Clinical trial results:
Phase II randomised, double blind, multicentre study to assess the efficacy of AZD2281 in the treatment of patients with platinum sensitive serous ovarian cancer following treatment with two or more platinum containing regimens

Summary

EudraCT number	2008-003439-18
Trial protocol	GB BE DE PL CZ ES EE FR AT NL
Global end of trial date	12 October 2023

Results information

Result version number	v1 (current)
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	D0810C00019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	1 Francis Crick Avenue, Cambridge Biomedical Campus, United Kingdom, CB2 0AA
Public contact	Tsveta Milenkova, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Anitra Fielding, AstraZeneca, ClinicalTrialTransparency@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	26 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2012
Global end of trial reached?	Yes
Global end of trial date	12 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy (assessed by PFS) of olaparib (capsule formulation) compared to placebo in the overall population.

Protection of trial subjects:

Repeat dose interruptions are to be allowed as required, for a maximum of 4 weeks (28 days) on each occasion. Where toxicity reoccur following re-challenge with AZD2281 or matching placebo, and where further dose interruptions are considered inadequate for management of toxicity, then the patient is to be considered for dose reduction or must permanently discontinue treatment. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of AZD2281 or matching placebo. If this has not resolved to at least NCI-CTCAE grade 1 by the dose interruption period and/or the patient has undergone 2 dose reductions already, the patient must discontinue treatment. When toxicity resolves, the patient may restart with a 50% does reduction

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2008
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: 31
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Israel: 26
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	United States: 44
Country: Number of subjects enrolled	Ukraine: 14

Worldwide total number of subjects	265
EEA total number of subjects	90

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)	185
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 28 August 2008 and the last patient was enrolled on 9 February 2010. Patients were enrolled at 82 centres in 16 countries. Of the 326 patients enrolled, 265 were randomized

Pre-assignment

Screening details:

It was planned that 250 women with advanced platinum sensitive serous ovarian cancer who had received 2 or more previous platinum-containing regimens and demonstrated an objective stable maintained response in the last platinum regimen prior to enrolment were to receive olaparib 400 mg bd or matching placebo in a 1:1 ratio. 265 randomised.

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

Blinding implementation details:

AZD2281 and placebo matched AZD2281 treatments were blinded. The active and placebo capsules were identical and presented in the same packaging to ensure blinding of the study medication.

Arms

Are arms mutually exclusive?	Yes
Arm title	olaparib 400 mg bd

Arm description:

AZD2281 olaparib (AZD2281) 400 mg oral capsules twice daily

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:

8 x 50 mg capsules consumed orally over 28 days at the same time each day with 240ml of water. they were swallowed whole at least 1 hour after food, and food could not be consumed 20 hours after taking a capsule

Arm title	Placebo bd

Arm description:

olaparib matching placebo oral capsules twice daily

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

Dosage and administration details:

the placebo was taken in the same way and form as the olaparib capsules

Number of subjects in period 1	olaparib 400 mg bd	Placebo bd
Started	136	129
Completed	28	11
Not completed	108	118
Adverse event, serious fatal	98	112
Lost to follow-up	2	3
Voluntary Discontinuation of Patient	7	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	olaparib 400 mg bd
Reporting group description:	
AZD2281 olaparib (AZD2281) 400 mg oral capsules twice daily	
Reporting group title	Placebo bd
Reporting group description:	
olaparib matching placebo oral capsules twice daily	

Reporting group values	olaparib 400 mg bd	Placebo bd	Total
Number of subjects	136	129	265
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)	91	94	185
From 65-84 years	45	35	80
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.9	58.5	
standard deviation	± 10.95	± 9.89	-
Gender, Male/Female Units: Subjects			
Female	136	129	265
Male	0	0	0
Time to progression			
The time to disease progression from the completion of the penultimate platinum containing therapy (last dose) prior to enrolment on the study.			
Units: Subjects			
>6 to 12 months	53	54	107
>12 months	83	75	158
Objective response			
Objective response to the last platinum containing regimen prior to enrolment on the study: -CR-Complete Response (defined as normal radiological findings and CA-125 within the normal range) -PR-Partial Response (defined as a RECIST PR and/or GCIG CA-125 response)			
Units: Subjects			
Complete response	57	63	120
Partial response	79	66	145
Race Units: Subjects			
White	130	126	256
Black or African American	2	1	3

Asian	2	2	4
Other	2	0	2
Jewish descent Units: Subjects			
Not Jewish Descent	115	112	227
Ashkenazi Jewish	17	12	29
sephardic Jewish	1	1	2
Mizrahim Jewish	2	1	3
Other	0	3	3
Missing	1	0	1
ECOG performance status Units: Subjects			
(0) Normal activity	110	95	205
(1) restricted activity	23	30	53
(2) in bed <=50% of the time	1	2	3
Unknown	2	2	4
Primary Tumour Location Units: Subjects			
Ovary	119	109	228
Fallopian tube	3	3	6
Primary peritoneal	14	16	30
Other	0	1	1
Tumour Grade Units: Subjects			
Well differentiated (G1)	0	0	0
Mod. Differentiated (G2)	36	34	70
Poorly differentiated (G3)	97	89	186
undifferentiated (G4)	2	4	6
unassessable (GX)	1	2	3
FIGO stage Units: Subjects			
Stage IB	0	1	1
stage IC	3	3	6
Stage II	1	0	1
Stage IIA	2	1	3
Stage IIB	3	1	4
Stage IIC	5	6	11
Stage III	10	7	17
Stage IIIA	4	3	7
Stage IIIB	8	12	20
Stage IIIC	81	76	157
Stage IV	17	17	34
Unknown	2	2	4
Platinum sensitivity Units: Subjects			
>6 - ≤12 months	53	54	107
>12 months	83	75	158
Objective Response Units: Subjects			
Complete Response	57	63	120
Partial Response	79	66	145

Number of weeks from completion of last platinum therapy to randomisation Units: Subjects			
≤8 weeks	131	125	256
>8 to ≤9 weeks	1	3	4
>9 to ≤10 weeks	0	1	1
>10 to ≤11 weeks	0	0	0
>11 to ≤12 weeks	0	0	0
>12 weeks	3	0	3
not progressing	1	0	1
Time from completion of final prior platinum chemotherapy to randomisation Units: days			
arithmetic mean	43.2	40.0	
full range (min-max)	15 to 517	14 to 70	-
Most recent progression to randomisation Units: days			
arithmetic mean	213.9	218.2	
full range (min-max)	90 to 1123	56 to 1115	-

End points

End points reporting groups	
Reporting group title	olaparib 400 mg bd
Reporting group description:	
AZD2281 olaparib (AZD2281) 400 mg oral capsules twice daily	
Reporting group title	Placebo bd
Reporting group description:	
olaparib matching placebo oral capsules twice daily	

Primary: Progression Free Survival (PFS) (According to Response Evaluation Criteria in Solid Tumours [RECIST])	
End point title	Progression Free Survival (PFS) (According to Response Evaluation Criteria in Solid Tumours [RECIST])
End point description:	
PFS was defined as the time from randomisation to the earlier date of radiological progression (per RECIST criteria) or death by any cause in the absence of objective progression. [Full analysis set (FAS)]	
End point type	Primary
End point timeframe:	
Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter	

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Number of progressions	60	94		

Statistical analyses

Statistical analysis title	Primary analysis of PFS
Statistical analysis description:	
HR < 1 favours olaparib	
Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.00001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.49

Primary: BRCA mutant subgroup: Progression Free Survival (PFS)

End point title	BRCA mutant subgroup: Progression Free Survival (PFS)

End point description:

PFS was defined as the time from randomisation to the earlier date of radiological progression (per RECIST criteria) or death by any cause in the absence of objective progression. [BRCA mutant analysis set]

End point type	Primary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	62		
Units: Number of progressions	26	46		

Statistical analyses

Statistical analysis title	Analysis of PFS for BRCA mutant subgroup

Statistical analysis description:

HR < 1 favours olaparib

Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.00001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.31

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS = time from randomisation to date of death from any cause. Patients who had not died at time of analysis were censored at last date patient was known to be alive.

End point type	Secondary

End point timeframe:

Follow up every 12 weeks post progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Number of deaths	98	112		

Statistical analyses

Statistical analysis title	Analysis of OS

Statistical analysis description:

HR < 1 favours olaparib

Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.02 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.95

Notes:

[1] - p-value is nominal

Secondary: BRCA mutant subgroup: Overall Survival (OS)

End point title	BRCA mutant subgroup: Overall Survival (OS)

End point description:

OS = time from randomisation to date of death from any cause. Patients who had not died at time of analysis were censored at last date patient was known to be alive. BRCA mutant subset.

End point type	Secondary

End point timeframe:

Follow up every 12 weeks post progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	62		
Units: Number of deaths	49	50		

Statistical analyses

Statistical analysis title	OS analysis for BRCA mutant subgroup
Statistical analysis description: HR < 1 favours olaparib	
Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.02 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.93

Notes:

[2] - p-value is nominal

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate was defined as the percentage of patients who have at least 1 confirmed visit response of CR or PR or have demonstrated SD or NED for at least 23 weeks (ie, 24 weeks +/- 1 week) prior to any evidence of progression. [FAS]

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: percentage of participants				
number (not applicable)	52.9	24.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) (According to RECIST)

End point title	Objective Response Rate (ORR) (According to RECIST)

End point description:

For each treatment group, the ORR was the number of Complete Response (CR) and Partial Response (PR) divided by the number of patients in the group in the FAS with measurable disease at baseline (displayed as a percentage below). Evaluable for response set

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	48		
Units: percentage of participants				
number (not applicable)	12.3	4.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Tumour Size at Week 24

End point title	Percentage Change From Baseline in Tumour Size at Week 24

End point description:

Percentage change from baseline to Week 24 in target tumour size.

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Percent change in tumour size				
least squares mean (full range (min-max))	0.0 (-100.0 to 45.0)	33.5 (-36.4 to 39.4)		

Statistical analyses

Statistical analysis title	Statistical analysis of the tumour size change
Statistical analysis description: LS mean < 0 favours olaparib	
Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01221
Method	ANCOVA
Parameter estimate	Difference in LS means
Point estimate	-33.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.4
upper limit	-7.4

Secondary: Duration of Response

End point title	Duration of Response
End point description: Duration of response = time from assessment prior to timepoint where PR or CR confirmed (i.e. initial assessment of PR/CR), until earliest date of objective progression or death. [Responding patients only]. There were insufficient responses to enable conclusions to be drawn.	
End point type	Secondary
End point timeframe: Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/-1 week) thereafter	

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Number of responses	7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response

End point title	Best Objective Response

End point description:

Best overall response from radiologic assessments. [FAS]

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1week) for the first 60 weeks, then every 24 weeks (+/- 1 week) thereafter

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Participants				
Complete Response	0	0		
Partial Response	7	2		
No evidence of disease	49	42		
Stable Disease >= 11 weeks	46	25		
Disease Progression	24	55		
Not Evaluable	10	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Percentage Change in Cancer Antigen 125 (CA-125) Levels

End point title	Best Percentage Change in Cancer Antigen 125 (CA-125) Levels

End point description:

Best percentage change from baseline in CA-125 level

End point type	Secondary

End point timeframe:

CA-125 was measured at baseline then every 28 days on treatment

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	128		
Units: percentage of change				
arithmetic mean (full range (min-max))	-16.67 (-100.00 to 346.15)	0.00 (-99.50 to 1436.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: RECIST and CA-125 Response Separately and Combined

End point title	RECIST and CA-125 Response Separately and Combined

End point description:

RECIST and CA-125 response separately and combined [Patients evaluable for either CA-125 response or RECIST response]

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1week) for the first 60 weeks, then every 24 weeks (+/- 1 week) thereafter and monthly for CA-125 measurements

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	53		
Units: Participants				
RECIST Response	16	2		
Confirmed RECIST Response	7	2		
Unconfirmed RECIST response	9	0		
CA-125 Response	1	1		
Confirmed RECIST or CA-125 Response	8	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement Rate for FACT-O Symptom Index (FOSI)

End point title	Improvement Rate for FACT-O Symptom Index (FOSI)

End point description:

The percentage of patients with an improvement in FOSI. Improvement was defined as a change from baseline of greater than or equal to +3. [Evaluable for FOSI set]

End point type	Secondary

End point timeframe:

Patient reported outcome questionnaire completed at baseline then every 28 days up to disease

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: percentage of evaluable participants				
number (not applicable)	17.1	14.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Earlier of CA-125 or RECIST Progression

End point title	Time to Earlier of CA-125 or RECIST Progression

End point description:

Time from randomisation to the earlier date of radiological progression (per RECIST criteria) or CA-125 or death by any cause in the absence of objective progression. [FAS]

End point type	Secondary

End point timeframe:

Radiologic scans performed at baseline then every 12 weeks (+/- 1 week) for the first 60 weeks, then every 24 weeks (+/- 1 week) thereafter and monthly for CA-125 measurements

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	129		
Units: Number of progressions	66	106		

Statistical analyses

Statistical analysis title	Analysis of time to CA-125/RECIST progression

Statistical analysis description:

HR < 1 favours olaparib

Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.00001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.47

Secondary: Improvement Rate for Trial Outcome Index (TOI)

End point title	Improvement Rate for Trial Outcome Index (TOI)

End point description:

The percentage of patients with an improvement in TOI. Improvement was defined as a change from baseline of greater than or equal to +7. [Evaluable for TOI set]

End point type	Secondary

End point timeframe:

Patient reported outcome questionnaire completed at baseline then every 28 days up to disease progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	111		
Units: percentage of evaluable participants				
number (not applicable)	20.0	18.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Trial Outcome Index(TOI)Time to Worsening

End point title	Trial Outcome Index(TOI)Time to Worsening

End point description:

The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O. [Evaluable for TOI set]

End point type	Secondary

End point timeframe:

Patient reported outcome questionnaire completed at baseline then every 28 days up to disease progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	111		
Units: Number worsening	64	56		

Statistical analyses

Statistical analysis title	Analysis of TOI time to worsening
Statistical analysis description: HR < 1 favours olaparib	
Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.68
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.55

Secondary: Improvement Rate for Total Functional Analysis of Cancer Therapy - Ovarian (FACT-O)

End point title	Improvement Rate for Total Functional Analysis of Cancer Therapy - Ovarian (FACT-O)
End point description: The percentage of patients with an improvement in total FACT-O. Improvement was defined as a change from baseline of greater than or equal to +9. [Evaluable for FACT-O set]	
End point type	Secondary
End point timeframe: Patient reported outcome questionnaire completed at baseline then every 28 days up to disease progression	

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	111		
Units: percentage of evaluable participants				
number (not applicable)	21.1	18.9		

Statistical analyses

No statistical analyses for this end point

Secondary: FACT-O Symptom Index (FOSI) Time to Worsening

End point title	FACT-O Symptom Index (FOSI) Time to Worsening

End point description:

The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O. [Evaluable for FOSI set]

End point type	Secondary

End point timeframe:

Patient reported outcome questionnaire completed at baseline then every 28 days up to disease progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Number worsening	77	67		

Statistical analyses

Statistical analysis title	Analysis of FOSI time to worsening

Statistical analysis description:

HR < 1 favours olaparib

Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.23
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.71

Secondary: Functional Analysis of Cancer Therapy - Ovarian (FACT-O) Time to Worsening

End point title	Functional Analysis of Cancer Therapy - Ovarian (FACT-O) Time to Worsening

End point description:

The time to worsening was compared between treatments for each of the TOI, FOSI and total FACT-O. [Evaluable for FACT-O set]

End point type	Secondary

End point timeframe:

Patient reported outcome questionnaire completed at baseline then every 28 days up to disease progression

End point values	olaparib 400 mg bd	Placebo bd		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	111		
Units: Number worsening	72	63		

Statistical analyses

Statistical analysis title	Analysis of FACT-O time to worsening

Statistical analysis description:

HR < 1 favours olaparib

Comparison groups	olaparib 400 mg bd v Placebo bd
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.39
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.64

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events will be collected from time of signed informed consent throughout the treatment period and up to and including the 30-day follow-up period

Adverse event reporting additional description:

128 participants in Placebo as 1 participant withdrew consent prior to treatment

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Olaparib 400 mg bd

Reporting group description: -

Serious adverse events	Placebo	Olaparib 400 mg bd	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 128 (8.59%)	31 / 136 (22.79%)	
number of deaths (all causes)	77	77	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE LEUKAEMIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER CANCER			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRADUCTAL PROLIFERATIVE BREAST LESION			

subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAPILLARY THYROID CANCER			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ESSENTIAL HYPERTENSION			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
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			
PYREXIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERNIA PAIN			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
IODINE ALLERGY			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ASTHMA			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	0 / 128 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHIECTASIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FEMUR FRACTURE			

subjects affected / exposed	0 / 128 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL HAEMATOMA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIOVASCULAR INSUFFICIENCY			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SYNCOPE			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGIC STROKE			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
APHASIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
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			
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PANCYTOPENIA			
subjects affected / exposed	0 / 128 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	0 / 128 (0.00%)	3 / 136 (2.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
INTRA-ABDOMINAL HAEMORRHAGE			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	1 / 128 (0.78%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED GASTRIC EMPTYING			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
subjects affected / exposed	2 / 128 (1.56%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	0 / 128 (0.00%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			

subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL INCARCERATED HERNIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	3 / 128 (2.34%)	2 / 136 (1.47%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOPOROSIS			

subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
LIVER ABSCESS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE EXACERBATION OF CHRONIC OBSTRUCTIVE AIRWAYS DISEASE			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOPHTHALMITIS			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
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 / 128 (0.00%)	1 / 136 (0.74%)	
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	1 / 128 (0.78%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT			

INFECTION			
subjects affected / exposed	0 / 128 (0.00%)	1 / 136 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 128 (0.78%)	0 / 136 (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 400 mg bd	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 128 (86.72%)	129 / 136 (94.85%)	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	2 / 128 (1.56%)	9 / 136 (6.62%)	
occurrences (all)	2	10	
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	16 / 128 (12.50%)	5 / 136 (3.68%)	
occurrences (all)	18	6	
HYPERTENSION			
subjects affected / exposed	4 / 128 (3.13%)	10 / 136 (7.35%)	
occurrences (all)	4	10	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	9 / 128 (7.03%)	21 / 136 (15.44%)	
occurrences (all)	10	28	
DYSGEUSIA			
subjects affected / exposed	8 / 128 (6.25%)	22 / 136 (16.18%)	
occurrences (all)	8	26	
HEADACHE			
subjects affected / exposed	17 / 128 (13.28%)	29 / 136 (21.32%)	
occurrences (all)	20	47	
NEUROPATHY PERIPHERAL			

subjects affected / exposed	3 / 128 (2.34%)	12 / 136 (8.82%)	
occurrences (all)	5	13	
PARAESTHESIA			
subjects affected / exposed	3 / 128 (2.34%)	7 / 136 (5.15%)	
occurrences (all)	5	9	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	50 / 128 (39.06%)	73 / 136 (53.68%)	
occurrences (all)	57	92	
ASTHENIA			
subjects affected / exposed	12 / 128 (9.38%)	19 / 136 (13.97%)	
occurrences (all)	15	26	
PYREXIA			
subjects affected / exposed	4 / 128 (3.13%)	13 / 136 (9.56%)	
occurrences (all)	4	16	
OEDEMA PERIPHERAL			
subjects affected / exposed	6 / 128 (4.69%)	12 / 136 (8.82%)	
occurrences (all)	7	14	
Blood and lymphatic system disorders			
NEUTROPENIA			
subjects affected / exposed	5 / 128 (3.91%)	7 / 136 (5.15%)	
occurrences (all)	7	8	
ANAEMIA			
subjects affected / exposed	7 / 128 (5.47%)	26 / 136 (19.12%)	
occurrences (all)	8	32	
Gastrointestinal disorders			
ABDOMINAL PAIN LOWER			
subjects affected / exposed	10 / 128 (7.81%)	7 / 136 (5.15%)	
occurrences (all)	10	7	
ABDOMINAL DISTENSION			
subjects affected / exposed	11 / 128 (8.59%)	21 / 136 (15.44%)	
occurrences (all)	13	24	
ABDOMINAL DISCOMFORT			
subjects affected / exposed	7 / 128 (5.47%)	6 / 136 (4.41%)	
occurrences (all)	7	7	
ABDOMINAL PAIN UPPER			

subjects affected / exposed	11 / 128 (8.59%)	25 / 136 (18.38%)	
occurrences (all)	11	28	
CONSTIPATION			
subjects affected / exposed	14 / 128 (10.94%)	30 / 136 (22.06%)	
occurrences (all)	15	41	
DIARRHOEA			
subjects affected / exposed	31 / 128 (24.22%)	36 / 136 (26.47%)	
occurrences (all)	39	62	
DYSPEPSIA			
subjects affected / exposed	11 / 128 (8.59%)	27 / 136 (19.85%)	
occurrences (all)	11	34	
NAUSEA			
subjects affected / exposed	46 / 128 (35.94%)	96 / 136 (70.59%)	
occurrences (all)	58	128	
STOMATITIS			
subjects affected / exposed	4 / 128 (3.13%)	12 / 136 (8.82%)	
occurrences (all)	4	15	
VOMITING			
subjects affected / exposed	18 / 128 (14.06%)	47 / 136 (34.56%)	
occurrences (all)	20	91	
ABDOMINAL PAIN			
subjects affected / exposed	34 / 128 (26.56%)	35 / 136 (25.74%)	
occurrences (all)	51	44	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	8 / 128 (6.25%)	17 / 136 (12.50%)	
occurrences (all)	8	20	
COUGH			
subjects affected / exposed	13 / 128 (10.16%)	23 / 136 (16.91%)	
occurrences (all)	14	33	
Skin and subcutaneous tissue disorders			
RASH			
subjects affected / exposed	12 / 128 (9.38%)	8 / 136 (5.88%)	
occurrences (all)	13	8	
PRURITUS			

subjects affected / exposed	3 / 128 (2.34%)	8 / 136 (5.88%)	
occurrences (all)	3	10	
DRY SKIN			
subjects affected / exposed	7 / 128 (5.47%)	3 / 136 (2.21%)	
occurrences (all)	7	3	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	9 / 128 (7.03%)	9 / 136 (6.62%)	
occurrences (all)	10	9	
DEPRESSION			
subjects affected / exposed	9 / 128 (7.03%)	11 / 136 (8.09%)	
occurrences (all)	10	11	
ANXIETY			
subjects affected / exposed	5 / 128 (3.91%)	8 / 136 (5.88%)	
occurrences (all)	6	8	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	18 / 128 (14.06%)	24 / 136 (17.65%)	
occurrences (all)	19	36	
BACK PAIN			
subjects affected / exposed	14 / 128 (10.94%)	25 / 136 (18.38%)	
occurrences (all)	16	37	
MUSCLE SPASMS			
subjects affected / exposed	5 / 128 (3.91%)	13 / 136 (9.56%)	
occurrences (all)	5	20	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	8 / 128 (6.25%)	10 / 136 (7.35%)	
occurrences (all)	8	10	
MYALGIA			
subjects affected / exposed	8 / 128 (6.25%)	7 / 136 (5.15%)	
occurrences (all)	9	7	
PAIN IN EXTREMITY			
subjects affected / exposed	7 / 128 (5.47%)	12 / 136 (8.82%)	
occurrences (all)	8	16	
Infections and infestations			

URINARY TRACT INFECTION			
subjects affected / exposed	6 / 128 (4.69%)	15 / 136 (11.03%)	
occurrences (all)	6	21	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	8 / 128 (6.25%)	18 / 136 (13.24%)	
occurrences (all)	8	24	
NASOPHARYNGITIS			
subjects affected / exposed	14 / 128 (10.94%)	21 / 136 (15.44%)	
occurrences (all)	17	26	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	17 / 128 (13.28%)	29 / 136 (21.32%)	
occurrences (all)	22	34	
HYPOMAGNESAEMIA			
subjects affected / exposed	9 / 128 (7.03%)	8 / 136 (5.88%)	
occurrences (all)	10	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2008	Primary objective expanded to include patients with HRD tumours
27 November 2008	The window between last dose of platinum-containing regimen and starting study treatment extended. Clarification of aspects of the study design
27 November 2008	The following text regarding achievement of primary endpoint added: Tumour evaluations using CT/MRI according to RECIST will continue in the study until sufficient efficacy events for the analysis of PFS in the overall population, and the HRD sub-group have been confirmed. At this point investigators will be notified that CT/MRI for study purposes are no longer required
27 November 2008	Assessment Visit windows amended. Clarification of HRQL, CA-125, and CT/MRI assessments
27 November 2008	Amendment of inclusion criterion
27 November 2008	Amendment of exclusion criterion
27 November 2008	Amendment of restrictions
27 November 2008	Addition of following text to discontinuation criteria: Patients may continue to receive study treatment following objective progression provided that, in the opinion of the investigator, the patient is benefiting from the treatment and does not meet any other discontinuation criteria
27 November 2008	Amendment of management of toxicity of olaparib text
14 May 2009	Number of recruiting sites increased
14 May 2009	Statistical methods text added
14 May 2009	Visit days amended
14 May 2009	Inclusion criteria amended
14 May 2009	Restriction text amended
14 May 2009	Procedures for randomisation amended with the addition of the following text: It is recommended that patients commence study treatment as soon as possible after randomisation, and ideally within 3 days
14 May 2009	Screening text amended
17 May 2010	Interim analysis of PFS
17 May 2010	Analysis of PFS in the HRD population was removed as a co-primary objective.

17 May 2010	Secondary objective text "To obtain archival tumour samples for analyses of candidate biomarkers to identify the HRD subset of tumours for which increased sensitivity to AZD2281 is expected." Changed to "To enable retrospective identification of tumours with increased sensitivity to olaparib by obtaining archival tumour samples for potential biomarker analyses." and moved to exploratory objective. Associated secondary outcome variable text on candidate biomarkers moved to exploratory variable section
17 May 2010	Clarification that subset of patients with HRD tumours removed as an analysis population
17 May 2010	Addition of text on pneumonitis events
17 May 2010	Wording on contraception updated
17 May 2010	The number and total volume of blood to be drawn from each patient for clinical chemistry and haematology assessments was decreased
17 May 2010	The end of trial definition has been changed
02 November 2010	Estimated date of last subject completed changed from Q3 2010 to Q4 2012
02 November 2010	Changed assessments for survival from every 12 weeks to every 8 weeks following treatment discontinuation
02 November 2010	Patients and investigators will not be routinely unblinded to study treatment prior to the final OS analysis. Following a request to the study sponsor, patients and investigators may be unblinded on an individual basis if the information is essential for safety or subsequent treatment decisions following confirmed disease progression
02 November 2010	Patients who remain on study treatment will attend clinic every 8 weeks and the following assessments will be performed: physical examination, ECOG status, vital signs, haematology, clinical chemistry, urinalysis, AEs and concomitant medications. Dispensing visits may be performed on a 4 weekly basis, at the investigator's discretion, at which AEs must be assessed as a minimum. Following the approval of amendment 4, and in line with the frequency of safety assessments, olaparib will be dispensed to patients every 56 days if local practice permits. No further CA-125 plasma samples will be required, no amylase and lipase will be tested, no HRQL assessments will be required, and aPTT and INR will only require testing when clinically indicated
01 November 2011	Addition of an interim analysis of OS, to be performed when approximately 100 deaths have occurred, with the final analysis of survival at the same maturity as the PFS analysis.
01 November 2011	Update of list of events olaparib is associated with; bone marrow findings consistent with myelodysplastic syndrome/acute myeloid leukaemia added to study treatment discontinuation criteria; amendment of management of toxicity of olaparib text; section added on bone marrow or blood cytogenetic analysis
17 October 2012	Estimated date of last subject completed changed from Q4 2012 to Q1 2015
17 October 2012	After the interim analysis of OS is performed when approximately 100 deaths have occurred, a subsequent interim analysis of survival will be performed at approximately the same maturity as the PFS analysis (~60% maturity) (per amendment 05). Additional analyses of OS data may be performed to meet Regulatory Agency requests or to assist in the understanding of the data, which in turn supports decision making at AstraZeneca. The final survival analysis will be performed at approximately 85% maturity (~222 deaths). Collection of survival data will not continue beyond 85% maturity

17 October 2012	Amendment of text describing circumstances under which code may be broken for SAEs, to clarify that investigators and patients would not be unblinded
17 October 2012	Timescale within which patients must be contacted following the data cut-off for the primary and all subsequent survival analyses to provide complete survival data reduced from 1 week to 4 days
17 October 2012	Time for reporting SAEs and follow up information to Parexel reduced from 'no later than the end of the next business day' to 'no later than 24 hours' of becoming aware of it
17 October 2012	The data cut-off date for analysis of the primary endpoint will be established when a total of 137 PFS events have been observed in the overall population. Analysis of OS will be performed when approximately 100 deaths have occurred and again at approximately the same maturity as the PFS analysis (~60% maturity). The final survival analysis will be performed at approximately 85% maturity (~222 deaths). There will be a final data cut-off defined when OS meets approximately 85% maturity, when the clinical study database will closed to new data and all patients will be unblinded. Patients who are receiving active treatment can either choose to discontinue from the study or where the investigator believes patients are gaining clinical benefit, patients may continue to receive study treatment. All patients will receive follow up care in accordance with standard local clinical practice.
30 May 2013	Section 7.2.3.3 was further clarified and Section 7.2.3.4 was added to request follow-up of current survival status at the final OS analysis. This includes those patients that withdraw consent or are classified as "lost to follow up."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

For OM DoR: The subset of patients evaluable for response who responded to study treatment.Values in results table may be under-estimates as some patients had not progressed at final analysis,so true duration is likely to be greater than in database.

Notes: