Clinical trial results:
Phase IB-II, open label, multicentre feasibility study of pazopanib in combination with Paclitaxel and Carboplatin in patients with platinumrefractory/ resistant ovarian, fallopian tube or peritoneal carcinoma.

Summary

EudraCT number	2010-024077-39
Trial protocol	BE NL ES
Global end of trial date	13 July 2020

Results information

Result version number	v1 (current)
This version publication date	28 August 2022
First version publication date	28 August 2022

Trial information

Trial identification

Sponsor protocol code	55092

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01402271
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Head Clinical Operations Dpt, European Organisation for Research and Treatment of Cancer, 0032 27741015, eortc@eortc.org
Scientific contact	Head Clinical Operations Dpt, European Organisation for Research and Treatment of Cancer, 0032 27741015, eortc@eortc.org

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	13 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 July 2020
Global end of trial reached?	Yes
Global end of trial date	13 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine the activity measured by progression free survival (PFS) according to the RECIST 1.1 of the combination of Pazopanib with weekly paclitaxel and carboplatin in platinum resistant ovarian, fallopian tube or peritoneal carcinoma at the optimum dose established in the phase I part.

Protection of trial subjects:

The study is conducted in agreement with the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the participating countries, whichever provides the greatest protection of the patient. The protocol has been written, and the study conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.
Safety data were reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Safety information was included in trial status reports which served as a basis of discussion during EORTC Group meetings.

Background therapy:

Standard arm:
According to institutional policies and patient's history:
- Scheme 1: paclitaxel weekly at a dose of 80 mg/m² for 18 courses
- Scheme 2: paclitaxel weekly at a dose of 80 mg/m² for 18 courses combined with bevacizumab at a dose of 15 mg/kg 3 weekly
- Scheme 3: paclitaxel weekly at a dose of 60mg/m² for 18 courses combined with carboplatin at an AUC of 2.7 weekly for 18 courses

Experimental arm: carboplatin AUC 2.0 weekly and paclitaxel 30 mg/m² weekly and Pazopanib 400 mg daily for 18 courses.

Evidence for comparator:

Several phase I/II studies were conducted previously with promising results. Du Bois et al (duBois A, Floquet A, Kim J, et al. Randomized, double-blind, phase III trial of pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (AEOC): results of an international Intergroup trial (AGO-OVAR16). Am Soc Clin Oncol. 2013;31 Suppl:LBA5503), presented the results of the AGO-OVAR-16 study of maintenance pazopanib in women with advanced newly diagnosed EOC. The trial was a double-blinded, multicenter Phase III study that randomized 940 women with advanced-stage EOC, FTC, or PPC to receive maintenance pazopanib versus placebo for 24 months. All patients had previously achieved a clinical response with first-line platinum-based therapy. Median PFS was significantly longer in the pazopanib group (17.9 versus 12.3, HR 0.77, 95% CI 0.64–0.91, P=0.0021).
Angiogenesis and especially targeting VEGF has been shown to be very interesting in gynaecological cancer. In preclinical models of ovarian cancer, anti-VEGF therapy has been shown to inhibit ascites formation, slow tumor growth and synergy with cytotoxic agents.

Actual start date of recruitment	01 November 2011
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	Netherlands: 48
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Belgium: 31
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	44
From 65 to 84 years	43
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The phase Ib part of the trial enrolled 28 patients by 3 centers from 3 countries (Netherlands, Belgium, Spain) between 24/08/2012.and 22/01/2014 across 4 different dose levels. Between 26 May 2015 and 15 May 2018, 60 patients were randomized by 7 centers from 3 countries (Netherlands, Belgium, Spain) in the phase II part.

Pre-assignment

Screening details:

Phase II: Histologically confirmed ovarian, fallopian tube, or peritoneal carcinoma with recurrent disease. At least one earlier platinum treatment can be included but should be platinum-resistant. Non-platinum treatment after proven platinum resistance disease is allowed. Evaluable disease by RECIST v. 1.1. WHO Performance status must be ≤ 2.

Period 1

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

Blinding implementation details:

Recruitment into dose levels occurs by allocation to the open dose level cohort in the phase Ib part. In the phase II part, patients are centrally randomized using a minimization technique for random treatment allocation stratifying by institution, number of prior lines (one vs more than one), WHO performance status (0/1 vs 2). The randomization has a 2:1 ratio with double the number of patients in the experimental arm.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard arm

Arm description:

According to institutional policies and patient's history, the patient can receive:
- Scheme 1: paclitaxel weekly at a dose of 80 mg/m² for 18 courses
- Scheme 2: paclitaxel weekly at a dose of 80 mg/m² for 18 courses combined with bevacizumab at a dose of 15 mg/kg 3 weekly
- Scheme 3: paclitaxel weekly at a dose of 60mg/m² for 18 courses combined with carboplatin at an AUC of 2.7 weekly for 18 courses

Arm type	standard of care

No investigational medicinal product assigned in this arm

Arm title	Experimental arm

Arm description:

Carboplatin AUC 2.0 weekly and paclitaxel 30 mg/m² weekly and Pazopanib 400 mg daily for 18 courses. Patients can continue pazopanib (at the standard dose of 800 mg per day) after the planned 18 courses of paclitaxel-carboplatin weekly until documented disease progression, unacceptable toxicity or patient refusal.

Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 400mg will be given daily orally. Pazopanib will not be administered on the day paclitaxel and carboplatin is administered. Between last pazopanib dose and start of the chemotherapy administration, and also between the end of chemotherapy administration and the next pazopanib dose a period of 24

hours should elapse. Pazopanib will be continued at a dose of 400 mg per day after the last paclitaxel-carboplatin dose, and escalated at the standard dose of 800 mg per day 2 - 4 weeks after the last paclitaxel-carboplatin dose until documented disease progression, unacceptable toxicity or patient refusal.

Arm title	Dose level 1

Arm description:

Paclitaxel 30 mg/m² weekly; Carboplatin 1.5 AUC weekly; Pazopanib 400 mg daily

Arm type	Dose level
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 400mg will be given daily orally. Pazopanib will not be administered on the day paclitaxel and carboplatin is administered. Between last pazopanib dose and start of the chemotherapy administration, and also between the end of chemotherapy administration and the next pazopanib dose a period of 24 hours should elapse. Pazopanib will be continued at a dose of 400 mg per day after the last paclitaxel-carboplatin dose, and escalated at the standard dose of 800 mg per day 2 - 4 weeks after the last paclitaxel-carboplatin dose until documented disease progression, unacceptable toxicity or patient refusal.

Arm title	Dose level 2

Arm description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 400 mg daily.

Arm type	Dose level
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 400mg will be given daily orally. Pazopanib will not be administered on the day paclitaxel and carboplatin is administered. Between last pazopanib dose and start of the chemotherapy administration, and also between the end of chemotherapy administration and the next pazopanib dose a period of 24 hours should elapse. Pazopanib will be continued at a dose of 400 mg per day after the last paclitaxel-carboplatin dose, and escalated at the standard dose of 800 mg per day 2 - 4 weeks after the last paclitaxel-carboplatin dose until documented disease progression, unacceptable toxicity or patient refusal.

Arm title	Dose level 3

Arm description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 800 mg daily

Arm type	Dose level
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 800mg will be given daily orally. Pazopanib will not be administered on the day paclitaxel and carboplatin is administered. Between last pazopanib dose and start of the chemotherapy administration, and also between the end of chemotherapy administration and the next pazopanib dose a period of 24

hours should elapse. Pazopanib will be continued at a dose of 800 mg per day after the last paclitaxel-carboplatin dose, and 2 - 4 weeks after the last paclitaxel-carboplatin dose until documented disease progression, unacceptable toxicity or patient refusal.

Arm title	Dose level 7

Arm description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 600 mg daily

Arm type	Dose level
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pazopanib 600mg will be given daily orally. Pazopanib will not be administered on the day paclitaxel and carboplatin is administered. Between last pazopanib dose and start of the chemotherapy administration, and also between the end of chemotherapy administration and the next pazopanib dose a period of 24 hours should elapse. Pazopanib will be continued at a dose of 600 mg per day after the last paclitaxel-carboplatin dose, and escalated at the standard dose of 800 mg per day 2 - 4 weeks after the last paclitaxel-carboplatin dose until documented disease progression, unacceptable toxicity or patient refusal.

Number of subjects in period 1	Standard arm	Experimental arm	Dose level 1
Started	21	39	8
Completed	9	14	6
Not completed	12	25	2
Consent withdrawn by subject	1	1	-
Physician decision	1	-	-
chemotherapy not started due to pleural empyema	-	-	-
Adverse event, non-fatal	3	10	-
progressive disease	7	13	-
clinical deterioration	-	1	-
Protocol deviation	-	-	2

Number of subjects in period 1	Dose level 2	Dose level 3	Dose level 7
Started	6	7	7
Completed	5	6	6
Not completed	1	1	1
Consent withdrawn by subject	-	-	-
Physician decision	-	-	-
chemotherapy not started due to pleural empyema	1	-	-
Adverse event, non-fatal	-	-	-

progressive disease	-	-	-
clinical deterioration	-	-	-
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups

Reporting group title	Standard arm

Reporting group description:

According to institutional policies and patient's history, the patient can receive:
- Scheme 1: paclitaxel weekly at a dose of 80 mg/m² for 18 courses
- Scheme 2: paclitaxel weekly at a dose of 80 mg/m² for 18 courses combined with bevacizumab at a dose of 15 mg/kg 3 weekly
- Scheme 3: paclitaxel weekly at a dose of 60mg/m² for 18 courses combined with carboplatin at an AUC of 2.7 weekly for 18 courses

Reporting group title	Experimental arm

Reporting group description:

Carboplatin AUC 2.0 weekly and paclitaxel 30 mg/m² weekly and Pazopanib 400 mg daily for 18 courses. Patients can continue pazopanib (at the standard dose of 800 mg per day) after the planned 18 courses of paclitaxel-carboplatin weekly until documented disease progression, unacceptable toxicity or patient refusal.

Reporting group title	Dose level 1

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 1.5 AUC weekly; Pazopanib 400 mg daily

Reporting group title	Dose level 2

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 400 mg daily.

Reporting group title	Dose level 3

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 800 mg daily

Reporting group title	Dose level 7

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 600 mg daily

Reporting group values	Standard arm	Experimental arm	Dose level 1
Number of subjects	21	39	8
Age categorical Units: Subjects			
Adults (18-64 years)	13	16	6
From 65-84 years	8	22	2
85 years and over	0	1	0
Age continuous Units: years			
median	60.9	66.4	59.7
inter-quartile range (Q1-Q3)	53.8 to 68.7	57.7 to 72.1	52.6 to 64.4
Gender categorical Units: Subjects			
Female	21	39	8
Male	0	0	0

WHO PS			
WHO performance status			
Units: Subjects			
PS 0	5	20	4
PS 1	14	18	4
PS 2	2	1	0
Tumor grade Units: Subjects			
Well differentiated	2	4	3
Moderately differentiated	3	0	1
Poorly differentiated	15	27	1
Unknown	1	8	3
Histology Units: Subjects			
Serous	17	33	5
Clear cell	1	3	2
Endometroid	1	1	0
Undifferentiated	1	1	0
Other/mixed	1	1	1
number of prior lines Units: Subjects			
one	4	6	0
more than one	17	33	8
Time since initial diagnosis Units: months			
median	25.9	38.1	26.7
inter-quartile range (Q1-Q3)	17.3 to 41.5	18.7 to 54.3	14.9 to 55.9
Time since last platinum based chemotherapy Units: weeks			
median	25.1	25.9	23.9
inter-quartile range (Q1-Q3)	19.3 to 43.6	19.9 to 45.0	15.6 to 31.1

Reporting group values	Dose level 2	Dose level 3	Dose level 7
Number of subjects	6	7	7
Age categorical Units: Subjects			
Adults (18-64 years)	1	4	4
From 65-84 years	5	3	3
85 years and over	0	0	0
Age continuous Units: years			
median	65.7	63.9	63.4
inter-quartile range (Q1-Q3)	65.0 to 66.6	55.2 to 66.4	49.2 to 67.7
Gender categorical Units: Subjects			
Female	6	7	7
Male	0	0	0
WHO PS			
WHO performance status			
Units: Subjects			

PS 0	1	1	2
PS 1	5	6	5
PS 2	0	0	0
Tumor grade Units: Subjects			
Well differentiated	3	1	3
Moderately differentiated	0	2	0
Poorly differentiated	3	3	2
Unknown	0	1	2
Histology Units: Subjects			
Serous	4	6	3
Clear cell	0	0	1
Endometroid	0	0	1
Undifferentiated	1	0	0
Other/mixed	1	1	2
number of prior lines Units: Subjects			
one	1	1	1
more than one	5	6	6
Time since initial diagnosis Units: months			
median	27.6	36.3	31.8
inter-quartile range (Q1-Q3)	12.1 to 39.3	25.1 to 71.7	25.7 to 53.2
Time since last platinum based chemotherapy Units: weeks			
median	34.0	18.4	28.2
inter-quartile range (Q1-Q3)	29.4 to 40.1	10.1 to 30.0	15.6 to 34.9

Reporting group values	Total		
Number of subjects	88		
Age categorical Units: Subjects			
Adults (18-64 years)	44		
From 65-84 years	43		
85 years and over	1		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical Units: Subjects			
Female	88		
Male	0		
WHO PS			
WHO performance status			
Units: Subjects			
PS 0	33		
PS 1	52		
PS 2	3		

Tumor grade Units: Subjects			
Well differentiated	16		
Moderately differentiated	6		
Poorly differentiated	51		
Unknown	15		
Histology Units: Subjects			
Serous	68		
Clear cell	7		
Endometroid	3		
Undifferentiated	3		
Other/mixed	7		
number of prior lines Units: Subjects			
one	13		
more than one	75		
Time since initial diagnosis Units: months			
median			
inter-quartile range (Q1-Q3)	-		
Time since last platinum based chemotherapy Units: weeks			
median			
inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Standard arm

Reporting group description:

According to institutional policies and patient's history, the patient can receive:
- Scheme 1: paclitaxel weekly at a dose of 80 mg/m² for 18 courses
- Scheme 2: paclitaxel weekly at a dose of 80 mg/m² for 18 courses combined with bevacizumab at a dose of 15 mg/kg 3 weekly
- Scheme 3: paclitaxel weekly at a dose of 60mg/m² for 18 courses combined with carboplatin at an AUC of 2.7 weekly for 18 courses

Reporting group title	Experimental arm

Reporting group description:

Carboplatin AUC 2.0 weekly and paclitaxel 30 mg/m² weekly and Pazopanib 400 mg daily for 18 courses. Patients can continue pazopanib (at the standard dose of 800 mg per day) after the planned 18 courses of paclitaxel-carboplatin weekly until documented disease progression, unacceptable toxicity or patient refusal.

Reporting group title	Dose level 1

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 1.5 AUC weekly; Pazopanib 400 mg daily

Reporting group title	Dose level 2

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 400 mg daily.

Reporting group title	Dose level 3

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 800 mg daily

Reporting group title	Dose level 7

Reporting group description:

Paclitaxel 30 mg/m² weekly; Carboplatin 2.0 AUC weekly; Pazopanib 600 mg daily

Primary: PFS at year 1

End point title	PFS at year 1

End point description:

Success is defined as alive and without confirmed progression at or after 1 year from randomization are considered a success. Patients who died or progressed before the 1 year mark will be considered as failures. Patients who are unevaluable for tumour assessment are considered as failures. If a patient was last without confirmed progression > 1 month before the 1 year mark and has a confirmed progression at the first post 1-year assessment, that patient is also considered a failure.

End point type	Primary

End point timeframe:

Up to 1 year after randomization. Progression assessed via RECIST 1.1.

End point values	Standard arm	Experimental arm	Dose level 1	Dose level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	39	0[1]	0[2]
Units: Subjects				
Alive without PD	1	1		
Dead/PD/NE	20	38		

Notes:

[1] - Arm used for dose level finding purpose only

[2] - Arm used for dose level finding purpose only

End point values	Dose level 3	Dose level 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: Subjects				
Alive without PD				
Dead/PD/NE				

Notes:

[3] - Arm used for dose level finding purpose only

[4] - Arm used for dose level finding purpose only

Statistical analyses

Statistical analysis title	PFS difference at 1 year

Statistical analysis description:

The decision rule states that in order to exclude a 10% 1-year PFS rate while accepting a 25 % rate, at least 7 patients out of 40 need to be alive and progression free at 1 year.

Comparison groups	Experimental arm v Standard arm
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	PFS % at year 1 in experimental arm
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	13.5

Notes:

[5] - Although only 39 patients were enrolled in the experimental arm, the decision rule can still be evaluated. As this study reported only 1 such patient out of 39 enrolled in the experimental, the criteria for success can not be met.

Secondary: Best overall response

End point title	Best overall response

End point description:

Best response observed during the trial according to RECIST 1.1

End point type	Secondary

End point timeframe:

Best response observed during the trial

End point values	Standard arm	Experimental arm	Dose level 1	Dose level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	39	0[6]	0[7]
Units: Subjects				
Partial Response	8	7		
Stable Disease	6	20		
Progressive Disease	7	9		
Early death	0	2		
Not evaluable	0	1		

Notes:

[6] - Arm used for dose level finding purpose only

[7] - Arm used for dose level finding purpose only

End point values	Dose level 3	Dose level 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Subjects				
Partial Response				
Stable Disease				
Progressive Disease				
Early death				
Not evaluable				

Notes:

[8] - Arm used for dose level finding purpose only

[9] - Arm used for dose level finding purpose only

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Proportion of patients who achieved a complete response , partial response or stable disease.

End point type	Secondary

End point timeframe:

Based on best response observed during trial

End point values	Standard arm	Experimental arm	Dose level 1	Dose level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	39	0[10]	0[11]
Units: Subjects				
CR/PR/SD	14	27		

Notes:

[10] - Arm used for dose level finding purpose only

[11] - Arm used for dose level finding purpose only

End point values	Dose level 3	Dose level 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Subjects				
CR/PR/SD				

Notes:

[12] - Arm used for dose level finding purpose only

[13] - Arm used for dose level finding purpose only

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression free survival will be defined as the time interval between the date of randomization and the date of disease progression or death (any cause), whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow-up examination.

End point type	Secondary

End point timeframe:

Based on survival status and tumour response observed during the trial

End point values	Standard arm	Experimental arm	Dose level 1	Dose level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	39	0[14]	0[15]
Units: months				
median (confidence interval 95%)	6.5 (2.6 to 7.6)	4.9 (3.4 to 6.7)	(to)	(to)

Notes:

[14] - Arm used for dose level finding purpose only

[15] - Arm used for dose level finding purpose only

End point values	Dose level 3	Dose level 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[16] - Arm used for dose level finding purpose only

[17] - Arm used for dose level finding purpose only

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival will be defined as the time interval between the date of randomization and the date of death. Patients who were still alive when last traced are censored at the date of the last follow-up.

End point type	Secondary

End point timeframe:

Based on the survival status observed during the trial

End point values	Standard arm	Experimental arm	Dose level 1	Dose level 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	39	0[18]	0[19]
Units: months				
median (confidence interval 95%)	11.2 (5.7 to 13.5)	11.5 (6.1 to 15.5)	(to)	(to)

Notes:

[18] - Arm used for dose level finding purpose only

[19] - Arm used for dose level finding purpose only

End point values	Dose level 3	Dose level 7		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[20] - Arm used for dose level finding purpose only

[21] - Arm used for dose level finding purpose only

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded as they occur and graded according to the CTCAE version 4.0 from time of enrollment until 30 days after last protocol treatment or if deemed related to study participation.

Adverse event reporting additional description:

AEs are evaluated using CTCAE v4 grading, SAEs using MedDra. AEs were also derived from laboratory toxicities if grade ≥3 and all laboratory toxicities that triggered a treatment modification, if not reported on an AE form, were added.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Standard arm

Reporting group description:

Standard arm

Reporting group title	Experimental arm

Reporting group description:

Experimental arm

Serious adverse events	Standard arm	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 21 (33.33%)	15 / 39 (38.46%)	
number of deaths (all causes)	20	32	
number of deaths resulting from adverse events	0	0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			

alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPRESSION FRACTURE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (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			
ANAEMIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
PANCYTOPENIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ENTEROCUTANEOUS FISTULA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASCITES			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ILEUS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL PSEUDO-OBSTRUCTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
FEMALE GENITAL TRACT FISTULA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA EXERTIONAL			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HYDRONEPHROSIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Infections and infestations			
BACTERAEMIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN ABSCESS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard arm	Experimental arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)	39 / 39 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 21 (19.05%)	8 / 39 (20.51%)	
occurrences (all)	8	11	
Vascular disorders			
FLUSHING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	3	
HEMATOMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
HOT FLASHES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
LYMPHOCELE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
HYPOTENSION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	3 / 21 (14.29%)	4 / 39 (10.26%)	
occurrences (all)	3	5	
HYPERTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 21 (28.57%)	20 / 39 (51.28%)	
occurrences (all)	19	66	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	1 / 39 (2.56%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
EDEMA FACE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
EDEMA LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	8 / 39 (20.51%)	
occurrences (all)	2	10	
FATIGUE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	13 / 21 (61.90%)	34 / 39 (87.18%)	
occurrences (all)	41	91	
FEVER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 21 (19.05%)	5 / 39 (12.82%)	
occurrences (all)	5	6	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	4 / 21 (19.05%)	9 / 39 (23.08%)	
occurrences (all)	6	14	
GENERAL DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INFUSION RELATED REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
INFUSION SITE EXTRAVASATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
INJECTION SITE REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	2	3	
INFUSION SITE REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
MALAISE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	8 / 39 (20.51%)	
occurrences (all)	3	15	

Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 21 (23.81%)	6 / 39 (15.38%)	
occurrences (all)	9	8	
AUTOIMMUNE DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
CYTOKINE RELEASE SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
ANAPHYLAXIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
VAGINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 21 (19.05%)	9 / 39 (23.08%)	
occurrences (all)	8	11	
DYSPNEA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	5 / 21 (23.81%)	18 / 39 (46.15%)	
occurrences (all)	8	24	
HOARSENESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
EPISTAXIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 21 (33.33%)	9 / 39 (23.08%)	
occurrences (all)	9	11	
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	5	
PRODUCTIVE COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VOICE ALTERATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
SORE THROAT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	2	
Psychiatric disorders			
INSOMNIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
DEPRESSION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 21 (4.76%)	2 / 39 (5.13%)	
occurrences (all)	1	2	
ANXIETY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	2 / 39 (5.13%)	
occurrences (all)	2	4	
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	3	
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 21 (28.57%)	10 / 39 (25.64%)	
occurrences (all)	18	37	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 21 (19.05%)	8 / 39 (20.51%)	
occurrences (all)	12	34	
WEIGHT LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	4 / 39 (10.26%)	
occurrences (all)	3	6	
PLATELET COUNT DECREASED			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	7 / 21 (33.33%)	11 / 39 (28.21%)	
occurrences (all)	23	40	
Injury, poisoning and procedural complications			
FRACTURE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	2	2	
BRUISING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - SCAPE WOUND			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RECTOVAGINAL FISTULA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Cardiac disorders			
PALPITATIONS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPERTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PERICARDIAL EFFUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Nervous system disorders			

ATAXIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
DIZZINESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 21 (28.57%)	9 / 39 (23.08%)	
occurrences (all)	8	15	
DYSESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
DYSGEUSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 21 (28.57%)	11 / 39 (28.21%)	
occurrences (all)	6	11	
SOMNOLENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	8 / 21 (38.10%)	11 / 39 (28.21%)	
occurrences (all)	9	12	
PARESTHESIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
SYNCOPE			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HEADACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	10 / 39 (25.64%)	
occurrences (all)	3	16	
Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ANEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 21 (42.86%)	14 / 39 (35.90%)	
occurrences (all)	28	36	
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
EAR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
HEARING IMPAIRED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
TINNITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	6 / 39 (15.38%)	
occurrences (all)	1	6	
Eye disorders			

BLURRED VISION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	7 / 39 (17.95%)	
occurrences (all)	3	8	
DRY EYE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
EYE DISORDER OTHER: SLING IN THE EYE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PHOTOPHOBIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
FLASHING LIGHTS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
VITREOUS HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RETINAL DETACHMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	2	
WATERING EYES			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 21 (4.76%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 21 (23.81%)	17 / 39 (43.59%)	
occurrences (all)	7	28	
ASCITES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	5 / 39 (12.82%)	
occurrences (all)	1	7	
COLITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
BLOATING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
COLONIC OBSTRUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
CONSTIPATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	9 / 21 (42.86%)	20 / 39 (51.28%)	
occurrences (all)	12	39	
DIARRHEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	7 / 21 (33.33%)	23 / 39 (58.97%)	
occurrences (all)	9	53	
DRY MOUTH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	2 / 39 (5.13%)	
occurrences (all)	5	2	
DYSPEPSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	7 / 39 (17.95%)	
occurrences (all)	3	9	
DYSPHAGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
FLATULENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ENTEROCUTANEOUS FISTULA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
LOWER GASTROINTESTINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
ILEUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	4 / 39 (10.26%)	
occurrences (all)	0	7	

GASTROINTESTINAL DISORDERS, OTHER - GASTRIC COMPLAINTS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	2	
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	7 / 39 (17.95%)	
occurrences (all)	13	10	
NAUSEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	18 / 21 (85.71%)	28 / 39 (71.79%)	
occurrences (all)	29	54	
ORAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PERIODONTAL DISEASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RECTAL ULCER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
VOMITING			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	8 / 21 (38.10%)	15 / 39 (38.46%)	
occurrences (all)	18	27	
TOOTHACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
STOMACH PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Hepatobiliary disorders			
HEPATIC PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ABSCESS GROIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPERHIDROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
ALOPECIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 21 (52.38%)	8 / 39 (20.51%)	
occurrences (all)	18	8	
DRY SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	2 / 39 (5.13%)	
occurrences (all)	3	2	
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PAIN OF SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
NAIL RIDGING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	0 / 39 (0.00%)	
occurrences (all)	2	0	
NAIL LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
NAIL CHANGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RASH ACNEIFORM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	0 / 39 (0.00%)	
occurrences (all)	3	0	
RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	3	1	
PRURITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	2 / 39 (5.13%)	
occurrences (all)	2	3	

RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	4 / 39 (10.26%)	
occurrences (all)	1	4	
SKIN AND SUBCUTANEOUS TISSUE DISORDER OTHER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS OTHER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN HYPOPIGMENTATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
SKIN RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
SKIN ULCERATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
PROTEINURIA			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	5 / 39 (12.82%)	
occurrences (all)	1	10	
HEMATURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RENAL AND URINARY DISORDERS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
RENAL AND URINARY DISORDERS - OTHER: DYSURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
URINARY INCONTINENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
URINARY TRACT PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Endocrine disorders			
CUSHINGOID			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
ARTHRITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	3	
BACK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 21 (19.05%)	2 / 39 (5.13%)	
occurrences (all)	7	3	
FLANK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCLE WEAKNESS UPPER LIMB			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
MUSCULOSKELETAL - OTHER, SPECIFY; MUSCLE CRAMPS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER,SPEC			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - CRAMPS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER, OTHER CRAMP			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
MUSCULOSKELETAL/CONNECTIVE TISSUE DISORDER - OTHER STIFFNESS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	3 / 39 (7.69%)	
occurrences (all)	1	5	
MYALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 21 (14.29%)	9 / 39 (23.08%)	
occurrences (all)	3	13	
NECK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
Infections and infestations			
BLADDER INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	3 / 39 (7.69%)	
occurrences (all)	2	6	
CATHETER RELATED INFECTION			

alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)		
occurrences (all)	0	1		
NAIL INFECTION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)		
occurrences (all)	0	6		
LUNG INFECTION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)		
occurrences (all)	0	3		
INFECTIONS AND INFESTATIONS - OTHER: PULMONARY INFECTION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)		
occurrences (all)	2	0		
EYE INFECTION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)		
occurrences (all)	0	1		
PHARYNGITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)		
occurrences (all)	2	0		
SEPSIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 21 (0.00%)	2 / 39 (5.13%)		
occurrences (all)	0	2		
SKIN INFECTION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 21 (9.52%)	0 / 39 (0.00%)		
occurrences (all)	5	0		
URINARY TRACT INFECTION				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	4 / 21 (19.05%)	5 / 39 (12.82%)	
occurrences (all)	4	6	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 21 (9.52%)	3 / 39 (7.69%)	
occurrences (all)	2	5	
VAGINAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
WOUND INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	8 / 21 (38.10%)	28 / 39 (71.79%)	
occurrences (all)	14	43	
HYPERGLYCEMIA AND GLUCOSE INTOLERANCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 21 (0.00%)	1 / 39 (2.56%)	
occurrences (all)	0	1	
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	5 / 39 (12.82%)	
occurrences (all)	1	9	
HYPOKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 21 (4.76%)	2 / 39 (5.13%)	
occurrences (all)	1	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2014	Substantial changes were made to accommodate the transition from phase Ib to phase II: - Change of inclusion criteria to exclude platinum refractory patients - Removal of all sections describing procedures applicable for the phase Ib part - Description of the results of the phase Ib part with the recommended dose level - Change of follow-up after end of chemotherapy of control arm and patients from the experimental arm that will go on Pazopanib maintenance treatment - Change of statistical analysis plan to remove the stratification according to platinum resistant versus refractory disease and to include stratification according to WHO performance status - Adaptation of PIS/IC.
26 September 2016	Based on the results of the AURELIA trial, changes in Standard arm have been introduced with possibility for the Principal Investigator to choose the standard treatment, according to institutional policies and patient's history, among : - paclitaxel weekly at a dose of 80 mg/m² for 18 courses - paclitaxel weekly at a dose of 80 mg/m² for 18 courses combined with bevacizumab at a dose of 15 mg/kg 3 weekly - paclitaxel weekly at a dose of 60mg/m² for 18 courses combined with carboplatin at an AUC of 2.7 weekly

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.

Posting of results is limited to the phase II part of the trial . The trial was amended after phase Ib to limit the patient population to resistant patients only despite the title of the trial retaining the term “platinum-refractory/resistant".

Notes: