Clinical trial results:
A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Maintenance Olaparib Monotherapy in Patients With gBRCA Mutated Metastatic Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum Based Chemotherapy

Summary

EudraCT number	2014-001589-85
Trial protocol	GB DE BE NL ES IT FR
Global end of trial date	27 January 2023

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	D081FC00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02184195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södartälje, Södartälje, Sweden, 151 85
Public contact	Global Clinical Leader, AstraZeneca AB, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Leader, AstraZeneca AB, +1 8772409479, information.center@astrazeneca.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	01 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of Olaparib maintenance monotherapy compared to placebo by progression free survival (PFS)

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2014
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	Belgium: 5
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 32
Worldwide total number of subjects	154
EEA total number of subjects	79

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)	113
From 65 to 84 years	41
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study randomised patients at a total of 59 study centres in 12 countries: United States of America (13), Germany (8), France (7), Israel (7), Spain (7), United Kingdom (6), Italy (4), Belgium (2), Republic of Korea (2), Australia (1), Canada (1) and Netherlands (1).

Pre-assignment

Screening details:

Screening Part 1 was only required if a patient's gBRCAm status was unknown and Screening Part 2 was for patients with known local germline BRCA (gBRCA) test. All other screening parameters were done as per the Study Schedule.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Olaparib 300 mg twice daily (bd)

Arm description:

Randomised participants received orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.

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:

Participants received 300mg twice daily (2 x 150mg) tablets.

Arm title	Placebo

Arm description:

Randomised participants received placebo tablets orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.

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

Dosage and administration details:

Participants received 300mg twice daily (2 x 150mg) tablets.

Number of subjects in period 1	Olaparib 300 mg twice daily (bd)	Placebo
Started	92	62
Completed	19	7
Not completed	73	55
Patient decision	5	2
Eligibility criteria not fulfilled	-	1
Death	67	44
Other	-	3
Lost to follow-up	1	5

Baseline characteristics

Reporting groups	
Reporting group title	Olaparib 300 mg twice daily (bd)
Reporting group description:	
Randomised participants received orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.	
Reporting group title	Placebo
Reporting group description:	
Randomised participants received placebo tablets orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.	

Reporting group values	Olaparib 300 mg twice daily (bd)	Placebo	Total
Number of subjects	92	62	154
Age categorical Units: Participants			
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)	64	49	113
From 65-84 years	28	13	41
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	58.2	56.4	
standard deviation	± 10.27	± 9.07	-
Sex: Female, Male Units: Participants			
Female	39	31	70
Male	53	31	84
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	0	5
White	82	59	141
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	2	6
Not Hispanic or Latino	88	60	148
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Olaparib 300 mg twice daily (bd)
Reporting group description:	
Randomised participants received orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.	
Reporting group title	Placebo
Reporting group description:	
Randomised participants received placebo tablets orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.	

Primary: Progression-free survival (PFS) by blinded independent central review (BICR) using modified Response Evaluation Criteria in Solid Tumours. This study used modified RECIST version (v) 1.1 (RECIST v1.1)

End point title	Progression-free survival (PFS) by blinded independent central review (BICR) using modified Response Evaluation Criteria in Solid Tumours. This study used modified RECIST version (v) 1.1 (RECIST v1.1)
End point description:	
To determine the efficacy of olaparib maintenance monotherapy compared to placebo by PFS. The PFS was defined as the time from randomisation until the date of objective radiological disease progression according to modified RECIST v1.1 or death (by any cause in the absence of disease progression) regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to disease progression. Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.	
End point type	Primary
End point timeframe:	
Up to 4 years	

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	7.4 (4.14 to 11.01)	3.8 (3.52 to 4.86)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo

Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0038
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.531
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.815

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

To determine the efficacy by assessment of OS of olaparib maintenance monotherapy compared to placebo. The OS was defined as the time from the date of randomization until death due to any cause.

Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.

End point type	Secondary

End point timeframe:

Upto 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	19.0 (15.28 to 26.32)	19.2 (14.32 to 26.12)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3487
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.564
upper limit	1.224

Secondary: Time from randomisation to second subsequent therapy or death (TSST)

End point title	Time from randomisation to second subsequent therapy or death (TSST)

End point description:

To determine the efficacy by assessment of TSST of olaparib maintenance monotherapy compared to placebo. The TSST was defined as time to second subsequent therapy or death.

Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	14.9 (9.13 to 19.78)	9.6 (8.34 to 12.98)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0111
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.611
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.418
upper limit	0.894

Secondary: Time from randomisation to first subsequent therapy or death (TFST)	
End point title	Time from randomisation to first subsequent therapy or death (TFST)

End point description:

To determine the efficacy by assessment of TFST of olaparib maintenance monotherapy compared to placebo. The TFST was defined as time to first subsequent therapy or death.

Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	9.0 (6.21 to 12.85)	5.4 (3.94 to 6.21)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.442
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.297
upper limit	0.658

Secondary: Time from randomisation to second progression (PFS2)	
End point title	Time from randomisation to second progression (PFS2)

End point description:

To determine efficacy by assessment of PFS2 of olaparib maintenance monotherapy compared to placebo. The PFS2 was defined as the time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary variable PFS or death.

Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	16.9 (8.21 to 23.85)	9.3 (8.15 to 13.54)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0613
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.659
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.426
upper limit	1.02

Secondary: Time from randomisation to study treatment discontinuation or death (TDT)

End point title	Time from randomisation to study treatment discontinuation or death (TDT)

End point description:

To determine the efficacy by assessment of TDT compared to placebo. compared to placebo. The TDT was defined as time to study treatment discontinuation or death.

Intention to treat (ITT): All randomised patients, Myriad confirmed Breast cancer susceptibility gene mutation (gBRCAm) subgroup.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Months				
median (confidence interval 95%)	7.5 (5.52 to 10.97)	3.8 (3.61 to 4.80)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.425
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.289
upper limit	0.627

Secondary: Disease control rate (DCR) by BICR using modified RECIST 1.1

End point title	Disease control rate (DCR) by BICR using modified RECIST 1.1

End point description:

Efficacy by assessment of disease control rate according to modified RECIST 1.1 of olaparib maintenance monotherapy compared to placebo.

Intention to treat (ITT): All randomised patients

End point type	Secondary

End point timeframe:

At 16 weeks

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	62		
Units: Participants				
Yes	51	24		
No	34	34		
Not evaluable/missing	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with objective response rate (ORR) by BICR using modified RECIST 1.1

End point title	Number of participants with objective response rate (ORR) by BICR using modified RECIST 1.1

End point description:

To determine efficacy by assessment of objective response rate according to modified RECIST 1.1 of olaparib maintenance monotherapy compared
to placebo. The ORR is defined as the number of with a BoR of CR and
PR according to the BICR data divided by the number of patients in the treatment group with measurable disease at baseline.

All randomised patients with measurable disease at baseline.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	49		
Units: Participants				
Participants with response	22	11		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3273
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.668
upper limit	3.61

Secondary: Adjusted mean change from baseline up to 6 months in global quality of life (QoL) score from the EORTC-QLQ-C30 questionnaire

End point title	Adjusted mean change from baseline up to 6 months in global quality of life (QoL) score from the EORTC-QLQ-C30 questionnaire

End point description:

To assess the effect of olaparib on health-related quality of life (QoL) as measured by the EORTC-QLQ-C30 global QoL scale. The EORTC-QLQ-C30 is defined as EORTC QLQ-C30: a questionnaire (30 questions) used to evaluate disease symptoms, functional impacts (eg, physical functioning), and HRQoL and to characterize clinical benefit from the patient perspective. The HRQoL score ranges from 0 to 100. A higher score indicates better QoL. A score change of 10 points was pre-defined as clinically meaningful.
bd twice daily.

Patient reported outcome (PRO) analysis set was defined as the analysis population for PRO data were a subset of the FAS (ITT) population who had evaluable baseline EORTC QLQ-C30 or QLQ-PAN26 forms where evaluable meant that at least 1 sub-scale baseline score could be determined from at least 1 of the 2 forms.

End point type	Secondary

End point timeframe:

From baseline up to 6 months

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	55		
Units: Unit on scale				
arithmetic mean (confidence interval 95%)	-1.03 (-3.826 to 1.759)	1.18 (-2.585 to 4.939)		

Statistical analyses

Statistical analysis title	Olaparib vs Placebo
Comparison groups	Olaparib 300 mg twice daily (bd) v Placebo

Number of subjects included in analysis	139
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.355
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.917
upper limit	2.496

Secondary: Number of participants with adverse events (AEs)

End point title	Number of participants with adverse events (AEs)

End point description:

To assess the safety and tolerability of olaparib maintenance monotherapy.
SAE: serious adverse events
CTCAE: Common Terminology Criteria for Adverse Events

Safety Analysis Set consisted of all patients who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 4 years

End point values	Olaparib 300 mg twice daily (bd)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	61		
Units: Participants				
Any AE	89	56		
Any AE of CTCAE Grade 3 or higher	44	15		
Any AE with outcome = death	1	0		
Any SAE (including events with outcome = death)	28	10		
AnyAE leading to withdrawal of olaparib/placebo	8	1		
Any AE leading to dose interruption	38	4		
Any AE leading to dose reduction	16	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent until 30 days after last dose + subsequent treatment-related events reported (maximum up to 4 years).

Adverse event reporting additional description:

Only 90 patients in Olaparib and 61 patients in Placebo group were reported for safety because 3 patients did not receive study treatment and were not reported in the safety table.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Randomised participants received placebo tablets orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.

Reporting group title	Olaparib 300 mg twice daily (bd)

Reporting group description:

Randomised participants received orally 300 mg bd which were made up of 2 x 150 mg tablets bd with 100 mg tablets used to manage dose reductions.

Serious adverse events	Placebo	Olaparib 300 mg twice daily (bd)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 61 (16.39%)	28 / 90 (31.11%)	
number of deaths (all causes)	52	67	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder papilloma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular stenosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 61 (3.28%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent malfunction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 61 (1.64%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 61 (1.64%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 61 (0.00%)	7 / 90 (7.78%)	
occurrences causally related to treatment / all	0 / 0	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric varices haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal perforation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Constipation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	1 / 61 (1.64%)	4 / 90 (4.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 61 (4.92%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 61 (1.64%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 61 (1.64%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bartholinitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 61 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Olaparib 300 mg twice daily (bd)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 61 (91.80%)	89 / 90 (98.89%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	10 / 90 (11.11%)	
occurrences (all)	1	16	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	8 / 90 (8.89%)	
occurrences (all)	1	14	
Blood creatinine increased			
subjects affected / exposed	2 / 61 (3.28%)	7 / 90 (7.78%)	
occurrences (all)	2	12	
Blood alkaline phosphatase increased			

subjects affected / exposed	3 / 61 (4.92%)	6 / 90 (6.67%)	
occurrences (all)	3	7	
Platelet count decreased			
subjects affected / exposed	0 / 61 (0.00%)	5 / 90 (5.56%)	
occurrences (all)	0	9	
Neutrophil count decreased			
subjects affected / exposed	0 / 61 (0.00%)	6 / 90 (6.67%)	
occurrences (all)	0	16	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	6 / 90 (6.67%)	
occurrences (all)	1	9	
Weight decreased			
subjects affected / exposed	3 / 61 (4.92%)	7 / 90 (7.78%)	
occurrences (all)	3	7	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 61 (4.92%)	5 / 90 (5.56%)	
occurrences (all)	3	12	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 61 (13.11%)	8 / 90 (8.89%)	
occurrences (all)	8	10	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 61 (3.28%)	6 / 90 (6.67%)	
occurrences (all)	2	6	
Dizziness			
subjects affected / exposed	3 / 61 (4.92%)	8 / 90 (8.89%)	
occurrences (all)	4	8	
Neuropathy peripheral			
subjects affected / exposed	7 / 61 (11.48%)	9 / 90 (10.00%)	
occurrences (all)	7	10	
Dysgeusia			
subjects affected / exposed	3 / 61 (4.92%)	6 / 90 (6.67%)	
occurrences (all)	3	6	
Paraesthesia			

subjects affected / exposed	4 / 61 (6.56%)	2 / 90 (2.22%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 61 (26.23%)	42 / 90 (46.67%)	
occurrences (all)	19	47	
Oedema peripheral			
subjects affected / exposed	5 / 61 (8.20%)	8 / 90 (8.89%)	
occurrences (all)	5	11	
Pyrexia			
subjects affected / exposed	4 / 61 (6.56%)	17 / 90 (18.89%)	
occurrences (all)	5	28	
Asthenia			
subjects affected / exposed	6 / 61 (9.84%)	16 / 90 (17.78%)	
occurrences (all)	6	24	
Influenza like illness			
subjects affected / exposed	0 / 61 (0.00%)	6 / 90 (6.67%)	
occurrences (all)	0	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 61 (16.39%)	26 / 90 (28.89%)	
occurrences (all)	12	35	
Thrombocytopenia			
subjects affected / exposed	4 / 61 (6.56%)	8 / 90 (8.89%)	
occurrences (all)	4	9	
Neutropenia			
subjects affected / exposed	4 / 61 (6.56%)	8 / 90 (8.89%)	
occurrences (all)	4	9	
Lymphopenia			
subjects affected / exposed	0 / 61 (0.00%)	5 / 90 (5.56%)	
occurrences (all)	0	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	10 / 61 (16.39%)	34 / 90 (37.78%)	
occurrences (all)	11	49	
Nausea			

subjects affected / exposed	15 / 61 (24.59%)	44 / 90 (48.89%)	
occurrences (all)	17	66	
Flatulence			
subjects affected / exposed	4 / 61 (6.56%)	2 / 90 (2.22%)	
occurrences (all)	4	3	
Abdominal distension			
subjects affected / exposed	6 / 61 (9.84%)	5 / 90 (5.56%)	
occurrences (all)	6	6	
Abdominal pain			
subjects affected / exposed	15 / 61 (24.59%)	26 / 90 (28.89%)	
occurrences (all)	17	39	
Dry mouth			
subjects affected / exposed	1 / 61 (1.64%)	8 / 90 (8.89%)	
occurrences (all)	2	8	
Abdominal pain upper			
subjects affected / exposed	9 / 61 (14.75%)	9 / 90 (10.00%)	
occurrences (all)	10	11	
Stomatitis			
subjects affected / exposed	3 / 61 (4.92%)	8 / 90 (8.89%)	
occurrences (all)	3	10	
Vomiting			
subjects affected / exposed	9 / 61 (14.75%)	23 / 90 (25.56%)	
occurrences (all)	12	49	
Constipation			
subjects affected / exposed	7 / 61 (11.48%)	25 / 90 (27.78%)	
occurrences (all)	8	33	
Dyspepsia			
subjects affected / exposed	5 / 61 (8.20%)	9 / 90 (10.00%)	
occurrences (all)	5	16	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 61 (3.28%)	5 / 90 (5.56%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	3 / 61 (4.92%)	10 / 90 (11.11%)	
occurrences (all)	4	11	
Cough			
subjects affected / exposed	2 / 61 (3.28%)	9 / 90 (10.00%)	
occurrences (all)	3	13	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 61 (4.92%)	12 / 90 (13.33%)	
occurrences (all)	4	15	
Pruritus			
subjects affected / exposed	4 / 61 (6.56%)	9 / 90 (10.00%)	
occurrences (all)	4	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 61 (1.64%)	8 / 90 (8.89%)	
occurrences (all)	1	8	
Anxiety			
subjects affected / exposed	2 / 61 (3.28%)	9 / 90 (10.00%)	
occurrences (all)	2	10	
Depression			
subjects affected / exposed	0 / 61 (0.00%)	5 / 90 (5.56%)	
occurrences (all)	0	6	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	4 / 61 (6.56%)	3 / 90 (3.33%)	
occurrences (all)	4	3	
Myalgia			
subjects affected / exposed	3 / 61 (4.92%)	6 / 90 (6.67%)	
occurrences (all)	5	6	
Pain in extremity			
subjects affected / exposed	4 / 61 (6.56%)	8 / 90 (8.89%)	
occurrences (all)	4	10	
Muscle spasms			
subjects affected / exposed	2 / 61 (3.28%)	6 / 90 (6.67%)	
occurrences (all)	2	9	
Arthralgia			

subjects affected / exposed	11 / 61 (18.03%)	19 / 90 (21.11%)	
occurrences (all)	11	25	
Back pain			
subjects affected / exposed	13 / 61 (21.31%)	24 / 90 (26.67%)	
occurrences (all)	13	28	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 61 (3.28%)	12 / 90 (13.33%)	
occurrences (all)	2	21	
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	6 / 90 (6.67%)	
occurrences (all)	0	8	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 61 (1.64%)	8 / 90 (8.89%)	
occurrences (all)	1	15	
Decreased appetite			
subjects affected / exposed	4 / 61 (6.56%)	24 / 90 (26.67%)	
occurrences (all)	5	29	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2014	Information in Section 1.4.1.1 Myelodysplastic syndrome/acute myeloid leukaemia, Table 1 Study Schedule, and Section 4.2 Treatment period were updated to ensure protocol consistency and correct typo.
28 February 2015	The study is sized based on the number of events required to detect superiority at the time of the primary PFS analysis. To ensure that the type I error is controlled at the 2.5% 1-sided level overall, the significance level was previously allocated between the interim and final PFS analyses, taking account of correlation between them. Removal of the interim superiority analysis as per FDA recommendation means that a 2.5% significance level can be allocated to the primary PFS analysis and therefore the number of PFS events required at the time of the primary PFS analysis is slightly reduced. Removal of the superiority analysis at the time of the interim analysis as per FDA recommendation, therefore OS and PFS2 will not be analysed at this time. To change the type of analysis used for EORTC QLQ-C30 global QoL score to MMRM analysis of adjusted mean change from baseline, which is independent of minimal important differences (MID) values that are not well-defined and is suitable for analysing continuous responses measured repeatedly over time. The MMRM statistical analysis will be based on actual scores, rather than pre-selected MIDs, and will analyse data from all time points. A supportive analysis of global HRQoL improvement rate will be conducted using the 'generic' cut off of 10% change from baseline as suggested in Osoba et al 2005. To provide additional data on the QT study that has been conducted. To ensure that the patient can start treatment within 8 weeks of their last chemotherapy dose. Due to the screening period, the original text meant that patients would have had to start treatment within 7 weeks of their last chemotherapy dose, this was not the intention. Extending this window by 7 days makes it clearer for the investigators and reduces the risk of protocol deviations.
30 August 2019	Updated with Regulatory Agency identifiers. Updated the study period based on the current study status. Clarification provided for patient continuing to receive treatment as open labelled drug via manual supply outside of the study setting once the IVRS/IWRS has been closed. Included this new section to clarify the SAEs reporting post 30-day follow-up period. Clarification text added on how safety reporting is performed in study. Clarification text provided on overdose. Clarification provided on the timing of follow-up for pregnancy, occurring during study treatment. Clarification provided on the dose reduction scenarios during study treatment period. Latest information on management of study drug related toxicity were added. Provide solution on the medication supply when achieving study closure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported