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 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 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 Units: Subjects			
Female	41	41	41

Reporting group values	Total		
Number of subjects	123		
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)	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: 1. Update of IB Olaparib 2. Update of Informed Consent

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported