



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

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

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

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| 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 |

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| 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: