Clinical trial results:
PAZOFOS: A Phase Ib and Randomised Phase II Trial of Pazopanib with or without Fosbretabulin in Advanced Recurrent Ovarian Cancer

Summary

EudraCT number	2013-005471-40
Trial protocol	GB
Global end of trial date	05 December 2017

Results information

Result version number	v1 (current)
This version publication date	28 June 2023
First version publication date	28 June 2023

Trial information

Trial identification

Sponsor protocol code	CFTSp074

Additional study identifiers

ISRCTN number	ISRCTN30090285
ClinicalTrials.gov id (NCT number)	NCT02055690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	Clinical Trials Project Manager, The Christie NHS Foundation Trust, +44 0161 918 7492, colin.lunt@christie.nhs.uk
Scientific contact	Clinical Trials Project Manager, The Christie NHS Foundation Trust, +44 0161 918 7492, colin.lunt@christie.nhs.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2017
Global end of trial reached?	Yes
Global end of trial date	05 December 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase Ib (dose escalation) objectives
(a) To propose a recommended dose for Phase II evaluation by: Establishing the maximum tolerated dose of Fosbretabulin in combination with Pazopanib.
(b) Assessing the safety and toxicity profile of Fosbretabulin in combination with Pazopanib.

Randomised Phase II objectives
To determine whether combining Fosbretabulin with pazopanib produces a significant improvement in progression free survival compared to Pazopanib alone.

Protection of trial subjects:

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety without prior authorisation from the MHRA and ethics committee. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health. USMs may be taken without prior authorisation from the competent authority or sponsor. Should the site initiate a USM, the Investigator must inform the MAHSC-CTU immediately. The notification should include the date of the USM, who took the decision and why the action was taken. The MAHSC-CTU will then notify the Sponsor, MHRA and the REC within three days of USM initiation.

Examples of issues requiring urgent safety measures include:
- A single report of a SAR with an unexpected outcome (e.g. death)
- An increase in rate of occurrence of SAR which is judged to be clinically important
- A post-trial SUSAR occurring after the subject has left the trial
- A new event relating to the use or development of an IMP likely to affect the safety of subjects e.g. an SAE that could be associated with the procedures and which could lead to modification of the trial conduct; lack of efficacy of an IMP used for a life-threatening disease; a major safety finding from a newly completed animal study
A protocol amendment is formally submitted within 3 days by the CI and CTPM to the relevant bodies in conjunction with the sponsor.

Annual progress reports will be submitted to the REC. A Development Safety Update Report (DSUR) is submitted annually to the MHRA and REC in accordance with requirements.

Background therapy:

All patients will receive oral metoclopramide 20 mg and paracetamol 1 g 30 minutes prior to administration of fosbretabulin, with dexamethasone 4 mg added if there is > grade 1 fatigue and nausea following the first infusion. Metoclopramide may be substituted by an alternative if necessary on the grounds of unsuitability for a patient. Note that ondansetron, granisetron and related drugs impact of the QTc.

Evidence for comparator:

Fosbretabulin is a synthetic phosphorylated prodrug of combretastatin A4, a naturally occurring derivative of the South African tree Combretum caffrum and a potent inhibitor of microtubule assembly. Evidence of its vascular disrupting activity was first obtained in rodent cancer models and then subsequently established in solid tumors in humans. Combretastatin A4 phosphate targets pre-existing tumor neovasculature, resulting in an acute, reversible reduction in tumor blood flow, leading to central necrosis within tumors. Although VDAs, such as fosbretabulin, have been shown to rapidly reduce blood flow to tumors, they have limited activity as single agents due to rapid regrowth of tumors. This is thought to be due to circulating endothelial progenitor cells repopulating the rim of tumor; kept viable due to surrounding normal vessels. VEGF inhibition has been shown to prevent circulating endothelial progenitor recruitment, and combining VEGF inhibitors with VDAs has in vivo additive anti-tumor

activity.

Actual start date of recruitment	21 July 2014
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	United Kingdom: 33
Worldwide total number of subjects	33
EEA total number of subjects	0

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)	19
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients were females age 18 or over, and had recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. All eligible patients had received ≥1 prior lines of platinum chemotherapy, had progressive evaluable disease according to RECIST v1.1 and/or GCIG CA-125 criteria and an ECOG performance status of 0-1

Pre-assignment

Screening details:

Screening consisted of an assessment of medical history and the following examinations to assess eligibility: Scan of abdomen and pelvis to allow for RECIST 1.1 assessment; ECG with QTc evaluation; Who performance status; safety laboratory assessments including haematology,clinical chemistry; pregnancy test; Translational research samples

Period 1

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

Blinding implementation details:

Because of the route of administration of fosbretabulin, the trial and therefore randomisation will not be blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Pazopanib and fosbretabulin

Arm description:

Pazopanib 600 mg once daily and fosbretabulin 54 mg/m2 on days 1, 8, 15, every 28 days

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

Dosage and administration details:

600 mg pazopanib administered orally (tablets) without food (≥1 h before or ≥ 2 h after a meal) once daily, every 28 days.

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

Dosage and administration details:

Fosbretabulin 54 mg/m2 was administered via a peripheral vein as a weekly intravenous infusion (10-min infusion time) on days 1, 8, 15, every 28 days, for a maximum of 6 cycles. The weekly dose of fosbretabulin was calculated according to body surface area (BSA) and capped at a BSA of 2.2m^2. When pazopanib and fosbretabulin were administered together pazopanib was administered ≥1 h prior to fosbretabulin.

Arm title	Single-agent pazopanib

Arm description:

Pazopanib 800 mg once daily, every 28 days

Arm type	Active comparator

Investigational medicinal product name	Pazopanib
Investigational medicinal product code	
Other name	Votrient
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg pazopanib administered orally (tablets) without food (≥1 h before or ≥ 2 h after a meal) once daily, every 28 days.

Number of subjects in period 1[1]	Pazopanib and fosbretabulin	Single-agent pazopanib
Started	11	10
Completed	11	10

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Pazofos consisted of both a phase 1b and a Phase II trial. The initial phase 1b dose finding non-randomised phase recruited 12 patients. This subset of data has been included as a subject analysis set in order to record baseline and endpoint results. The remaining 21 patients were recruited to the randomised phase II trial where they received either pazopanib 600mg OD and fosbretabulin, or 800mg OD pazopanib alone.

Baseline characteristics

Reporting groups	
Reporting group title	Pazopanib and fosbretabulin
Reporting group description:	
Pazopanib 600 mg once daily and fosbretabulin 54 mg/m2 on days 1, 8, 15, every 28 days	
Reporting group title	Single-agent pazopanib
Reporting group description:	
Pazopanib 800 mg once daily, every 28 days	

Reporting group values	Pazopanib and fosbretabulin	Single-agent pazopanib	Total
Number of subjects	11	10	21
Age categorical			
Age at point of trial consent			
Units: Subjects			
Adults (18-64 years)	9	5	14
From 65-84 years	2	5	7
85 years and over	0	0	0
Age continuous			
Age at point of trial consent			
Units: years			
arithmetic mean	59.3	60.3	
standard deviation	± 8.3	± 10.7	-
Gender categorical			
Units: Subjects			
Female	11	10	21
Male	0	0	0
WHO performance status			
Units: Subjects			
00	7	5	12
01	4	5	9
Primary tumour location			
Units: Subjects			
Ovarian	9	8	17
Fallopian tubes	1	1	2
Primary peritoneal	1	1	2
Histology type			
Units: Subjects			
Serious	10	9	19
Endometrioid	0	0	0
Clear cell	0	1	1
Mucinous	0	0	0
Undifferentiated	1	0	1
Histological grade			
Units: Subjects			
High-grade	10	10	20
Low-grade	0	0	0
Unknown	1	0	1

FIGO stage at diagnosis Units: Subjects			
01	0	3	3
02	2	0	2
03	9	6	15
04	0	1	1
Prior bevacizumab Units: Subjects			
Yes	3	2	5
No	8	8	16
Platinum-free interval Units: Subjects			
≤6 months	6	7	13
>6 months	5	3	8
Age at diagnosis Units: years			
arithmetic mean	56.9	60.3	
full range (min-max)	42 to 71	31 to 68	-
Prior lines of chemotherapy Units: prior lines			
median	3	2	
full range (min-max)	1 to 4	1 to 5	-

Subject analysis sets

Subject analysis set title	Phase 1b patients
Subject analysis set type	Safety analysis

Subject analysis set description:

Twelve patients were enrolled in the Phase 1b trial. The primary endpoints of the phase 1b trial were to determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of pazopanib and fosbretabulin. The MTD was defined if no more than 1 patient, out of a maximum of 6 patients at the same dose level, experienced a DLT. Initially, 3 patients received dose level 1 and 3 patients received dose level 2 without a DLT. However due to multiple delayed grade ≥ 2 toxicities at dose level 2, experienced by patients after completing cycle 1; in particular hypertension and neutropenia, dose level 2 was expanded by a further 3 patients in order to elucidate better the toxicity profile. One of these 3 patients developed a DLT, reported as grade 3 fatigue, and dose level 2 was defined as the MTD. Consequently, dose level 1 was also expanded to include another 3 patients, and no DLTs were reported. Therefore, dose level 1 (600mg Pazopanib OD) was defined as the RP2D.

Reporting group values	Phase 1b patients		
Number of subjects	12		
Age categorical			
Age at point of trial consent			
Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at point of trial consent			
Units: years arithmetic mean standard deviation	±		

Gender categorical Units: Subjects			
Female Male			
WHO performance status Units: Subjects			
00 01	7 5		
Primary tumour location Units: Subjects			
Ovarian Fallopian tubes Primary peritoneal	12 0 0		
Histology type Units: Subjects			
Serious Endometrioid Clear cell Mucinous Undifferentiated	11 1 0 0 0		
Histological grade Units: Subjects			
High-grade Low-grade Unknown	11 1 0		
FIGO stage at diagnosis Units: Subjects			
01 02 03 04	0 0 9 3		
Prior bevacizumab Units: Subjects			
Yes No	2 10		
Platinum-free interval Units: Subjects			
≤6 months >6 months			
Age at diagnosis Units: years arithmetic mean full range (min-max)	 58.8 40 to 70		
Prior lines of chemotherapy Units: prior lines median full range (min-max)	 5 1 to 10		

End points

End points reporting groups

Reporting group title	Pazopanib and fosbretabulin
Reporting group description:	
Pazopanib 600 mg once daily and fosbretabulin 54 mg/m2 on days 1, 8, 15, every 28 days	
Reporting group title	Single-agent pazopanib
Reporting group description:	
Pazopanib 800 mg once daily, every 28 days	
Subject analysis set title	Phase 1b patients
Subject analysis set type	Safety analysis
Subject analysis set description:	
Twelve patients were enrolled in the Phase 1b trial. The primary endpoints of the phase 1b trial were to determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of pazopanib and fosbretabulin. The MTD was defined if no more than 1 patient, out of a maximum of 6 patients at the same dose level, experienced a DLT. Initially, 3 patients received dose level 1 and 3 patients received dose level 2 without a DLT. However due to multiple delayed grade ≥ 2 toxicities at dose level 2, experienced by patients after completing cycle 1; in particular hypertension and neutropenia, dose level 2 was expanded by a further 3 patients in order to elucidate better the toxicity profile. One of these 3 patients developed a DLT, reported as grade 3 fatigue, and dose level 2 was defined as the MTD. Consequently, dose level 1 was also expanded to include another 3 patients, and no DLTs were reported. Therefore, dose level 1 (600mg Pazopanib OD) was defined as the RP2D.	

Primary: Phase II: Progression-free survival

End point title	Phase II: Progression-free survival
End point description:	
The primary objective of the randomised phase 2 trial was to determine whether combining pazopanib with fosbretabulin significantly improved PFS compared to single-agent pazopanib in recurrent advanced ovarian cancer.	
End point type	Primary
End point timeframe:	
Progression-free survival was defined as the date from randomisation to the first date of either progressive disease (according to RECIST v1.1) or death.	

End point values	Pazopanib and fosbretabulin	Single-agent pazopanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Months				
median (confidence interval 95%)	7.6 (4.1 to 999)	3.7 (1.0 to 8.1)		

Statistical analyses

Statistical analysis title	Efficacy analysis of Progression-free survival
Statistical analysis description:	
The phase 2 trial was powered to detect a PFS Hazard Ratio (HR) of 0.65 in the pazopanib and fosbretabulin group versus the pazopanib group (equivalent to an improvement in PFS at 6 months from 20% to 35%).	
Comparison groups	Pazopanib and fosbretabulin v Single-agent pazopanib

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.06
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	1.03

Notes:

[1] - The primary analysis method was a Cox regression with the trial arm as the key covariate and adjusting for the two binary factors controlled for in the randomisation algorithm (platinum-free interval: >6 versus ≤6 months and prior bevacizumab treatment: yes/no).

Primary: Phase 1b: maximum tolerated dose (MTD) of pazopanib and fosbretabulin

End point title	Phase 1b: maximum tolerated dose (MTD) of pazopanib and fosbretabulin[2]

End point description:

The primary endpoints of the phase 1b trial were to determine the dose limiting toxicities (DLTs) and maximum tolerated dose (MTD) of pazopanib and fosbretabulin; defined if no more than 1 patient, out of a maximum of 6 patients at the same dose level, experienced a DLT.
- dose level 1: pazopanib 600 mg OD and fosbretabulin 54 mg/m2 days 1, 8, 15, every 28 days
- dose level 2: pazopanib 800 mg OD and fosbretabulin 54 mg/m2 days 1, 8, 15, every 28 days
Initially, 3 patients received dose level 1 and 3 patients received dose level 2 without a DLT. However due to multiple delayed grade ≥ 2 toxicities at dose level 2, dose level 2 was expanded by a further 3 patients (6 total). One of these 3 patients developed a DLT, reported as grade 3 fatigue, and dose level 2 was defined as the MTD. Dose level 1 was expanded by a further 3 patients (6 total) and no further DLTs were reported. Consequently, dose level 1 was defined as the R2PD.

End point type	Primary

End point timeframe:

From screening until progressive disease or intolerable toxicity

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The dose finding phase 1b trial did not necessitate a formal statistical analysis. MTD was defined as the dose level where no more than 1 DLT was experienced.

End point values	Phase 1b patients			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Number of patients who experienced DLT				
Number of DLTs at dose level 1	0			
Number of DLTs at dose level 2	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs including SAEs must be reported for eligible patients from the time of registration/randomisation until 30 days after the last dose of IMP or until resolution (whichever is the later).

Adverse event reporting additional description:

Adverse events causally related to either Pazopanib or fosbretabulin, across both trial phases.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Phase II: Pazopanib alone
Reporting group description: -	
Reporting group title	Phase 1b: Pazopanib 600 mg plus fosbretabulin
Reporting group description: -	
Reporting group title	Phase 1b: Pazopanib 800 mg plus fosbretabulin
Reporting group description: -	
Reporting group title	Phase II: Pazopanib and fosbretabulin

Reporting group description: -

Serious adverse events	Phase II: Pazopanib alone	Phase 1b: Pazopanib 600 mg plus fosbretabulin	Phase 1b: Pazopanib 800 mg plus fosbretabulin
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
AST/ALT increased	Additional description: AST/ALT increased		
subjects affected / exposed	3 / 10 (30.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thromboembolic Event	Additional description: Thromboembolic Event		
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension	Additional description: Hypertension		

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia	Additional description: Sinus bradycardia		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia	Additional description: Febrile Neutropenia		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal perforation	Additional description: Intestinal perforation		
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase II: Pazopanib and fosbretabulin		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
AST/ALT increased	Additional description: AST/ALT increased		

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thromboembolic Event	Additional description: Thromboembolic Event		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension	Additional description: Hypertension		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia	Additional description: Sinus bradycardia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile Neutropenia	Additional description: Febrile Neutropenia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal perforation	Additional description: Intestinal perforation		

subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Phase II: Pazopanib alone	Phase 1b: Pazopanib 600 mg plus fosbretabulin	Phase 1b: Pazopanib 800 mg plus fosbretabulin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	6 / 6 (100.00%)	6 / 6 (100.00%)
Investigations			
GGT increased	Additional description: GGT increased		
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
AST/ALT increased	Additional description: AST/ALT increased		
subjects affected / exposed	0 / 10 (0.00%)	5 / 6 (83.33%)	3 / 6 (50.00%)
occurrences (all)	0	5	3
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1 / 10 (10.00%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	1	4	3
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	2 / 10 (20.00%)	5 / 6 (83.33%)	5 / 6 (83.33%)
occurrences (all)	2	5	5
Nervous system disorders			
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Syncope	Additional description: Syncope		

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 10 (10.00%)	5 / 6 (83.33%)	5 / 6 (83.33%)
occurrences (all)	1	5	5
Chest pain	Additional description: Chest pain		
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Non-specific pain	Additional description: Non-specific pain		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	4 / 6 (66.67%)
occurrences (all)	0	2	4
Constipation	Additional description: Constipation		
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	3 / 6 (50.00%)
occurrences (all)	0	1	3
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 10 (20.00%)	5 / 6 (83.33%)	6 / 6 (100.00%)
occurrences (all)	2	5	6
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 10 (0.00%)	4 / 6 (66.67%)	5 / 6 (83.33%)
occurrences (all)	0	4	5
Mucositis oral	Additional description: Mucositis oral		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oral mucositis	Additional description: Oral mucositis		

subjects affected / exposed	0 / 10 (0.00%)	3 / 6 (50.00%)	5 / 6 (83.33%)
occurrences (all)	0	3	5
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	4 / 6 (66.67%)
occurrences (all)	1	2	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash	Additional description: Rash		
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Pruritus	Additional description: Pruritus		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
PPE syndrome	Additional description: PPE syndrome		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Renal and urinary disorders			
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	0 / 10 (0.00%)	4 / 6 (66.67%)	3 / 6 (50.00%)
occurrences (all)	0	4	3
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Phase II: Pazopanib and fosbretabulin		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	10 / 11 (90.91%)		
Investigations			
GGT increased	Additional description: GGT increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
AST/ALT increased	Additional description: AST/ALT increased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension	Additional description: Hypertension		
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	6		
Nervous system disorders			
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Syncope	Additional description: Syncope		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Chest pain	Additional description: Chest pain		

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Non-specific pain	Additional description: Non-specific pain		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Mucositis oral	Additional description: Mucositis oral		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Oral mucositis	Additional description: Oral mucositis		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			

Rash	Additional description: Rash		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
PPE syndrome	Additional description: PPE syndrome		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Proteinuria	Additional description: Proteinuria		
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypophosphataemia	Additional description: Hypophosphataemia		
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypomagnesaemia	Additional description: Hypomagnesaemia		
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2015	Substantial amendment 01: Update to Fosbretabulin Investigational Medicinal product Dossier (IMPD) due to change in manufacturer.
18 March 2015	Substantial amendment 02: Protocol version change 1.0 to 2.0. Allows patient to continue to receive both IMPs for more than 6 cycles until disease progression.
17 March 2016	Substantial amendment 03: Protocol version change 2.0 to 3.0. 1) Clarification about phase II follow up times and new secondary objective and endpoint added, 2) Update to eligibility criteria, 3) Change in translational research sample collection
23 February 2017	Substantial amendment 04: Protocol version change 3.0 to 4.0. 1) update to eligibility criteria, 2) update of IMP manufacturers name.
12 June 2017	Substantial amendment 05: Safety measure implementation. Treatment with fosbrestabulin temporarily suspended while investigation into SAE events takes place.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 June 2017	The decision was made to bring the Phase II trial to early termination due to safety concerns in regards to the emergence of treatment-related, reversible myocardial injury. In the phase 1b trial, 2 patients developed treatment-related cardiac adverse events. In the randomised phase II trial, grade 3 cardiac events were reported in 2 additional patients. As a result, IMP and funding provider Novartis made the decision to discontinue the Phase II trial on safety grounds with immediate effect.	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31932108