



Clinical trial results:

A randomized, open label, phase II trial of bevacizumab plus weekly paclitaxel followed by bevacizumab monotherapy maintenance versus weekly paclitaxel followed by observation in patients with relapsed ovarian sex-cord stromal tumours

Summary

EudraCT number	2012-002841-39
Trial protocol	DE BE IT
Global end of trial date	28 April 2021

Results information

Result version number	v1 (current)
This version publication date	16 August 2023
First version publication date	16 August 2023

Trial information

Trial identification

Sponsor protocol code	GINECO-OV-222
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ARCAGY-GINECO
Sponsor organisation address	8 rue Lamennais , Paris, France, 75008
Public contact	Andrea Zanuzzi, AGO Research GmbH, 0049 20195981216, azanuzzi@ago-ovar.de
Scientific contact	Andrea Zanuzzi, AGO Research GmbH, 0049 20195981216, azanuzzi@ago-ovar.de

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	27 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical benefit of combining bevacizumab long-term treatment to weekly paclitaxel measured by the non-progression rate after 6 months of treatment

Protection of trial subjects:

This study was conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever afforded the greater protection to the individual. The study fully adhered to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator ensured compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where "Guideline for Good Clinical Practice" exists, the sponsor and the investigators strictly ensured adherence to the stated provisions.

Background therapy:

Bleomycin, etoposide and cisplatin (BEP), and most recently, the combination of paclitaxel + carboplatin have been shown to be effective (overall survival: 69% at 5 years) and may become the standard of care for adjuvant and post-operative treatment of metastatic disease. However, despite advances in therapy, these tumours still tend to recur over long periods, often requiring multiple treatments including surgery, radiotherapy, chemotherapy, and hormonal agents. There is no standardized approach for the treatment of recurrent disease. But all of these approaches have limited efficacy and new approaches are needed to improve clinical outcome of SCSTs patients.

Evidence for comparator:

Few case reports support the use of anti-angiogenic agents alone or in combination with chemotherapies in relapsed ovarian sex-cord stromal tumours. In particular, bevacizumab, a monoclonal antibody targeted against the pro-angiogenic vascular endothelial growth factor (VEGF), hold significant therapeutic potential. Tao et al. have reported response rate of 38% and a clinical benefit rate of 63% in 8 patients with recurrent ovarian granulosa cell tumours treated with bevacizumab.

In epithelial ovarian cancer, encouraging data have been obtained with bevacizumab in combination with chemotherapy. Two clinical trials sponsored by the Gynaecologic Oncology Group are ongoing in recurrent ovarian sex-cord stromal tumours: 1) a phase II trial evaluating the anti-tumour activity of bevacizumab alone (GOG-0251, NTC00748657) and 2) a phase II trial evaluating the efficacy of paclitaxel alone (GOG-0187, NTC00006227). Our proposal is to investigate the clinical interest of combining bevacizumab to weekly paclitaxel for the treatment of recurrent sex-cord stromal tumours previously treated by platinum-based chemotherapy.

Actual start date of recruitment	03 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 2
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Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	60
EEA total number of subjects	58

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)	49
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 28/02/2013 and 27/10/2016

Pre-assignment

Screening details:

60 patients were randomized in the study: 32 in the control arm (A) and 28 in the experimental arm (B)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A - Paclitaxel alone

Arm description:

Arm A: patients will receive paclitaxel alone at the dose 80 mg/m² administered by intravenous injection at D1, D8 and D15 every 4 weeks for 6 cycles. Thereafter, patients will be followed-up with imaging exams every 12 weeks. At the time of confirmed progression, patients could receive bevacizumab 15 mg/kg every 3 weeks for 12 months following investigator's decision. In some cases, longer therapy may be allowed after discussion with the Principal Investigator/Sponsor.

Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Concentrate (6 mg/mL) for solution for infusion

Dilution : 0.9 % sodium chloride solution to a final concentration of 0.3 to 1.2 mg/mL

Dose : 80 mg/m², IV (D1, D8, D15 / 28-day cycle)

Treatment duration : Maximum of 6 cycles

Arm title	Arm B - Paclitaxel and Bevacizumab
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Arm description:

Arm B: patients will receive paclitaxel at the dose 80 mg/m² administered by intravenous injection at D1, D8 and D15 every 4 weeks + Bevacizumab at the dose 10 mg/kg administered by intravenous injection every 2 weeks (D1 and D15) for 6 cycles. Thereafter, patients will receive IV injection of bevacizumab 15 mg/kg every 3 weeks for up to 1 year.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Concentrate (25 mg/mL) for solution for infusion in preservative-free, single use vials of 4 or 16 mL (100 or 400 mg of Bevacizumab)

Dilution : 0.9 % sodium chloride solution to a final concentration of 1.4 to 16.5°mg/mL.

Dose : During chemotherapy cycles: 10 mg/kg IV, D1 and D15
After 6th cycle of chemotherapy: 15 mg/kg IV, D1 every 3 weeks

Treatment duration: Until disease progression and for a maximum of 1 year

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

Concentrate (6 mg/mL) for solution for infusion

Dilution : 0.9 % sodium chloride solution to a final concentration of 0.3 to 1.2 mg/mL

Dose : 80 mg/m², IV (D1, D8, D15 / 28-day cycle)

Treatment duration : Maximum of 6 cycles

Number of subjects in period 1	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab
Started	32	28
Interim analysis 1	10 ^[1]	10 ^[2]
Interim analysis 2	20 ^[3]	20 ^[4]
Completed	32	27
Not completed	0	1
SAE and did not receive study treatment	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 32 patients randomized. Interim analysis at 10 and 20 randomized.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 28 patients randomized. Interim analysis at 10 and 20 randomized. 1 patient withdrawn from study (no treatment received)

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 32 patients randomized. Interim analysis at 10 and 20 randomized.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 28 patients randomized. Interim analysis at 10 and 20 randomized. 1 patient withdrawn from study (no treatment received)

Baseline characteristics

Reporting groups

Reporting group title	Arm A - Paclitaxel alone
Reporting group description:	
Arm A: patients will receive paclitaxel alone at the dose 80 mg/m ² administered by intravenous injection at D1, D8 and D15 every 4 weeks for 6 cycles. Thereafter, patients will be followed-up with imaging exams every 12 weeks. At the time of confirmed progression, patients could receive bevacizumab 15 mg/kg every 3 weeks for 12 months following investigator's decision. In some cases, longer therapy may be allowed after discussion with the Principal Investigator/Sponsor.	
Reporting group title	Arm B - Paclitaxel and Bevacizumab
Reporting group description:	
Arm B: patients will receive paclitaxel at the dose 80 mg/m ² administered by intravenous injection at D1, D8 and D15 every 4 weeks + Bevacizumab at the dose 10 mg/kg administered by intravenous injection every 2 weeks (D1 and D15) for 6 cycles. Thereafter, patients will receive IV injection of bevacizumab 15 mg/kg every 3 weeks for up to 1 year.	

Reporting group values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab	Total
Number of subjects	32	28	60
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)	26	23	49
From 65-84 years	6	5	11
85 years and over	0	0	0
Age continuous			
Age at inclusion			
Units: years			
arithmetic mean	58.2	54.6	
standard deviation	± 10.66	± 11.31	-
Gender categorical			
Units: Subjects			
Female	32	28	60
BMI classification OMS			
Units: Subjects			
BMI 18.5 kg/m ²	2	1	3
BMI [18.5 ; 25] kg/m ²	14	10	24
BMI [25 ; 30] kg/m ²	5	8	13
BMI = 30 kg/m ²	11	9	20
ECOG performance status at registration			
Units: Subjects			
0 Normal activity	25	17	42

1 Symptomatic but ambulatory self-care	6	11	17
2 Ambulatory more than 50% of the time	1	0	1
FIGO stage at diagnosis Units: Subjects			
Missing	13	10	23
One	12	12	24
Two	3	1	4
Three and Four	4	5	9
Progression before the study diagnosed by CT scan Units: Subjects			
Progression before the study diagnosed by CT scan	31	27	58
Other : CA-125	0	1	1
Other : Symptomatic of global health deterioration	1	0	1
Initial surgery Units: Subjects			
Unknown	1	1	2
Conservative	11	13	24
Radical	20	14	34
Quality of initial surgery Units: Subjects			
Unknown	6	3	9
Optimal	16	20	36
Sub optimal	10	5	15
Number of previous chemotherapy lines Units: Subjects			
<= 2	24	23	47
> 2	8	5	13
Platinum-free interval Units: Subjects			
Missing	1	0	1
< 6 months	5	2	7
>= 6 months and < 12 months	5	4	9
>= 12 months	21	22	43
Previous radiotherapy Units: Subjects			
Previous radiotherapy	4	2	6
NA	28	26	54
Previous hormonotherapy Units: Subjects			
Previous hormonotherapy	8	9	17
NA	24	19	43
Previous immunotherapy Units: Subjects			
Previous immunotherapy	0	0	0
NA	32	28	60
Cardiovascular history Units: Subjects			
Cardiovascular history	9	11	20

Status of cardiovascular history : Past	2	2	4
Status of cardiovascular history : Active	7	9	16
NA	14	6	20
ECG abnormality at baseline Units: Subjects			
Missing	1	1	2
No	31	27	58
Endocrine history Units: Subjects			
Hypothyroidism	2	6	8
Diabetes Mellitus	0	4	4
Other	3	1	4
NA	27	17	44
Abnormality during physical examination at baseline Units: Subjects			
No	27	26	53
Abdominal pain	1	1	2
Abdominal distension	1	0	1
Ascites	0	1	1
Hepatomegaly	1	0	1
Induration of vagina, neuropathia 1°	1	0	1
Pelvic and iliac fossa palpable	1	0	1
Relevant medical history : Past Units: Subjects			
Relevant medical history : Past	24	22	46
NA	8	6	14
Relevant medical history : Active Units: Subjects			
Relevant medical history : Active	20	20	40
NA	12	8	20
Previous chemotherapy: PEB or PVB Units: Subjects			
PEB or PVB	21	19	40
NA	11	9	20
Previous chemotherapy: Platine based Units: Subjects			
Platine based	13	13	26
NA	19	15	34
Previous chemotherapy: Platine alone Units: Subjects			
Platine alone	6	2	8
NA	26	26	52
Previous chemotherapy: Other Units: Subjects			
Other	3	3	6
NA	29	25	54

Age at diagnosis Units: Years median full range (min-max)	46.5 24 to 71	43.5 26 to 70	-
Height Units: centimetre median full range (min-max)	160.5 149 to 180	161.0 150 to 178	-
Weight Units: kilogram(s) median full range (min-max)	69.5 48 to 96	72.5 48 to 107	-
BMI Units: kilogram(s)/square metre median full range (min-max)	25.4 17 to 38	27.5 18 to 42	-
Number of surgeries before randomisation Units: Surgery median full range (min-max)	3 1 to 8	2 1 to 6	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population for the final analysis is defined as all randomized patients.	

Reporting group values	ITT population		
Number of subjects	60		
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)	49		
From 65-84 years	11		
85 years and over	0		
Age continuous			
Age at inclusion			
Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female	60		

BMI classification OMS Units: Subjects			
BMI 18.5 kg/m2	3		
BMI [18.5 ; 25] kg/m2	24		
BMI [25 ; 30] kg/m2	13		
BMI = 30 kg/m2	20		
ECOG performance status at registration Units: Subjects			
0 Normal activity	42		
1 Symptomatic but ambulatory self-care	17		
2 Ambulatory more than 50% of the time	1		
FIGO stage at diagnosis Units: Subjects			
Missing	23		
One	24		
Two	4		
Three and Four	9		
Progression before the study diagnosed by CT scan Units: Subjects			
Progression before the study diagnosed by CT scan	58		
Other : CA-125	1		
Other : Symptomatic of global health deterioration	1		
Initial surgery Units: Subjects			
Unknown	2		
Conservative	24		
Radical	34		
Quality of initial surgery Units: Subjects			
Unknown	9		
Optimal	36		
Sub optimal	15		
Number of previous chemotherapy lines Units: Subjects			
<= 2			
> 2			
Platinum-free interval Units: Subjects			
Missing			
< 6 months			
>= 6 months and < 12 months			
>= 12 months			
Previous radiotherapy Units: Subjects			
Previous radiotherapy	6		
NA	54		
Previous hormonotherapy Units: Subjects			

Previous hormonotherapy	17		
NA	43		
Previous immunotherapy			
Units: Subjects			
Previous immunotherapy	0		
NA	60		
Cardiovascular history			
Units: Subjects			
Cardiovascular history	20		
Status of cardiovascular history : Past	4		
Status of cardiovascular history : Active	16		
NA	40		
ECG abnormality at baseline			
Units: Subjects			
Missing	2		
No	58		
Endocrine history			
Units: Subjects			
Hypothyroidism	8		
Diabetes Mellitus	4		
Other	4		
NA	44		
Abnormality during physical examination at baseline			
Units: Subjects			
No	53		
Abdominal pain	2		
Abdominal distension	1		
Ascites	1		
Hepatomegaly	1		
Induration of vagina, neuropathia 1°	1		
Pelvic and iliac fossa palpable	1		
Relevant medical history : Past			
Units: Subjects			
Relevant medical history : Past	46		
NA	14		
Relevant medical history : Active			
Units: Subjects			
Relevant medical history : Active	40		
NA	20		
Previous chemotherapy: PEB or PVB			
Units: Subjects			
PEB or PVB	40		
NA	20		
Previous chemotherapy: Platine based			
Units: Subjects			
Platine based	26		
NA	34		
Previous chemotherapy: Platine alone			

Units: Subjects			
Platine alone	8		
NA	52		
Previous chemotherapy: Other			
Units: Subjects			
Other	6		
NA	54		
Age at diagnosis			
Units: Years			
median			
full range (min-max)			
Height			
Units: centimetre			
median	161.0		
full range (min-max)	149 to 180		
Weight			
Units: kilogram(s)			
median			
full range (min-max)			
BMI			
Units: kilogram(s)/square metre			
median			
full range (min-max)			
Number of surgeries before randomisation			
Units: Surgery			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	Arm A - Paclitaxel alone
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Reporting group description:

Arm A: patients will receive paclitaxel alone at the dose 80 mg/m² administered by intravenous injection at D1, D8 and D15 every 4 weeks for 6 cycles. Thereafter, patients will be followed-up with imaging exams every 12 weeks. At the time of confirmed progression, patients could receive bevacizumab 15 mg/kg every 3 weeks for 12 months following investigator's decision. In some cases, longer therapy may be allowed after discussion with the Principal Investigator/Sponsor.

Reporting group title	Arm B - Paclitaxel and Bevacizumab
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Reporting group description:

Arm B: patients will receive paclitaxel at the dose 80 mg/m² administered by intravenous injection at D1, D8 and D15 every 4 weeks + Bevacizumab at the dose 10 mg/kg administered by intravenous injection every 2 weeks (D1 and D15) for 6 cycles. Thereafter, patients will receive IV injection of bevacizumab 15 mg/kg every 3 weeks for up to 1 year.

Subject analysis set title	ITT population
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

The ITT population for the final analysis is defined as all randomized patients.

Primary: The 6-month progression-free rate

End point title	The 6-month progression-free rate
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End point description:

The Bayesian analysis thus gave an estimated progression-free rate (PFR) at 6 months [95% credible interval] of 70.6% [54.5%; 84.4%] in arm A vs 72.4% [55.1%; 86.8%] in arm B.

End point type	Primary
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End point timeframe:

Overall trial

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	27		
Units: percent				
number (confidence interval 95%)				
Mean estimated progression-free rate at 6 months %	70.6 (54.5 to 84.4)	72.4 (55.1 to 86.8)		

Attachments (see zip file)	Primary endpoint - The 6-month progression-free rate/Figure 5 -
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Statistical analyses

Statistical analysis title	Bayesian estimation
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Comparison groups	Arm A - Paclitaxel alone v Arm B - Paclitaxel and Bevacizumab
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Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57 ^[1]
Method	bayesian estimation

Notes:

[1] - The probability (bayesian estimation) that the estimated progression-free rate in arm B is higher than the estimated progression-free rate arm A was 0.57.

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
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End point description:

Progression-free survival (PFS) was calculated from the date of randomization to the date of event defined as the first documented disease progression or death from any cause. Patients with no event at the time of analysis were censored at the date of last adequate tumour assessment.

The median PFS was 14.7 months (95%CI [11.5; 18.3]) in arm A compared to 14.9 months (95%CI [8.3; 19.3]) in arm B.

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	27		
Units: percent				
number (confidence interval 95%)				
PFS-rate at 6 months (%)	71.9 (52.9 to 84.3)	77.8 (57.1 to 89.3)		

Attachments (see zip file)	Secondary endpoint - Progression-free survival (PF/Figure 6
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Statistical analyses

No statistical analyses for this end point

Secondary: Objective response

End point title	Objective response
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End point description:

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	27		
Units: percent				
number (confidence interval 95%)				
Objective response	25.0 (11.5 to 43.4)	44.4 (25.5 to 64.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response
End point description:	
Best overall response was complete response (CR) for 2 patients (7.4%) of arm B, partial response (PR) in 8 patients (25.0%) of arm A and 10 patients (37.0%) of arm B, stable disease (SD) for 17 patients (53.1%) of arm A and 12 patients (44.4%) of arm B, progressive disease (PD) in 7 patients (21.9%) of arm A and 3 patients (11.1%) of arm B.	
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	27		
Units: Patients				
Complete response	0	2		
Partial response	8	10		
Stable disease	17	12		
Progressive disease	7	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response
End point description:	
Duration of response applies only to patients whose best overall response was a complete response (CR) or a partial response (PR). It was measured from the time of first documented response (CR or PR) until the first documented disease progression or death due to underlying cancer.	

End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: month				
median (confidence interval 95%)				
Median Duration of response	18.0 (7.1 to 22.6)	15.9 (6.6 to 22.5)		

Attachments (see zip file)	Duration of response/Figure 7 Duration of response.JPG
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was calculated from the date of randomization to the date of death from any cause.	
Patients who are alive at the time of analysis will be censored at the date of last contact.	
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A - Paclitaxel alone	Arm B - Paclitaxel and Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	28		
Units: percent				
number (confidence interval 95%)				
OS-rate at 6 months (95% CI)	96.9 (79.8 to 99.6)	92.6 (73.5 to 98.1)		
OS-rate at 12 months (95% CI)	93.8 (77.3 to 98.4)	92.6 (73.5 to 98.1)		
OS-rate at 24 months (95% CI)	87.2 (69.3 to 95.0)	72.5 (50.7 to 85.8)		

Attachments (see zip file)	Overall survival (OS)/Figure 8 Overall survival (OS).JPG
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Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) post switch

End point title	Progression-free survival (PFS) post switch ^[2]
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End point description:

Progression-free survival post switch (PFS) applies only to patients of arm A who had switched and was calculated from the date of switch to the date of event defined as the first documented disease progression or death from any cause. Patients with no event at the time of analysis were censored at the date of last adequate tumour assessment.

End point type	Secondary
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End point timeframe:

Overall trial

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Progression-free survival post switch (PFS) applies only to patients of arm A who had switched and was calculated from the date of switch to the date of event defined as the first documented disease progression or death from any cause. Patients with no event at the time of analysis were censored at the date of last adequate tumour assessment.

End point values	Arm A - Paclitaxel alone			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: percent				
number (confidence interval 95%)				
PFS post switch-rate at 6 months (95% CI)	62.5 (34.9 to 81.1)			

Attachments (see zip file)	Progression-free survival post switch (PFS) /Figure 9
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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Reporting groups

Reporting group title	Arm A - Paclitaxel
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Reporting group description: -

Reporting group title	Arm B - Paclitaxel and Bevacizumab
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Reporting group description: -

Serious adverse events	Arm A - Paclitaxel	Arm B - Paclitaxel and Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 32 (18.75%)	10 / 27 (37.04%)	
number of deaths (all causes)	6	10	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanome in situ type dubreuilh			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Bleeding			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertention			
subjects affected / exposed	1 / 32 (3.13%)	7 / 27 (25.93%)	
occurrences causally related to treatment / all	2 / 2	17 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract right eye			

subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sub-hepatic eventration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Episode of confusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Maniac bend			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Confusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Tromboembolic event			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left inner leg lymphedema			

subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver hematoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Femur fracture			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture at right arm			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection without neutropenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			

subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A - Paclitaxel	Arm B - Paclitaxel and Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 32 (96.88%)	27 / 27 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Left breast nodule			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Melanome in situ type dubreuilh			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Vascular disorders			
Bleeding			
subjects affected / exposed	5 / 32 (15.63%)	17 / 27 (62.96%)	
occurrences (all)	5	17	
Hypertention			
subjects affected / exposed	26 / 32 (81.25%)	25 / 27 (92.59%)	
occurrences (all)	26	25	
Thromboembolic event			
subjects affected / exposed	1 / 32 (3.13%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Surgical and medical procedures			
Carpel tunnel surgery			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Eventration at the surgery scar area			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Eventration on hepatic surgery scar			

subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Liver surgery			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Sub-hepatic eventration			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 32 (62.50%)	21 / 27 (77.78%)	
occurrences (all)	20	21	
Nausea/vomiting			
subjects affected / exposed	13 / 32 (40.63%)	10 / 27 (37.04%)	
occurrences (all)	13	10	
Pain			
subjects affected / exposed	11 / 32 (34.38%)	14 / 27 (51.85%)	
occurrences (all)	11	14	
Cephalalgia			
subjects affected / exposed	0 / 32 (0.00%)	3 / 27 (11.11%)	
occurrences (all)	0	3	
Cognitive disturbance			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Condition deterioration			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Confusion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 32 (6.25%)	4 / 27 (14.81%)	
occurrences (all)	2	4	
Dizziness			

subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)
occurrences (all)	1	1
Dry cough		
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)
occurrences (all)	1	1
Dry mouth		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Dry mucosa in nose and mouth		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Dysgeusia		
subjects affected / exposed	3 / 32 (9.38%)	6 / 27 (22.22%)
occurrences (all)	3	6
Ear, nose, throat disorders		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Episode of confusion		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Fever		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Headache		
subjects affected / exposed	1 / 32 (3.13%)	5 / 27 (18.52%)
occurrences (all)	1	5
Hoarseness		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Influence		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Insomnia		
subjects affected / exposed	2 / 32 (6.25%)	1 / 27 (3.70%)
occurrences (all)	2	1
Malaise		

subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Nasal dryness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Right arm pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Taste disturbances			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Broken tooth			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Weight gain			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Gingival bleeding			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Right calf pain			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	31 / 32 (96.88%)	27 / 27 (100.00%)	
occurrences (all)	31	27	
Reproductive system and breast disorders			

Vaginal dryness subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Rhinitis subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	3 / 27 (11.11%) 3	
Dyspnoea subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Dyspnea subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 4	7 / 27 (25.93%) 7	
Pleural effusion subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Pneumothorax subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Pulmonary fibrosis subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	3 / 27 (11.11%) 3	
Depressive mood subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Maniac bend subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Irritation subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Product issues			

Palmar-plantar erythrodysesthesia subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	3 / 27 (11.11%) 3	
Fall on ice subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Hot flush subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 27 (7.41%) 2	
Cardiac disorders Sinus bradycardia in ECG subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Tachycardia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Hypertensive peak at 17.11 on 24 sep 2013 subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Nervous system disorders Neuropathy subjects affected / exposed occurrences (all)	18 / 32 (56.25%) 18	21 / 27 (77.78%) 21	
Leg neuropathic pain subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Nocturnal legs impatience subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Sleep disorders subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	2 / 27 (7.41%) 2	
Tremor subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Balance disorder			

subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Cervicalgia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	10 / 32 (31.25%)	8 / 27 (29.63%)	
occurrences (all)	10	8	
Creatinemia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	6 / 32 (18.75%)	7 / 27 (25.93%)	
occurrences (all)	6	7	
Thrombocytopenia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Ascites			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Edema			
subjects affected / exposed	9 / 32 (28.13%)	5 / 27 (18.52%)	
occurrences (all)	9	5	
Hematoma lower legs			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hyperkalemia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Hyperlipidemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridemia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 27 (0.00%)	
occurrences (all)	2	0	

Hypoalbuminemia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Left inner leg lymphedema subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	2 / 27 (7.41%) 2	
Lymphopenia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Eye disorders Advancing cataract right eye subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Blurred vision subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Cataract right eye subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Eye disorder subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Xerophthalmia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	11 / 32 (34.38%) 11	11 / 27 (40.74%) 11	
Diarrhea subjects affected / exposed occurrences (all)	13 / 32 (40.63%) 13	11 / 27 (40.74%) 11	
Abdominal cramps			

subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Bloating		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Bowel obstruction		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Esophageal reflux		
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	2
Gastroenteritis		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Gastrointestinal pain		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Gastroesophageal reflux		
subjects affected / exposed	1 / 32 (3.13%)	5 / 27 (18.52%)
occurrences (all)	1	5
Hemorrhoids		
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)
occurrences (all)	1	1
Hiatal hernia		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Melena		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Occlusive syndrome		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Oesophagitis		

subjects affected / exposed	2 / 32 (6.25%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Pharyngeal burns			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	1 / 32 (3.13%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
Direct bilirubin increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
GGT			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Hypertransaminasemia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
GGT increase			
subjects affected / exposed	1 / 32 (3.13%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
ALAT increase			
subjects affected / exposed	2 / 32 (6.25%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Hepatic metolysis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Liver hematoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 32 (34.38%)	15 / 27 (55.56%)	
occurrences (all)	11	15	
Mucositis			
subjects affected / exposed	7 / 32 (21.88%)	4 / 27 (14.81%)	
occurrences (all)	7	4	
Acneous			
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Cat bite			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cheek rash			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Corneal ulcer			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Cutaneous dryness			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Cutaneous eruption			
subjects affected / exposed	2 / 32 (6.25%)	1 / 27 (3.70%)	
occurrences (all)	2	1	
Depigmentation of the trunk			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	4 / 32 (12.50%)	2 / 27 (7.41%)	
occurrences (all)	4	2	
Erythema			
subjects affected / exposed	2 / 32 (6.25%)	4 / 27 (14.81%)	
occurrences (all)	2	4	
Exanthema			

subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Facial redness		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Gingival abscess		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Gingivitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Hyperpigmentation neck, hands, feet		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Mouth ulceration		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Palpebral erythma		
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)
occurrences (all)	1	0
Pruritic vesicles		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Psoriasis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Rash		
subjects affected / exposed	3 / 32 (9.38%)	2 / 27 (7.41%)
occurrences (all)	3	2
Scalp folliculitis		
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)
occurrences (all)	0	1
Skin dryness		
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)
occurrences (all)	1	1
Vitiligo		

subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Xerosis			
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Rash in the left calf			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 32 (12.50%)	18 / 27 (66.67%)	
occurrences (all)	4	18	
Burns micturition			
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Hematoria			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Interference in urinary flow			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Urinary frequency			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Urinary track obstruction (asymptomatic hydronephrosis) subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Endocrine disorders			
Diabetes mellitus type II subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Glycemia subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 2	0 / 27 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	7 / 32 (21.88%) 7	12 / 27 (44.44%) 12	
Nail loss subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	8 / 27 (29.63%) 8	
Acute osteoarthritis subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Calf cramps subjects affected / exposed occurrences (all)	1 / 32 (3.13%) 1	0 / 27 (0.00%) 0	
Femur fracture subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Mascular cramps subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Open fracture right arm subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Sprained ankle			

subjects affected / exposed occurrences (all)	0 / 32 (0.00%) 0	1 / 27 (3.70%) 1	
Infections and infestations			
Infection without neutropenia			
subjects affected / exposed	9 / 32 (28.13%)	10 / 27 (37.04%)	
occurrences (all)	9	10	
Cold			
subjects affected / exposed	2 / 32 (6.25%)	4 / 27 (14.81%)	
occurrences (all)	2	4	
Dental infection			
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Erysipele			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Mycotic infection after surgery			
subjects affected / exposed	0 / 32 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Rhinopharyngitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Bronchial infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Herpes lips			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Left hallux infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Eye stye			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 27 (7.41%)	
occurrences (all)	0	2	
Hypercholesterolemia			
subjects affected / exposed	1 / 32 (3.13%)	1 / 27 (3.70%)	
occurrences (all)	1	1	
Hyperuricemia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Increased creatinine			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Triglycerides			
subjects affected / exposed	1 / 32 (3.13%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 November 2012	Substantial Amendment #1 was approved
13 December 2012	Substantial Amendment #2 was approved
28 February 2013	Substantial Amendment #3 was approved
10 July 2013	Substantial Amendment #4 was approved
11 September 2013	Substantial Amendment #5 was approved
22 October 2014	Substantial Amendment #6 was approved
25 February 2015	Substantial Amendment #7 was approved
22 July 2015	Substantial Amendment #8 was approved
16 December 2015	Substantial Amendment #9 was approved
09 September 2016	Substantial Amendment #10 was approved
13 November 2018	Substantial Amendment #11 was approved

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Absence of a bevacizumab-alone arm
The choice of a 6-month progression-free rate as the primary outcome given the observed median PFS exceeding 12 months
It is unclear whether the results apply to very rare tumor types

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33030515>