# Clinical trial results:
# Best Approach in Recurrent-Ovarian-Cancer-with Cediranib-Olaparib: an Italian multicenter randomized phase II study of weekly paclitaxel vs. Cediranib-Olaparib with continuous schedule vs. Cediranib-Olaparib with intermittent schedule in patients with platinum resistant high grade epithelial ovarian, fallopian tube, or primary peritoneal cancer_The BAROCCO study

## Summary

| | |
|---|---|
| EudraCT number | 2016-003964-38 |
| Trial protocol | IT |
| Global end of trial date | 25 April 2021 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 13 July 2022 |
| First version publication date | 13 July 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | IRFMN-OVA-7289 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Istituto di Ricerche Farmacologiche Mario Negri IRCCS |
| Sponsor organisation address | Via Mario Negri 2, Milan, Italy, |
| Public contact | Laboratorio Metodologia della Ricerca Clinica, IRCCS - Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 039 0239014684, eliana.rulli@marionegri.it |
| Scientific contact | Laboratorio Metodologia della Ricerca Clinica, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 039 0239014684, eliana.rulli@marionegri.it |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 01 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 April 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The study primary objective is to compare the efficacy of Olaparib and Cediranib vs. weekly paclitaxel in terms of progression free survival (PFS) in platinum refractory or resistant recurrent ovarian cancerT
The primary objective for safety is to compare the safety of Olaparib and Cediranib as intermittent vs. continuous regimen in terms of number of evacuations per day.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 June 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Italy: 123 |
| Worldwide total number of subjects | 123 |
| EEA total number of subjects | 123 |

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) | 77 |

| | |
|---|---|
| From 65 to 84 years | 46 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients will be randomized in a 1:1:1 ratio to the treatments as specified below:
- Paclitaxel 80 mg/mq every week.
- Cediranib 20 mg/day + Olaparib 600 mg/day (300 mg twice daily) given every day.
- Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg/day (300 mg twice daily) given 7 days per weeks.

Treatment will be continued until

### Pre-assignment

Screening details:

NA

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Paclitaxel (ARM A) |

Arm description:

Paclitaxel 80 mg/mq every week.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel 80 mg/mq every week.

| | |
|---|---|
| **Arm title** | Cediranib+Olaparib (ARM B) |

Arm description:

Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day.

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

Dosage and administration details:

Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day.

| | |
|---|---|
| Investigational medicinal product name | Olaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day.

| | |
|---|---|
| **Arm title** | Cediranib-Olaparib (ARM C) |

Arm description:

Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks.

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

Dosage and administration details:

Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks.

| | |
|---|---|
| Investigational medicinal product name | Olaparib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks.

| **Number of subjects in period 1** | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) |
|---|---|---|---|
| Started | 41 | 41 | 41 |
| Completed | 41 | 41 | 41 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Paclitaxel (ARM A) |
| Reporting group description: | |
| Paclitaxel 80 mg/mq every week. | |
| Reporting group title | Cediranib+Olaparib (ARM B) |
| Reporting group description: | |
| Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day. | |
| Reporting group title | Cediranib-Olaparib (ARM C) |
| Reporting group description: | |
| Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks. | |

| Reporting group values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) |
|---|---|---|---|
| Number of subjects | 41 | 41 | 41 |
| Age categorical<br>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) | 25 | 24 | 28 |
| From 65-84 years | 16 | 17 | 13 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| median | 62.5 | 64.2 | 59.9 |
| inter-quartile range (Q1-Q3) | 56.6 to 69.7 | 54.0 to 68.4 | 54.6 to 68.4 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 41 | 41 | 41 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 123 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 77 | | |

| | | | |
|---|---|---|---|
| From 65-84 years | 46 | | |
| 85 years and over | 0 | | |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Units: years | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 123 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT analysis set is defined as all randomized patients, without major violations of eligibility criteria. Patients will be analyzed according to randomization arm.

| | |
|---|---|
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |

Subject analysis set description:

the PP analysis set is defined as all patients of the ITT analysis set, who received at least 4 weeks of treatment, unless they interrupted before for disease progression or death. Patients randomized to the control arm, receiving the experimental treatment and patients randomized to the experimental arm, receiving the control treatment will be excluded.

| | |
|---|---|
| Subject analysis set title | Safety 1 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety 1 Analysis Set is defined as all patients included of the ITT Analysis Set, who were randomized to the two experimental arms, excluding patients who interrupted before 4 weeks, unless the interruption is due to diarrhea. Patients randomized to the continue schedule (arm B), receiving in the first cycle the intermittent schedule (as arm C) and patients randomized to the intermittent schedule, receiving the continue schedule will be excluded.

| | |
|---|---|
| Subject analysis set title | Safety 2 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety 2 Analysis Set is defined as all patients included of the ITT Analysis Set, who received at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be considered in the treatment arm they actually received.

| **Reporting group values** | ITT | PP | Safety 1 |
|---|---|---|---|
| Number of subjects | 123 | 106 | 65 |
| 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) | 77 | 68 | 46 |

| | | | |
|---|---|---|---|
| From 65-84 years | 46 | 38 | 19 |
| 85 years and over | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| Age continuous | | | |
| Units: years | | | |
| median | 62.5 | 62.1 | 59.9 |
| inter-quartile range (Q1-Q3) | 55.2 to 69.3 | 55.2 to 68.7 | 54.0 to 65.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 123 | 106 | 65 |

| **Reporting group values** | Safety 2 | | |
|---|---|---|---|
| Number of subjects | 110 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 70 | | |
| From 65-84 years | 40 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| median | 62.4 | | |
| inter-quartile range (Q1-Q3) | 55.2 to 68.7 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 110 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Paclitaxel (ARM A) |
| Reporting group description: | |
| Paclitaxel 80 mg/mq every week. | |
| Reporting group title | Cediranib+Olaparib (ARM B) |
| Reporting group description: | |
| Cediranib 20 mg/day + Olaparib 600 mg / day (i.e. 300 mg BD) given every day. | |
| Reporting group title | Cediranib-Olaparib (ARM C) |
| Reporting group description: | |
| Cediranib 20 mg/day given 5 days per weeks + Olaparib 600 mg / day (i.e. 300 mg BD) given 7 days per weeks. | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| The ITT analysis set is defined as all randomized patients, without major violations of eligibility criteria. Patients will be analyzed according to randomization arm. | |

| | |
|---|---|
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| the PP analysis set is defined as all patients of the ITT analysis set, who received at least 4 weeks of treatment, unless they interrupted before for disease progression or death. Patients randomized to the control arm, receiving the experimental treatment and patients randomized to the experimental arm, receiving the control treatment will be excluded. | |
| Subject analysis set title | Safety 1 |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety 1 Analysis Set is defined as all patients included of the ITT Analysis Set, who were randomized to the two experimental arms, excluding patients who interrupted before 4 weeks, unless the interruption is due to diarrhea. Patients randomized to the continue schedule (arm B), receiving in the first cycle the intermittent schedule (as arm C) and patients randomized to the intermittent schedule, receiving the continue schedule will be excluded. | |
| Subject analysis set title | Safety 2 |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety 2 Analysis Set is defined as all patients included of the ITT Analysis Set, who received at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be considered in the treatment arm they actually received. | |

### Primary: PFS (ITT)

| | |
|---|---|
| End point title | PFS (ITT) |
| End point description: | |
| The study primary endpoint is the PFS defined as the time from randomization to the date of first progression or death for any cause, whichever comes first | |
| End point type | Primary |
| End point timeframe: | |
| Study treatment | |

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | ITT |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 41 | 41 | 41 | 123 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.1 (1.9 to 6.3) | 5.6 (3.2 to 7.4) | 3.8 (2.0 to 5.8) | 4.0 (2.0 to 6.7) |

## Statistical analyses

| Statistical analysis title | Progression Free Survival (Arm B vs Arm A) |
|---|---|

Statistical analysis description:

PFS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib+Olaparib (ARM B) v ITT |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.14 |

| Statistical analysis title | Progression Free Survival (Arm C vs Arm A) |
|---|---|

Statistical analysis description:

PFS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v ITT |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.55 |

## Primary: PFS (PP)

| End point title | PFS (PP) |
|---|---|

End point description:

PFS is defined as the time from randomization to the date of first progression or death for any cause, whichever comes first.

| End point type | Primary |
|---|---|

End point timeframe:

Study treatment

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | PP |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 27 | 40 | 39 | 106 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 3.8 (1.9 to 6.7) | 5.6 (3.2 to 7.4) | 3.8 (2.0 to 5.8) | 4.2 (2.1 to 6.7) |

## Statistical analyses

| Statistical analysis title | Progression Free Survival (Arm B vs Arm A) |
|---|---|

Statistical analysis description:

PFS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| Comparison groups | Paclitaxel (ARM A) v Cediranib+Olaparib (ARM B) v PP |
|---|---|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.29 |

| Statistical analysis title | Progression Free Survival (Arm C vs Arm A) |
|---|---|

Statistical analysis description:

PFS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times,

and event-free rates at selected times will be calculated. Differences in PFS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v PP |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.79 |

## Secondary: PFS2 (ITT)

| | |
|---|---|
| End point title | PFS2 (ITT) |

End point description:

PFS2 defined as time from randomization to second disease progression according to RECIST 1.1 or to clinical assessment, or death by any cause.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Study treatment

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | ITT |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 41 | 41 | 41 | 123 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 8.8 (6.9 to 21.5) | 11.6 (8.4 to 18.4) | 9.6 (5.5 to 14.1) | 10.0 (6.4 to 17.4) |

## Statistical analyses

| Statistical analysis title | Second Progression Free Survival (Arm B vs Arm A) |
|---|---|

Statistical analysis description:

PFS2 will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS2 between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib+Olaparib (ARM B) v ITT |

| | |
|---|---|
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.42 |

| **Statistical analysis title** | Second Progression Free Survival (Arm C vs Arm A) |
|---|---|

Statistical analysis description:

PFS2 will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS2 between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v ITT |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.8 |

## Secondary: PFS2 (PP)

| End point title | PFS2 (PP) |
|---|---|

End point description:

PFS2 defined as time from randomization to second disease progression according to RECIST 1.1 or to clinical assessment, or death by any cause.

| End point type | Secondary |
|---|---|

End point timeframe:

Study treatment

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | PP |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 27 | 40 | 39 | 106 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.3 (7.4 to 21.5) | 11.6 (8.4 to 18.4) | 9.6 (5.5 to 14.1) | 10.2 (6.5 to 18.4) |

## Statistical analyses

| Statistical analysis title | Second Progression Free Survival (Arm B vs Arm A) |
|---|---|

Statistical analysis description:

PFS2 will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS2 between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib+Olaparib (ARM B) v PP |
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.48 |

| Statistical analysis title | Second Progression Free Survival (Arm C vs Arm A) |
|---|---|

Statistical analysis description:

PFS2 will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in PFS2 between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v PP |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.65 |
| upper limit | 1.86 |

| Secondary: OS (ITT) | |
|---|---|
| End point title | OS (ITT) |
| End point description: | |
| Overall Survival (OS), defined for each patient as the time from randomization to the date of death for any cause. | |
| End point type | Secondary |
| End point timeframe: | |
| Study treatment | |

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | ITT |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 41 | 41 | 41 | 123 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.3 (7.4 to 21.5) | 11.6 (8.4 to 23.0) | 9.6 (5.5 to 14.1) | 10.2 (6.5 to 17.4) |

## Statistical analyses

| Statistical analysis title | Overall survival (Arm B vs Arm A) |
|---|---|
| Statistical analysis description: | |
| OS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in OS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs). | |
| Comparison groups | Paclitaxel (ARM A) v Cediranib+Olaparib (ARM B) v ITT |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.46 |

| Statistical analysis title | Overall survival (Arm C vs Arm A) |
|---|---|
| Statistical analysis description: | |
| OS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in OS between arms will be also | |

tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v ITT |
| Number of subjects included in analysis | 205 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.13 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.92 |

## Secondary: OS (PP)

| | |
|---|---|
| End point title | OS (PP) |

End point description:

Overall Survival (OS), defined for each patient as the time from randomization to the date of death for any cause.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Study treatment

| End point values | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) | PP |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 27 | 40 | 39 | 106 |
| Units: percentage | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.3 (7.4 to 21.5) | 11.6 (8.4 to 23) | 9.6 (5.5 to 14.1) | 10.2 (7.1 to 18.8) |

## Statistical analyses

| Statistical analysis title | Overall survival (Arm B vs Arm A) |
|---|---|

Statistical analysis description:

OS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in OS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Cediranib+Olaparib (ARM B) v Paclitaxel (ARM A) v PP |

| | |
|---|---|
| Number of subjects included in analysis | 173 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.53 |

| **Statistical analysis title** | Overall survival (Arm C vs Arm A) |
|---|---|

Statistical analysis description:

OS will be described with the Kaplan-Meier method. KM estimates for median and quartile event times, and event-free rates at selected times will be calculated. Differences in OS between arms will be also tested by univariate and multivariate Cox's models including stratification variables and other clinical-biological features as covariates. Results will be presented as hazard ratios (HRs) and their 95% confidence intervals (95% CIs).

| | |
|---|---|
| Comparison groups | Paclitaxel (ARM A) v Cediranib-Olaparib (ARM C) v PP |
| Number of subjects included in analysis | 172 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.16 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.99 |

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: During the study | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | NCI-CTCAE |
| Dictionary version | 4.0 |
| **Reporting groups** | |
| Reporting group title | Paclitaxel (ARM A) |
| Reporting group description: Paclitaxel | |
| Reporting group title | Cediranib+Olaparib (ARM B) |
| Reporting group description: Cediranib+Olaparib Continuous schedule | |
| Reporting group title | Cediranib-Olaparib (ARM C) |
| Reporting group description: Cediranib+Olaparib Intermittent schedule | |

| Serious adverse events | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 41 (56.10%) | 23 / 41 (56.10%) | 23 / 41 (56.10%) |
| number of deaths (all causes) | 1 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 41 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 41 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 41 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 3 / 41 (7.32%) | 5 / 41 (12.20%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Female genital tract fistula | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 41 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 41 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary obstruction | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 0 / 41 (0.00%) | 1 / 41 (2.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 0 / 41 (0.00%) | 1 / 41 (2.44%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 0 / 41 (0.00%) | 0 / 41 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Paclitaxel (ARM A) | Cediranib+Olaparib (ARM B) | Cediranib-Olaparib (ARM C) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 31 / 41 (75.61%) | 31 / 41 (75.61%) | 31 / 41 (75.61%) |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 41 (7.32%) | 3 / 41 (7.32%) | 2 / 41 (4.88%) |
| occurrences (all) | 16 | 3 | 2 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 13 / 41 (31.71%) | 9 / 41 (21.95%) |
| occurrences (all) | 1 | 22 | 18 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 6 / 41 (14.63%) | 10 / 41 (24.39%) |
| occurrences (all) | 13 | 22 | 16 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 41 (21.95%) | 21 / 41 (51.22%) | 18 / 41 (43.90%) |
| occurrences (all) | 15 | 42 | 30 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 6 / 41 (14.63%) | 24 / 41 (58.54%) | 22 / 41 (53.66%) |
| occurrences (all) | 7 | 41 | 32 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 41 (4.88%) | 6 / 41 (14.63%) | 3 / 41 (7.32%) |
| occurrences (all) | 2 | 21 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 41 (2.44%) | 18 / 41 (43.90%) | 17 / 41 (41.46%) |
| occurrences (all) | 1 | 37 | 26 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 26 March 2018 | PRINCIPAL CHANGES:<br>1. Update of IB Olaparib<br>2. Update of Informed Consent |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported