%				
number (not applicable)	33.3	77.8	25	25

Notes:

[2] - 9 eligible patients with paired data pre and post treatment with olaparib

[3] - 4 patients with paired data before and after second surgery/biopsy.

[4] - 8 eligible patients with paired data pre- and post treatment with olaparib and durvalumab.

Statistical analyses

No statistical analyses for this end point

Secondary: pCRR - Pathologic complete response rate

End point title	pCRR - Pathologic complete response rate[5]

End point description:

pCRR is defined as the percentage of patients achieving complete disappearance of tumour cells in the primary tumour and regional lymph nodes. Therefore, pCRR can be assessed only in patients who will undergo surgery.

End point type	Secondary

End point timeframe:

On week 4 only for operable patients

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: We have provided the percentage of patients with pCR in the groups of patients who received treatment with olaparib.

End point values	Cisplatin / Olaparib	Olaparib only	Durvalumab/Olaparib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	10[6]	12	
Units: percentage of patients				
number (not applicable)	8.3	0	8.3	

Notes:

[6] - Eligible patients treated with olaparib monotherapy

Statistical analyses

No statistical analyses for this end point

Secondary: ORR - Overall Response Rate

End point title	ORR - Overall Response Rate[7]

End point description:

To assess the objective response rate (ORR) defined as the percentage of patients achieving a complete or partial response as the best response according to RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Imaging studies were performed at baseline and on week 4

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: We have provided statistics for the percentage of patients with an objective tumor response for all three groups of patients treated with olaparib but not for the control group.

End point values	Cisplatin / Olaparib	Olaparib only	Durvalumab/Olaparib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	9[8]	12	
Units: percentage of patients				
number (not applicable)				
ORR	8.3	11.1	16.7	

Notes:

[8] - Eligible patients evaluable for response

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability of treatment

End point title	Tolerability of treatment[9]

End point description:

To assess the tolerability of treatment

End point type	Secondary

End point timeframe:

From the 1st day of therapy and every week for 4 weeks maximum and 90 days after last therapy administration

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: We have provided statistics for eligible patients who received at least one dose of the study drug (s). Therefore, statistics have been provided for all three groups of patients treated with olaparib but not for the control group.

End point values	Cisplatin / Olaparib	Olaparib only	Durvalumab/Olaparib	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	10[10]	12	
Units: number of patients				
Any adverse event	11	10	9	
Fatal adverse events	0	0	0	
Serious adverse events	1	0	1	

Notes:

[10] - Eligible patients who received at least one dose of the study drug.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mutations in genes associated with DNA repair

End point title	Mutations in genes associated with DNA repair

End point description:

End point type	Other pre-specified

End point timeframe:

At baseline, on day of surgery or the 2nd biopsy (at days 23-29)

End point values	Cisplatin / Olaparib	Olaparib only	No treatment	Durvalumab/Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	10[11]	5	12
Units: number of patients				
Mutations in DDR pre-treatment	3	1	1	0
Mutations in DDR post-treatment	1	0	0	0

Notes:

[11] - Eligible patients

Statistical analyses

No statistical analyses for this end point

Other pre-specified: CTCs-circulating tumor cells

End point title	CTCs-circulating tumor cells[12]

End point description:

To identify circulating tumor cells (CTCs) evaluated for DNA repair biomarkers and PD-L1

End point type	Other pre-specified

End point timeframe:

At baseline, a day before surgery and 90 days after surgery

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PDL-1 CTCs were only assessed in the group of patients treated with olaparib and durvalumab.

End point values	Durvalumab/Olaparib			
Subject group type	Reporting group			
Number of subjects analysed	6[13]			
Units: number of patients				
Increase in PDL-1 after treatment	2			
Decrease in PDL-1 after treatment	3			
No change in PDL-1 after treatment	1			

Notes:

[13] - Patients with paired data before and after treatment with olaparib and durvalumab.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Immunohistochemistry (IHC) analysis

End point title	Immunohistochemistry (IHC) analysis

End point description:

Immunohistochemistry (IHC) analysis of STING activation and immune response

End point type	Other pre-specified

End point timeframe:

At baseline and at the day of the surgery or 2nd biopsy (at days 23-29 days)

End point values	Cisplatin / Olaparib	Olaparib only	No treatment	Durvalumab/Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[14]	9[15]	4[16]	7[17]
Units: number of patients				
Increase in STING levels post treatment/surgery	2	3	1	0
Decrease in STING levels post treatment/surgery	6	4	3	4
No change in STING levels post treatment/surgery	4	2	0	3

Notes:

[14] - Eligible patients with paired data at both timepoints (pre- and post- treatment/ surgery/biopsy.

[15] - Eligible patients with paired data at both timepoints (pre- and post- treatment/ surgery/biopsy.

[16] - Patients with paired data at both timepoints (pre- and post- treatment/ surgery/biopsy.

[17] - Eligible patients with paired data at both timepoints (pre- and post- treatment/ surgery/biopsy.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: RNA-sequencing in fresh tumor samples

End point title	RNA-sequencing in fresh tumor samples
End point description:	
RNA-sequencing in fresh tumor samples of the study population	
End point type	Other pre-specified
End point timeframe:	
At baseline and at the day of the surgery or 2nd biopsy (at days 23-29 days)	

End point values	Cisplatin / Olaparib	Olaparib only	No treatment	Durvalumab/Olaparib
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[18]	9[19]	3[20]	8[21]
Units: number of patients				
Increase in PDL-1 mRNA post treatment/surgery	5	4	2	7
Decrease in PDL-1 mRNA post treatment/surgery	6	5	1	1
No change in PDL-1 mRNA post treatment/surgery	0	0	0	0
Increase in PDL-2 mRNA post treatment/surgery	7	4	2	7
Decrease in PDL-2 mRNA post treatment/surgery	4	5	1	1
No change in PDL-2 mRNA post treatment/surgery	0	0	0	0
Increase in CD8A mRNA post treatment/surgery	9	7	1	6

Decrease in CD8A mRNA post treatment/surgery	2	2	2	2
No change in CD8A post treatment/surgery	0	0	0	0
Increase in IRF mRNA post treatment/surgery	3	3	1	2
Decrease in IRF mRNA post treatment/surgery	8	6	2	6
No change in IRF mRNA post treatment/surgery	0	0	0	0

Notes:

[18] - Eligible patients with paired data at both timepoints (pre- and post-treatment/surgery/biopsy).

[19] - Eligible patients with paired data at both timepoints (pre- and post-treatment/surgery/biopsy).

[20] - Patients with paired data at both timepoints (pre- and post-treatment/surgery/biopsy).

[21] - Eligible patients with paired data at both timepoints (pre- and post-treatment/surgery/biopsy).

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the 1st day of therapy and every week for 4 weeks maximum and 90 days after last therapy administration

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Olaparib - Cisplatin
Reporting group description: -	
Reporting group title	Olaparib monotherapy
Reporting group description: -	
Reporting group title	Olaparib - durvalumab
Reporting group description: -	
Reporting group title	No treatment

Reporting group description: -

Serious adverse events	Olaparib - Cisplatin	Olaparib monotherapy	Olaparib - durvalumab
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 12 (8.33%)
number of deaths (all causes)	8	6	2
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Post – operative haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colonic haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	No treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Post – operative haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			

Colonic haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Olaparib - Cisplatin	Olaparib monotherapy	Olaparib - durvalumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	11 / 12 (91.67%)	9 / 12 (75.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Carotid artery thrombosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Edema face			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	3 / 12 (25.00%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Localised oedema	Additional description: Localised oedema in lips		

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood creatine increased			
subjects affected / exposed	3 / 12 (25.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
INR increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Total protein low			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Neutrophil count decreased			
subjects affected / exposed	4 / 12 (33.33%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	4	1	0
Platelet count decreased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Weight gain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Weight loss			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	4 / 12 (33.33%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	4	2	0
Injury, poisoning and procedural complications			
Post - operative pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 12 (16.67%)	7 / 12 (58.33%)	2 / 12 (16.67%)
occurrences (all)	2	7	2
Leukocytosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Oral haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oral pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hepatobiliary disorders			
Urea increased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	3	1	0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	3	0	0

Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Hyperkalaemia			
subjects affected / exposed	2 / 12 (16.67%)	3 / 12 (25.00%)	0 / 12 (0.00%)
occurrences (all)	2	5	0
Hypertriglyceridaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
LDH increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	No treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Carotid artery thrombosis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
General disorders and administration			

site conditions			
Edema face			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Localised oedema	Additional description: Localised oedema in lips		
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood creatine increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
INR increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Total protein low			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Platelet count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Weight gain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Weight loss subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Injury, poisoning and procedural complications Post - operative pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Somnolence subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Leukocytosis			

subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Tongue ulceration subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Oral haemorrhage subjects affected / exposed occurrences (all) Oral pain subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Hepatobiliary disorders Urea increased subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash maculo-papular subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypertriglyceridaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
LDH increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2017	changes in ICF v1.2, SUPPLEMENTARY ICF v1.O. New IB for OLAPARIB v14. New Site.
01 November 2018	changes in PROTOCOL v1.2, ICF MAIN v1.3, ICF BIOSAMPLE v1.1, ICF PRGNANCY v1.2. New IB of DURVALUMAB v11. INCREASE IN THE NUMBER OF PARTICIPANTS FROM 39 TO 41. EXTENTION OF DURATION FROM 1 YEAR & 3 MONTHS TO 2 YEARS & 7 MONTHS.
27 February 2019	New IB for Durvalumab v13. Extention of duration of Clinical Trial from 2 years & 7 months to 3 years & 1 month
10 April 2019	Changes in ICF Main v1.4. New IB for Olaparib v16

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported