Clinical trial results:
Multicenter, randomized, non-comparative, open-label phase II trial on the efficacy and safety of the combination of bevacizumab and trabectedin with or without carboplatin in adult women with platinum partially sensitive recurring ovarian cancer.

Summary

EudraCT number	2012-003866-42
Trial protocol	IT
Global end of trial date	15 March 2018

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-6152

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
Sponsor organisation address	Via Mario Negri 2, Milan, Italy, 20156
Public contact	Laboratorio di Metodologia per la Ricerca Clinica , Istituto di Ricerche Farmacologiche Mario Negri, 039 0239014684, eliana.rulli@marionegri.it
Scientific contact	Laboratorio di Metodologia per la Ricerca Clinica , Istituto di Ricerche Farmacologiche Mario Negri, 039 0239014686, 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	18 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2018
Global end of trial reached?	Yes
Global end of trial date	15 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study is aimed at assessing the efficacy and the safety of the combination of bevacizumab and trabectedin with or without carboplatin in adult women with epithelial ovarian cancer at first or second recurrence occurred 6-12 months after the end of the most recent platinum-containing regimen. According to the Bryant and Day design the primary endpoints will be the proportion of progression-free patients at 6 months (PFS-6) for the efficacy, and the proportion of patients with severe toxicity for the safety at the same time-point. Disease progression will be determined using the RECIST criteria, version 1.1.

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2013
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: 71
Worldwide total number of subjects	71
EEA total number of subjects	71

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)	43
From 65 to 84 years	28

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 71 patients were randomized or registered at 8 sites in Italy.
The overall duration of the project is expected to be 48 months, divided as follows: 36 months for recruitment, followed by 12 months of treatment and follow-up for each patient.

Pre-assignment

Screening details:

NA

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BT (Arm A)

Arm description:

Patients in BT arm will receive Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21days

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin 1.1 mg/m2, bevacizumab 15 mg/kg day 1 every 21days

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trabectedin 1.1 mg/m2, bevacizumab 15 mg/kg day 1 every 21days

Arm title	BT+C (Arm B)

Arm description:

Patients in BT+C arm will receive cycles 1-6: Carboplatin AUC 4 day 1 every 28 days, Trabectedin 0.8 mg/m2 day 1 every 28 days, Bevacizumab 10 mg/kg day 1 and day 15.
As of cycle 7: Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21 days.

Arm type	Experimental
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

cycles 1-6: carboplatin AUC 4 day 1 every 28 days, trabectedin 0.8 mg/m2 day 1 every 28 days, bevacizumab 10 mg/kg day 1 and day 15.
As of cycle 7: trabectedin 1.1 mg/m2 and bevacizumab 15 mg/kg day 1 every

21 days.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

cycles 1-6: carboplatin AUC 4 day 1 every 28 days, trabectedin 0.8 mg/m2 day 1 every 28 days, bevacizumab 10 mg/kg day 1 and day 15.
As of cycle 7: trabectedin 1.1 mg/m2 and bevacizumab 15 mg/kg day 1 every 21 days.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

cycles 1-6: carboplatin AUC 4 day 1 every 28 days, trabectedin 0.8 mg/m2 day 1 every 28 days, bevacizumab 10 mg/kg day 1 and day 15.
As of cycle 7: trabectedin 1.1 mg/m2 and bevacizumab 15 mg/kg day 1 every 21 days.

Number of subjects in period 1	BT (Arm A)	BT+C (Arm B)
Started	50	21
Completed	46	20
Not completed	4	1
Major violation of eligibility criteria	3	1
Intercurrent illness	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BT (Arm A)
Reporting group description:	
Patients in BT arm will receive Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21days	
Reporting group title	BT+C (Arm B)
Reporting group description:	
Patients in BT+C arm will receive cycles 1-6: Carboplatin AUC 4 day 1 every 28 days, Trabectedin 0.8 mg/m2 day 1 every 28 days, Bevacizumab 10 mg/kg day 1 and day 15. As of cycle 7: Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21 days.	

Reporting group values	BT (Arm A)	BT+C (Arm B)	Total
Number of subjects	50	21	71
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)	29	14	43
From 65-84 years	21	7	28
85 years and over	0	0	0
Age continuous Units: years			
median	60.8	59.4	
inter-quartile range (Q1-Q3)	52.1 to 69.9	54.0 to 66.1	-
Gender categorical Units: Subjects			
Female	50	21	71

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
the ITT includes all subjects who provided informed consent and were randomized/registered to one of the treatment arms excluding those with any major violation of the eligibility criteria.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population includes all randomized/registered patients, without major violations of eligibility criteria, who have received at least 12 weeks of treatment (unless interrupted treatment for progressive disease, drug toxicity or death), and whose disease is assessed.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

the Safety population includes all subjects who provided informed consent and were randomized/registered to one of the treatment arms, who had no major violations of eligibility criteria, and who received at least one dose of treatment.

Reporting group values	ITT	PP	Safety
Number of subjects	67	66	66
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)	42	42	42
From 65-84 years	25	24	24
85 years and over	0	0	0
Age continuous Units: years			
median	60.7	60.7	60.7
inter-quartile range (Q1-Q3)	53.1 to 68.3	53.1 to 67.3	53.1 to 68.3
Gender categorical Units: Subjects			
Female	67	66	67

End points

End points reporting groups

Reporting group title	BT (Arm A)
Reporting group description:	
Patients in BT arm will receive Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21days	
Reporting group title	BT+C (Arm B)
Reporting group description:	
Patients in BT+C arm will receive cycles 1-6: Carboplatin AUC 4 day 1 every 28 days, Trabectedin 0.8 mg/m2 day 1 every 28 days, Bevacizumab 10 mg/kg day 1 and day 15. As of cycle 7: Trabectedin 1.1 mg/m2 and Bevacizumab 15 mg/kg day 1 every 21 days.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
the ITT includes all subjects who provided informed consent and were randomized/registered to one of the treatment arms excluding those with any major violation of the eligibility criteria.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population includes all randomized/registered patients, without major violations of eligibility criteria, who have received at least 12 weeks of treatment (unless interrupted treatment for progressive disease, drug toxicity or death), and whose disease is assessed.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
the Safety population includes all subjects who provided informed consent and were randomized/registered to one of the treatment arms, who had no major violations of eligibility criteria, and who received at least one dose of treatment.	

Primary: PFS-6 (BT)

End point title	PFS-6 (BT)
End point description:	
The PFS-6, defined as the percentage of patients who are alive and progression free at 6 months after the randomization.	
End point type	Primary
End point timeframe:	
6 months	

End point values	BT (Arm A)	BT+C (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	17		
Units: Patients	25	14		

Statistical analyses

Statistical analysis title	Progression Free Survival Rate at 6 months (BT)
Comparison groups	BT (Arm A) v BT+C (Arm B)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Proportion of responder
Point estimate	69.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	57.6
upper limit	79.6

Notes:

[1] - Since the trail was non-comparative, no statistical comparison between arms was planned and performed

Primary: ST-6 (BT)

End point title	ST-6 (BT)

End point description:

The Proportion of patients with severe toxicity within 6 months from randomization.

End point type	Primary

End point timeframe:

6 months

End point values	BT (Arm A)	BT+C (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	17		
Units: Patients	6	8		

Statistical analyses

Statistical analysis title	ST-6 (BT)
Comparison groups	BT+C (Arm B) v BT (Arm A)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Proportion of pts with severe toxicity
Point estimate	16.7
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	9
upper limit	27.4

Notes:

[2] - Since the trail was non-comparative, no statistical comparison between arms was planned and performed

Primary: PFS-6 (BT+C)

End point title	PFS-6 (BT+C)

End point description:

The PFS-6, defined as the percentage of patients who are alive and progression free at 6 months after the randomization.

End point type	Primary

End point timeframe:

6 months

End point values	BT (Arm A)	BT+C (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	17		
Units: patients	25	14		

Statistical analyses

Statistical analysis title	Progression Free Survival Rate at 6 months (BT+C)
Comparison groups	BT (Arm A) v BT+C (Arm B)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Proportion of responder
Point estimate	82.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	64.8
upper limit	93.3

Notes:

[3] - Since the trail was non-comparative, no statistical comparison between arms was planned and performed

Primary: ST-6 (BT+C)

End point title	ST-6 (BT+C)

End point description:

The Proportion of patients with severe toxicity within 6 months from randomization.

End point type	Primary

End point timeframe:

6 months

End point values	BT (Arm A)	BT+C (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	17		
Units: Patients	6	8		

Statistical analyses

Statistical analysis title	ST-6 (BT+C)
Comparison groups	BT+C (Arm B) v BT (Arm A)
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Proportion of pts with severe toxicity
Point estimate	47.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	29.7
upper limit	65

Notes:

[4] - Since the trail was non-comparative, no statistical comparison between arms was planned and performed

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment. Treatment was continued until progressive disease, major toxicity, patient's intolerance or unwillingness to continue treatment, or at the physician's discretion.
The median number cycles was 10.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4

Reporting groups

Reporting group title	BT (Arm A)
Reporting group description:	
Bevacizumab+Trabectedin	
Reporting group title	BT+C (Arm B)
Reporting group description:	
Carboplatin+Bevacizumab+Trabectedin	

Serious adverse events	BT (Arm A)	BT+C (Arm B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 47 (23.40%)	7 / 20 (35.00%)	
number of deaths (all causes)	20	9	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 47 (2.13%)	3 / 20 (15.00%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutropenia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
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 / 47 (2.13%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BT (Arm A)	BT+C (Arm B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 47 (82.98%)	18 / 20 (90.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 47 (53.19%)	14 / 20 (70.00%)	
occurrences (all)	65	65	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	22 / 47 (46.81%)	15 / 20 (75.00%)	
occurrences (all)	44	44	
Lymphocyte count decreased			
subjects affected / exposed	14 / 47 (29.79%)	5 / 20 (25.00%)	
occurrences (all)	84	42	
Neutrophil count decreased			
subjects affected / exposed	27 / 47 (57.45%)	14 / 20 (70.00%)	
occurrences (all)	87	51	
Platelet count decreased			
subjects affected / exposed	5 / 47 (10.64%)	16 / 20 (80.00%)	
occurrences (all)	5	71	
White blood cell decreased			

subjects affected / exposed	25 / 47 (53.19%)	12 / 20 (60.00%)	
occurrences (all)	73	64	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	32 / 47 (68.09%)	14 / 20 (70.00%)	
occurrences (all)	102	14	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	31 / 47 (65.96%)	13 / 20 (65.00%)	
occurrences (all)	86	77	
Constipation			
subjects affected / exposed	26 / 47 (55.32%)	12 / 20 (60.00%)	
occurrences (all)	26	78	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2015	PRINCIPAL CHANGES: 1. INCLUSION CRITERIA -> adding an inclusion criteria 2. STATISTICAL ANALYSIS -> changes in PFS percentage in patients in both arms 3. NON SUBSTANTIAL CHANGES -> changes regarding centers, contact and text formulation 4. INSURANCE -> update of the insurance certificate 5. INVESTIGATOR BROCHURE -> update of the document 6. INFORMED CONSENT -> update of the document
30 June 2016	PRINCIPAL CHANGES: 1. TREATMENT -> closure of the treatment arm B 2. ADVERSE EVENT -> changes in text formulation regarding severe toxicity 3. STUDY POPULATION -> more details about study population 4. INCLUSION CRITERIA -> changes in one inclusion criteria 5. TRABECTEDINE -> Trabectedine dose reduction 6. ADVERSE EVENT -> changes in AE reporting 7. CONTACTS -> changes regarding study referents 8. CENTERS -> adding a clinical centre 9. DATA PROTECTION FORM -> update of the document
01 February 2018	PRINCIPAL CHANGES: 1. INVESTIGATIONAL MEDICAL PRODUCT2 -> changes of the certified site for the release of IMP2, Bevacizumab (AVASTIN)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31537908