



Clinical trial results:

A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Olaparib Alone or in Combination With Bevacizumab Compared to Bevacizumab with a Fluoropyrimidine in Participants with Unresectable or Metastatic Colorectal Cancer who Have Not Progressed Following First-line Induction (LYNK-003)

Summary

EudraCT number	2019-000698-22
Trial protocol	BE HU FR LT LV
Global end of trial date	06 November 2023

Results information

Result version number	v1 (current)
This version publication date	03 November 2024
First version publication date	03 November 2024

Trial information

Trial identification

Sponsor protocol code	7339-003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04456699
WHO universal trial number (UTN)	-
Other trial identifiers	jRCT2031200146: jRCT, LYNK-003: MSD

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@msd.com

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	06 November 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an efficacy and safety study of olaparib alone or in combination with bevacizumab being compared to bevacizumab with a fluoropyrimidine in participants with unresectable or metastatic colorectal cancer who have not progressed following first-line induction. The primary hypotheses are: Olaparib + Bevacizumab is superior to a fluoropyrimidine + Bevacizumab with respect to progression-free survival (PFS) using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) as assessed by blinded independent central review (BICR); Olaparib is superior to a fluoropyrimidine + Bevacizumab with respect to PFS using RECIST 1.1 as assessed by BICR. As of amendment 5 study enrollment is being discontinued and study participants randomized to one of the two experimental arms (olaparib plus bevacizumab or olaparib monotherapy) must discontinue study intervention. Participants who are still on study treatment will no longer have tumor response assessments by BICR.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	Türkiye: 40

Country: Number of subjects enrolled	Ukraine: 12
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Colombia: 28
Worldwide total number of subjects	335
EEA total number of subjects	89

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)	184
From 65 to 84 years	149
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants were randomized 1:1:1 to receive either Olaparib + bevacizumab, Olaparib, or Bevacizumab + chemotherapy.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Olaparib + bevacizumab

Arm description:

Participants received olaparib (300 mg twice daily [BID] oral) + Bevacizumab (5 mg/kg intravenous [IV] once every 2 weeks [Q2W]) until progressive disease or end of study.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	MVASI TM Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg or 7.5 mg/kg Q2W or Q3W IV infusion until progressive disease or end of study

Investigational medicinal product name	Olaparib
Investigational medicinal product code	
Other name	LYNPARZA TM
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg BID, oral until progressive disease or end of study

Arm title	Olaparib
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Arm description:

Participants received olaparib (300 mg BID) oral, until progressive disease or end of study.

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

Dosage and administration details:

300 mg BID, oral until progressive disease or end of study

Arm title	Bevacizumab + chemotherapy
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Arm description:

Participants received investigator's choice of either bevacizumab (7.5 mg/kg IV once every three weeks (Q3W)) + capecitabine (1000 mg/m² BID for 14 days, then 7 days off, Q3W) or bevacizumab (5

mg/kg IV Q2W) + 5-FU (2400 mg/m² IV over 46 to 48 hours Q2W; bolus 5-FU (400 mg/m²) was added prior to infusional 5-FU, per local standards and at the investigator's discretion). Leucovorin or levoleucovorin 400 mg/m² (leucovorin) or 200 mg/m² (levoleucovorin) Q2W IV infusion was added per investigator's discretion. Treatment continued until progressive disease or end of study.

Arm type	Active comparator
Investigational medicinal product name	5-FU
Investigational medicinal product code	
Other name	Fluorouracil Adrucil Efudex
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2400 mg/m² over 46 to 48 hours Q2W IV infusion until disease progression or end of study; bolus 5-FU (400mg/m²) can be added prior to infusional 5-FU, per local standards and at the investigator's discretion

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	XELODA [®]
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m² oral capsule BID for 14 days, then 7 days off, Q3W) until progressive disease or end of study

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	MVASI [™] Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg or 7.5 mg/kg Q2W or Q3W IV infusion until progressive disease or end of study

Investigational medicinal product name	Leucovorin/ levoleucovorin
Investigational medicinal product code	
Other name	Folinic Acid Fusilev [®] Khapzory [™]
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m² (leucovorin) or 200 mg/m² (levoleucovorin) may be added to Bevacizumab + 5-FU per investigator's discretion Q2W IV infusion until progressive disease or end of study

Number of subjects in period 1	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy
Started	111	115	109
Treated	111	113	108
Completed	0	0	0
Not completed	111	115	109
Adverse event, serious fatal	48	50	52
Consent withdrawn by subject	8	4	5
Physician decision	-	-	2
Sponsor Decision	55	61	50

Baseline characteristics

Reporting groups

Reporting group title	Olaparib + bevacizumab
Reporting group description:	
Participants received olaparib (300 mg twice daily [BID] oral) + Bevacizumab (5 mg/kg intravenous [IV] once every 2 weeks [Q2W]) until progressive disease or end of study.	
Reporting group title	Olaparib
Reporting group description:	
Participants received olaparib (300 mg BID) oral, until progressive disease or end of study.	
Reporting group title	Bevacizumab + chemotherapy
Reporting group description:	
Participants received investigator's choice of either bevacizumab (7.5 mg/kg IV once every three weeks (Q3W)) + capecitabine (1000 mg/m ² BID for 14 days, then 7 days off, Q3W) or bevacizumab (5 mg/kg IV Q2W) + 5-FU (2400 mg/m ² IV over 46 to 48 hours Q2W; bolus 5-FU (400 mg/m ²) was added prior to infusional 5-FU, per local standards and at the investigator's discretion). Leucovorin or levoleucovorin 400 mg/m ² (leucovorin) or 200 mg/m ² (levoleucovorin) Q2W IV infusion was added per investigator's discretion. Treatment continued until progressive disease or end of study.	

Reporting group values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy
Number of subjects	111	115	109
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	68	66	50
From 65-84 years	42	49	58
85 years and over	1	0	1
Age Continuous Units: Years			
arithmetic mean	59.5	61.1	63.2
standard deviation	± 12.8	± 10.7	± 11.3
Sex: Female, Male Units: Participants			
Female	50	49	44
Male	61	66	65
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	10	5	4
Asian	25	40	30
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	71	64	66
More than one race	2	3	4

Unknown or Not Reported	3	3	4
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	18	16	10
Not Hispanic or Latino	88	93	94
Unknown or Not Reported	5	6	5
Response to Prior Induction			
Participants last scan prior to folinic acid/fluorouracil/oxaliplatin (FOLFOX) + bevacizumab or capecitabine and oxaliplatin (CAPOX) + bevacizumab treatment was assessed by blinded independent central review (BICR) per (Response Evaluation Criteria in Solid Tumors RECIST) 1.1 criteria to evaluate presence of stable disease (SD; Neither sufficient shrinkage to qualify for partial response [PR] nor sufficient increase to qualify for progressive disease), complete response (CR; Disappearance of all target lesions) or PR (At least a 30% decrease in sum of diameters of target lesions).			
Units: Subjects			
CR/PR	49	48	47
Stable Disease (SD)	62	67	62
Number of Induction Cycles			
Number of induction cycles received was assessed at the baseline and categorized as: 1) 6-8 cycles for FOLFOX + bevacizumab or 4-6 cycles for CAPOX + bevacizumab and 2) >8 cycles for FOLFOX + bevacizumab or >6 cycles for CAPOX + bevacizumab.			
Units: Subjects			
6-8cycles of FOLFOX+Bev or 4-6cycles of CAPOX+Bev	53	57	53
>8cycles of FOLFOX+Bev or >6cycles for CAPOX+Bev	58	58	56
Mutation Status			
Participants were assessed for BRAF and/or Ras mutations versus wild type for both (BRAFWt + RASwt) at baseline.			
Units: Subjects			
BRAF and RAS all wild type	32	33	29
BRAF or RAS Mutation	79	82	80

Reporting group values	Total		
Number of subjects	335		
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)	184		
From 65-84 years	149		
85 years and over	2		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	143		
Male	192		

Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	19		
Asian	95		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	201		
More than one race	9		
Unknown or Not Reported	10		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	44		
Not Hispanic or Latino	275		
Unknown or Not Reported	16		
Response to Prior Induction			
Participants last scan prior to folinic acid/fluorouracil/oxaliplatin (FOLFOX) + bevacizumab or capecitabine and oxaliplatin (CAPOX) + bevacizumab treatment was assessed by blinded independent central review (BICR) per (Response Evaluation Criteria in Solid Tumors RECIST) 1.1 criteria to evaluate presence of stable disease (SD; Neither sufficient shrinkage to qualify for partial response [PR] nor sufficient increase to qualify for progressive disease), complete response (CR; Disappearance of all target lesions) or PR (At least a 30% decrease in sum of diameters of target lesions).			
Units: Subjects			
CR/PR	144		
Stable Disease (SD)	191		
Number of Induction Cycles			
Number of induction cycles received was assessed at the baseline and categorized as: 1) 6-8 cycles for FOLFOX + bevacizumab or 4-6 cycles for CAPOX + bevacizumab and 2) >8 cycles for FOLFOX + bevacizumab or >6 cycles for CAPOX + bevacizumab.			
Units: Subjects			
6-8cycles of FOLFOX+Bev or 4-6cycles of CAPOX+Bev	163		
>8cycles of FOLFOX+Bev or >6cycles for CAPOX+Bev	172		
Mutation Status			
Participants were assessed for BRAF and/or Ras mutations versus wild type for both (BRAFWt + RASwt) at baseline.			
Units: Subjects			
BRAF and RAS all wild type	94		
BRAF or RAS Mutation	241		

End points

End points reporting groups

Reporting group title	Olaparib + bevacizumab
Reporting group description: Participants received olaparib (300 mg twice daily [BID] oral) + Bevacizumab (5 mg/kg intravenous [IV] once every 2 weeks [Q2W]) until progressive disease or end of study.	
Reporting group title	Olaparib
Reporting group description: Participants received olaparib (300 mg BID) oral, until progressive disease or end of study.	
Reporting group title	Bevacizumab + chemotherapy
Reporting group description: Participants received investigator's choice of either bevacizumab (7.5 mg/kg IV once every three weeks (Q3W)) + capecitabine (1000 mg/m ² BID for 14 days, then 7 days off, Q3W) or bevacizumab (5 mg/kg IV Q2W) + 5-FU (2400 mg/m ² IV over 46 to 48 hours Q2W; bolus 5-FU (400 mg/m ²) was added prior to infusional 5-FU, per local standards and at the investigator's discretion). Leucovorin or levoleucovorin 400 mg/m ² (leucovorin) or 200 mg/m ² (levoleucovorin) Q2W IV infusion was added per investigator's discretion. Treatment continued until progressive disease or end of study.	

Primary: Progression Free Survival (PFS) Using Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 as Assessed by Blinded Independent Central Review (BICR)

End point title	Progression Free Survival (PFS) Using Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1 as Assessed by Blinded Independent Central Review (BICR)
End point description: PFS was defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first. Per RECIST 1.1, PD was defined as $\geq 20\%$ increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥ 5 mm. Note: The appearance of one or more new lesions was also considered PD. PFS using RECIST 1.1 as assessed by BICR is presented. The analysis population included all randomized participants.	
End point type	Primary
End point timeframe: Up to approximately 30 months	

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	115	109	
Units: Months				
median (confidence interval 95%)	3.7 (3.4 to 5.3)	3.6 (2.0 to 3.7)	5.5 (3.8 to 5.6)	

Statistical analyses

Statistical analysis title	Hazard Ratio
Statistical analysis description: Based on Cox regression model with Efron's method of tie handling with treatment as a covariate	

stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Comparison groups	Olaparib + bevacizumab v Bevacizumab + chemotherapy
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9774 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.97

Notes:

[1] - One-sided p-value based on log-rank test stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Statistical analysis title	Hazard Ratio
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Statistical analysis description:

Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Comparison groups	Olaparib v Bevacizumab + chemotherapy
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9993 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	2.49

Notes:

[2] - One-sided p-value based on log-rank test stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS was defined as the time from randomization to death due to any cause. The OS is presented. A value of 9999 indicates that no data were calculated. The analysis population consists of all randomized participants.

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	115	109	
Units: Months				
median (confidence interval 95%)	21.2 (15.1 to 9999)	21.6 (17.2 to 9999)	19.9 (13.8 to 22.5)	

Statistical analyses

Statistical analysis title	Hazard Ratio
Comparison groups	Olaparib v Bevacizumab + chemotherapy
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.2491 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.3

Notes:

[3] - Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

[4] - One-sided p-value based on log-rank test stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Statistical analysis title	Hazard Ratio
Statistical analysis description:	
Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.	
Comparison groups	Olaparib + bevacizumab v Bevacizumab + chemotherapy
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1527 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.21

Notes:

[5] - One-sided p-value based on log-rank test stratified by prior FOLFOX/CAPOX + Bev induction response, number of induction cycles and mutation status.

Secondary: Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR

End point title	Objective Response Rate (ORR) per RECIST 1.1 as Assessed by BICR
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End point description:

ORR was defined as the percentage of participants who have a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: At least a 30% decrease in the sum of diameters of target lesions) per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The analysis population consisted of all randomized participants who had a measurable disease.

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	107	105	
Units: Percentage of Participants				
number (confidence interval 95%)	4.8 (1.6 to 10.9)	1.9 (0.2 to 6.6)	4.8 (1.6 to 10.8)	

Statistical analyses

Statistical analysis title	Hazards Ratio
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Statistical analysis description:

Based on Miettinen & Nurminen method stratified by prior FOLFOX/CAPOX + Bev induction response, cycles and mutation status.

Comparison groups	Olaparib v Bevacizumab + chemotherapy
Number of subjects included in analysis	212
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.902 ^[6]
Method	Miettinen & Nurminen
Parameter estimate	Difference in Percentage
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	2.3

Notes:

[6] - Based on stratified Miettinen & Nurminen method. One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0.

Statistical analysis title	Difference in Percentage
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Statistical analysis description:

Based on Miettinen & Nurminen method stratified by prior FOLFOX/CAPOX + Bev induction response, cycles and mutation status.

Comparison groups	Olaparib + bevacizumab v Bevacizumab + chemotherapy
Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5272 ^[7]
Method	Miettinen and Nurminen
Parameter estimate	Difference in Percentage
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7
upper limit	6.5

Notes:

[7] - Based on stratified Miettinen & Nurminen method. One-sided p-value for testing H0: difference in % = 0 versus H1: difference in % > 0.

Secondary: Number of Participants Discontinuing Study Intervention Due to an AE

End point title	Number of Participants Discontinuing Study Intervention Due to an AE
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End point description:

An AE was defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who discontinued study intervention due to an AE was reported for each arm. The analysis population included all randomized participants who received at least 1 dose of study treatment.

End point type	Secondary
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End point timeframe:

Up to approximately 30 months

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	113	108	
Units: Participants	6	4	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with One or More Adverse Events (AE)

End point title	Number of Participants with One or More Adverse Events (AE)
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End point description:

An AE was defined as any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. The number of participants who experienced at least one AE was reported for each arm. The analysis population included all randomized participants who received at least 1 dose of study

treatment.

End point type	Secondary
End point timeframe:	
Up to approximately 30 months	

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	111	113	108	
Units: Participants	101	91	96	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR

End point title	Duration of Response (DOR) per RECIST 1.1 as Assessed by BICR
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End point description:

For participants who demonstrate a confirmed CR (disappearance of all target lesions) or PR (at least 30% decrease in the sum of diameters [SD] of target lesions) per RECIST 1.1, DOR is defined as the time from first documented evidence of a CR or PR until progressive disease (PD) or death. DOR for participants who had not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Per RECIST 1.1, PD is defined as at least 20% increase in SD of target lesions and an absolute increase of at least 5 mm in SD. The appearance of one or more new lesions is also considered PD. DOR assessments were based on BICR with confirmation. The DOR as assessed using RECIST 1.1 for all participants who experience a confirmed CR or PR will be presented. A value of 9999 indicates that no data were calculated. The analysis population included all randomized participants who received at least one dose of treatment and had either a CR or a PR.

End point type	Secondary
End point timeframe:	
Up to approximately 30 months	

End point values	Olaparib + bevacizumab	Olaparib	Bevacizumab + chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	2	5	
Units: Months				
median (confidence interval 95%)	9999 (3.6 to 9999)	9999 (9999 to 9999)	9999 (9999 to 9999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 38 months

Adverse event reporting additional description:

All-cause mortality=all randomized participants (n=335) & adverse events (AEs)=participants who received ≥ 1 dose of study treatment. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" & "Disease progression" unrelated to study treatment were excluded as AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Olaparib + Bevacizumab
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Reporting group description:

Participants received olaparib (300 mg twice daily [BID] oral) + Bevacizumab (5 mg/kg intravenous [IV] once every 2 weeks [Q2W]) until progressive disease or end of study.

Reporting group title	Bevacizumab + Chemotherapy
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Reporting group description:

Participants received investigator's choice of either bevacizumab (7.5 mg/kg IV once every three weeks (Q3W)) + capecitabine (1000 mg/m² BID for 14 days, then 7 days off, Q3W) or bevacizumab (5 mg/kg IV Q2W) + 5-FU (2400 mg/m² IV over 46 to 48 hours Q2W; bolus 5-FU (400 mg/m²) was added prior to infusional 5-FU, per local standards and at the investigator's discretion). Leucovorin or levoleucovorin 400 mg/m² (leucovorin) or 200 mg/m² (levoleucovorin) Q2W IV infusion was added per investigator's discretion. Treatment continued until progressive disease or end of study.

Reporting group title	Olaparib
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Reporting group description:

Participants received olaparib (300 mg BID) oral, until progressive disease or end of study.

Serious adverse events	Olaparib + Bevacizumab	Bevacizumab + Chemotherapy	Olaparib
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 111 (14.41%)	14 / 108 (12.96%)	13 / 113 (11.50%)
number of deaths (all causes)	49	52	51
number of deaths resulting from adverse events	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cancer pain			

subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
White blood cell count decreased			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Human rhinovirus test positive			

subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Injury, poisoning and procedural complications			
Stoma site haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Ischaemic stroke			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Seizure			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal stenosis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	2 / 113 (1.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nausea			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Intestinal perforation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 111 (0.90%)	1 / 108 (0.93%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Small intestinal perforation			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Vomiting			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 111 (0.00%)	2 / 108 (1.85%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 111 (0.90%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			
subjects affected / exposed	1 / 111 (0.90%)	1 / 108 (0.93%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Biliary tract infection			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonsillar abscess			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine infection			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Escherichia sepsis			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (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
Pneumonia			
subjects affected / exposed	0 / 111 (0.00%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin candida			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 111 (0.90%)	1 / 108 (0.93%)	1 / 113 (0.88%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 111 (0.00%)	1 / 108 (0.93%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 111 (0.90%)	0 / 108 (0.00%)	0 / 113 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Olaparib + Bevacizumab	Bevacizumab + Chemotherapy	Olaparib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	94 / 111 (84.68%)	86 / 108 (79.63%)	74 / 113 (65.49%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 111 (4.50%)	6 / 108 (5.56%)	6 / 113 (5.31%)
occurrences (all)	6	8	7
Blood creatinine increased			
subjects affected / exposed	4 / 111 (3.60%)	6 / 108 (5.56%)	2 / 113 (1.77%)
occurrences (all)	4	9	2
Weight decreased			
subjects affected / exposed	7 / 111 (6.31%)	6 / 108 (5.56%)	2 / 113 (1.77%)
occurrences (all)	7	6	2
Platelet count decreased			
subjects affected / exposed	2 / 111 (1.80%)	7 / 108 (6.48%)	6 / 113 (5.31%)
occurrences (all)	3	8	7
Neutrophil count decreased			
subjects affected / exposed	9 / 111 (8.11%)	3 / 108 (2.78%)	7 / 113 (6.19%)
occurrences (all)	20	5	8
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 111 (9.91%)	10 / 108 (9.26%)	0 / 113 (0.00%)
occurrences (all)	12	13	0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	3 / 111 (2.70%)	4 / 108 (3.70%)	7 / 113 (6.19%)
occurrences (all)	5	4	7
Headache			
subjects affected / exposed	7 / 111 (6.31%)	3 / 108 (2.78%)	1 / 113 (0.88%)
occurrences (all)	7	3	1
Dysgeusia			
subjects affected / exposed	10 / 111 (9.01%)	3 / 108 (2.78%)	3 / 113 (2.65%)
occurrences (all)	12	4	4
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 8	2 / 108 (1.85%) 2	1 / 113 (0.88%) 1
Neutropenia subjects affected / exposed occurrences (all)	9 / 111 (8.11%) 14	1 / 108 (0.93%) 3	5 / 113 (4.42%) 6
Anaemia subjects affected / exposed occurrences (all)	32 / 111 (28.83%) 35	8 / 108 (7.41%) 9	21 / 113 (18.58%) 25
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	16 / 111 (14.41%) 22	11 / 108 (10.19%) 14	8 / 113 (7.08%) 8
Fatigue subjects affected / exposed occurrences (all)	14 / 111 (12.61%) 15	10 / 108 (9.26%) 11	15 / 113 (13.27%) 15
Pyrexia subjects affected / exposed occurrences (all)	10 / 111 (9.01%) 10	7 / 108 (6.48%) 9	5 / 113 (4.42%) 5
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 9	2 / 108 (1.85%) 2	4 / 113 (3.54%) 5
Abdominal pain subjects affected / exposed occurrences (all)	19 / 111 (17.12%) 22	13 / 108 (12.04%) 14	8 / 113 (7.08%) 8
Vomiting subjects affected / exposed occurrences (all)	13 / 111 (11.71%) 17	11 / 108 (10.19%) 14	7 / 113 (6.19%) 13
Stomatitis subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 9	11 / 108 (10.19%) 13	4 / 113 (3.54%) 4
Nausea subjects affected / exposed occurrences (all)	31 / 111 (27.93%) 38	24 / 108 (22.22%) 35	23 / 113 (20.35%) 26
Diarrhoea			

subjects affected / exposed	11 / 111 (9.91%)	15 / 108 (13.89%)	9 / 113 (7.96%)
occurrences (all)	16	15	9
Constipation			
subjects affected / exposed	16 / 111 (14.41%)	14 / 108 (12.96%)	11 / 113 (9.73%)
occurrences (all)	18	15	11
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	6 / 111 (5.41%)	4 / 108 (3.70%)	0 / 113 (0.00%)
occurrences (all)	7	6	0
Cough			
subjects affected / exposed	6 / 111 (5.41%)	3 / 108 (2.78%)	3 / 113 (2.65%)
occurrences (all)	6	3	3
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 111 (0.90%)	8 / 108 (7.41%)	0 / 113 (0.00%)
occurrences (all)	1	8	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 111 (0.90%)	10 / 108 (9.26%)	3 / 113 (2.65%)
occurrences (all)	1	13	3
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 111 (5.41%)	5 / 108 (4.63%)	1 / 113 (0.88%)
occurrences (all)	6	7	1
Back pain			
subjects affected / exposed	8 / 111 (7.21%)	8 / 108 (7.41%)	3 / 113 (2.65%)
occurrences (all)	8	9	3
Arthralgia			
subjects affected / exposed	9 / 111 (8.11%)	8 / 108 (7.41%)	7 / 113 (6.19%)
occurrences (all)	13	9	8
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 111 (4.50%)	6 / 108 (5.56%)	4 / 113 (3.54%)
occurrences (all)	6	9	4
Metabolism and nutrition disorders			

Hyperglycaemia			
subjects affected / exposed	0 / 111 (0.00%)	10 / 108 (9.26%)	1 / 113 (0.88%)
occurrences (all)	0	12	1
Decreased appetite			
subjects affected / exposed	15 / 111 (13.51%)	12 / 108 (11.11%)	18 / 113 (15.93%)
occurrences (all)	15	13	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2019	The major changes of Amendment 1 (AM1) were addition of routine urinalysis prior to each dose of bevacizumab in Arms 1 & 3 and prior to Day 1 of each cycle in Arm 2, clarified reporting of Myelo Dysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) diagnosis throughout the study, clarified the definition of uncontrolled hypertension and clarified that participants with persistent alopecia and/or Grade ≤ 3 neuropathy from previous anticancer therapy were no longer excluded.
19 May 2020	The major changes of AM2 were addition of blood draws for olaparib pharmacokinetics and added information on participants who began treatment with bevacizumab must remain on bevacizumab throughout the study and participants who began treatment with biosimilar bevacizumab must remain on the same biosimilar throughout the study.
22 November 2021	The major changes of AM3 were addition of Blinded Independent Central Review (BICR) confirmation of non-PD status prior to randomization and added dose of Bevacizumab for Arm 3.
05 January 2022	The major changes of AM4 were addition of information related to need for confirmation of non-PD by BICR from induction imaging and the timing of the submission and addition of leucovorin to list of medications whose label must be checked for prohibited concomitant medications.
26 October 2022	The major changes of AM5 were stopped study enrollment due to futility and study participants discontinued study intervention and no crossover from either experimental arm to Standard of Care (SOC) arm was allowed. Participants on SOC were allowed to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported