Clinical trial results:
Randomized phase II trial of cabazitaxel or prolonged infusional ifosfamide in metastatic or inoperable locally advanced dedifferentiated liposarcoma

Summary

EudraCT number	2012-003672-39
Trial protocol	BE GB FR IT NL
Global end of trial date	02 February 2021

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	1202-STBSG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01913652
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and Treatment of Cancer (EORTC)
Sponsor organisation address	Avenue E. Mounierlaan 83/11, Brussels, Belgium, 1200
Public contact	Head Project Management &Regulatory, European Organaisation for Research and Treatment of Cancer (EORTC), +32 27741044, regulatory@eortc.be
Scientific contact	Head Project Management &Regulatory, European Organaisation for Research and Treatment of Cancer (EORTC), +32 27741044, regulatory@eortc.be

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	17 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2021
Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to determine whether cabazitaxel or prolonged infusional ifosfamide demonstrate sufficient antitumor activity (as measured by progression free survival at 12 weeks) in patients with metastatic or inoperable locally advanced dedifferentiated (DD) liposarcoma to justify further investigation of the efficacy of these treatment options in a phase III setting.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Soft tissue sarcomas (STS) are a rare group of malignant heterogenous tumors (> 50 histological subtypes, including liposarcoma, the commonest subtype of STS) with distinct genetic, pathological and clinical profiles, and varying patterns of tumor spread. The optimal cytotoxic treatment for this group of patients remains uncertain. Single agents which are most effective include doxorubicin and ifosfamide, but objective response rates and progression-free survival times remain modest. There is clearly a need to improve treatment options for liposarcoma. Eribulin, a antimicrotubule agent that targets the protein tubulin in cells, interfering with cancer cell division and growth , has demonstrated activity in STS. Therefore, it is reasonable to explore whether other anti-microtubule agent like cabazitaxel have a role in STS. Cabazitaxel has been shown to be a relatively safe, effective and tolerated. This drug has been approved by FDA for prostate cancer. The main objective of this trial is to determine whether cabazitaxel demonstrate sufficient antitumor activity for liposarcoma.

Evidence for comparator: -

Actual start date of recruitment	01 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Italy: 18

Worldwide total number of subjects	40
EEA total number of subjects	29

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)	18
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 40 patients were registered by 10 institutions in 4 countries between 26th March 2015 and 4th March 2019. After review, 2 patients were found not eligible for this trial (one diagnosis of DD liposarcoma not confirmed and the other with an unstable medical condition).

Pre-assignment

Screening details:

--Metastatic or inoperable locally advanced dedifferentiated liposarcoma
-Age 18-75 yrs
-WHO performance status 0-1
-One previous chemotherapy regimen for locally advanced or metastatic dedifferentiated liposarcoma
-Adequate haematological, renal and hepatic function

Pre-assignment period milestones

Number of subjects started	40
Number of subjects completed	40

Period 1

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

Arms

Arm title	Cabazitaxel

Arm description:

- Cabazitaxel 25mg/m² IV infusion over 1 hour every 21 days.
- The day of first treatment is defined as day 1 of cycle 1.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Infusion

Dosage and administration details:

Cabazitaxel will be administered at a dose of 25 mg/m² by intravenous infusion, over 1 hour, on day 1 of each 21 day cycle.

Treatment should be administered until disease progression, unacceptable toxicity or patient's refusal.

Number of subjects in period 1	Cabazitaxel
Started	40
Completed	0
Not completed	40
Clinical progression	2
Patient decision	2

Physician decision	2
Start of new anti-cancer treatment	1
Disease progression	22
Still on treatment at analysis	1
Toxicity	9
Unconfirmed PD related death	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall period - Full patient population
Reporting group description:	
Forty patients (40) were enrolled into this trials, amongst whom 2 patients were found not eligible after review (one diagnosis of DD liposarcoma not confirmed and the other with an unstable medical condition).	

Reporting group values	Overall period - Full patient population	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	18	
From 65-84 years	22	22	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	63.03		
standard deviation	± 9.57	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	21	21	
Grade Units: Subjects			
Grade I	1	1	
Grade II	33	33	
Grade III	6	6	
WHO performance status Units: Subjects			
PS 0	22	22	
PS 1	18	18	
Tumor differentiation Units: Subjects			
High	1	1	
Moderate	2	2	
Poor/undifferentiated	37	37	
Concomitant non-malignant disease Units: Subjects			
No	8	8	
Yes	32	32	

Subject analysis sets	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Among the 40 patients that were enrolled, after review, 2 patients were found not eligible for this trial (one diagnosis of DD liposarcoma not confirmed and the other with an unstable medical condition). Thus, this reporting subgroup consist of the 38 eligible patients that were enrolled and started treatment.

Subject analysis set title	Final decision rule population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The first 37 patients who are eligible and have started their allocated treatment (at least one dose of the study drug).
The Simon two-stage design was applied, 17 (stage 1) or 37 (stage 2) eligible and treated patients were required. In stage 2, if 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation of the drug in this disease.
Note that the minimum number of successes needed in stage 1 to continue to stage 2 was achieved (i.e. at least 4 out of 17).

Reporting group values	Per protocol population	Final decision rule population	
Number of subjects	38	37	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	18	17	
From 65-84 years	20	20	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	62.71	62.81	
standard deviation	±	± 9.82	
Gender categorical Units: Subjects			
Female	18	17	
Male	20	20	
Grade Units: Subjects			
Grade I	0	0	
Grade II	32	31	
Grade III	6	6	
WHO performance status Units: Subjects			

PS 0	21	21	
PS 1	17	16	
Tumor differentiation Units: Subjects			
High	0	0	
Moderate	2	2	
Poor/undifferentiated	36	35	
Concomitant non-malignant disease Units: Subjects			
No	8	8	
Yes	30	29	

End points

End points reporting groups

Reporting group title	Cabazitaxel

Reporting group description:

- Cabazitaxel 25mg/m² IV infusion over 1 hour every 21 days.
- The day of first treatment is defined as day 1 of cycle 1.

Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol

Subject analysis set description:

Among the 40 patients that were enrolled, after review, 2 patients were found not eligible for this trial (one diagnosis of DD liposarcoma not confirmed and the other with an unstable medical condition). Thus, this reporting subgroup consist of the 38 eligible patients that were enrolled and started treatment.

Subject analysis set title	Final decision rule population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The first 37 patients who are eligible and have started their allocated treatment (at least one dose of the study drug).
The Simon two-stage design was applied, 17 (stage 1) or 37 (stage 2) eligible and treated patients were required. In stage 2, if 11 or more successes are observed in those 37 patients, we will conclude that the results of this trial warrant further investigation of the drug in this disease.
Note that the minimum number of successes needed in stage 1 to continue to stage 2 was achieved (i.e. at least 4 out of 17).

Primary: Progression free survival(PFS) at 12 weeks

End point title	Progression free survival(PFS) at 12 weeks

End point description:

Progression free survival at 12 weeks is measured as a binary variable, based on the locally assessed disease evaluation performed 12 weeks after start of treatment. Patients will be considered as "success" if this assessment indicates "stable disease" or a "response" as defined by RECIST v1.1. All other cases will be considered as failures (including patients who have progressed, symptomatically deteriorated or died before the 12 week evaluation, patients with an unknown progression status at 12 weeks, or patients who started new anti-tumor therapy in the absence of progressive disease).

End point type	Primary

End point timeframe:

PFS (binary) performed 12 weeks after start of treatment.

End point values	Per protocol population	Final decision rule population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: Subjects				
Success	21	21		
Failure	17	16		

Statistical analyses

Statistical analysis title	Primary endpoint- Simon optimal two-stage design

Statistical analysis description:

The Simon optimal two-stage design was used, with the following hypotheses : P0 was taken as 20% - success in 20% of the cases was considered as unacceptable, and would not warrant further investigation. P1 was taken as 40% - success in 40% of the cases was considered as an acceptable result warranting further investigation of the drug in this histology. Type I error and type II error are fixed at 10%. Under these hypotheses, a total of 37 eligible and treated patients were needed.

Comparison groups	Per protocol population v Final decision rule population
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	proportion, conditional 1-sided 95% CI
Parameter estimate	binomial proportion
Point estimate	0.57
Confidence interval	
level	95 %
sides	1-sided
lower limit	0.408

Notes:

[1] - Progression free survival at 12 weeks after start of treatment was taken as a binary indicator of success or failure and was reported as a proportion with a conditional 95% confidence interval as recommended by Koyama and Chen (Stat Med. 2008).
This is a single arm test - two arms were provided due to EUDRACT reporting system limitation. The primary test is performed in the final decision rule population only.
[2] - Conditional p-value as recommended by Koyama and Chen (Stat Med. 2008).

Secondary: Response at 12 weeks -Local investigator

End point title	Response at 12 weeks -Local investigator

End point description:

End point type	Secondary

End point timeframe:

Based on the locally assessed disease evaluation performed 12 weeks after start of treatment.

End point values	Per protocol population	Final decision rule population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	37		
Units: Subjects				
Stable	21	21		
Progression	12	11		
Early death	1	1		
Not evaluable	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS at 12 weeks (binary)-Central review

End point title	PFS at 12 weeks (binary)-Central review

End point description:

End point type	Secondary

End point timeframe:

Based on disease evaluation (as defined by RECIST v1.1) performed 12 weeks after start of treatment via central review.

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Subjects				
Success	16			
Failure	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Response at 12 weeks-Central review

End point title	Response at 12 weeks-Central review

End point description:

End point type	Secondary

End point timeframe:

Based on disease evaluation (as defined by RECIST v1.1) performed 12 weeks after start of treatment via central review.

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Subjects				
Stable	16			
Progression	5			
Early death	1			
Not evaluable	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)-Local investigator

End point title	Progression free survival (PFS)-Local investigator

End point description:

Progression free survival was computed from the date of start of treatment to the first documented date of progression (according to RECIST v1.1 as assessed by local reviewer) or death, whatever the cause, whichever occurs first. Patients alive and free from progression at the time of the analysis will be censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

PFS was computed from the date of start of treatment to the first documented date of progression (according to RECIST v1.1) or death, whatever the cause, whichever occurs first.

End point values	Cabazitaxel	Per protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40	38		
Units: Months				
median (confidence interval 95%)	6.5 (2.8 to 10.3)	6.5 (2.8 to 10.3)		

Statistical analyses

Statistical analysis title	PFS- Per protocol population

Statistical analysis description:

Progression free survival will be computed from the date of start of treatment to the first documented date of progression (according to RECIST v1.1) or death, whatever the cause, whichever occurs first. Patients alive and free from progression at the time of the analysis will be censored at the date of last follow-up.
PFS was estimated by the Kaplan-Meier (KM) method. Median PFS was provided with its 95% confidence interval.

Comparison groups	Cabazitaxel v Per protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[3]
Method	Kaplan-Meier
Parameter estimate	Median PFS estimate
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	10.3

Notes:

[3] - This is a single arm assessment and PFS was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation.

Secondary: PFS-Central review

End point title	PFS-Central review

End point description:

Progression free survival was computed from the date of start of treatment to the first documented date of progression (according to RECIST v1.1 as assessed by central reviewer) or death, whatever the cause, whichever occurs first. Patients alive and free from progression at the time of the analysis will be censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

Progression free survival was computed from the date of start of treatment to the first documented date of progression or death, whatever the cause, whichever occurs first.

End point values	Cabazitaxel	Per protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40[4]	38[5]		
Units: Months				
median (confidence interval 95%)	8.3 (2.8 to 10.7)	8.3 (2.8 to 10.7)		

Notes:

[4] - This is a single arm test - two arms were provided due to EUDRACT reporting system limitation

[5] - This analysis was only performed in the per protocol population

Statistical analyses

Statistical analysis title	PFS - Per protocol population (Central review)
Comparison groups	Cabazitaxel v Per protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
Method	Kaplan-Meier
Parameter estimate	Median PFS estimate
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	10.7

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

Time to progression was computed from the date of start of treatment to the first documented date of progression (measured according to the RECIST v1.1 , as assess by local reviewers) or death due to progressive disease, whichever occurs first. Patients free from progression at the time of analysis were censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

TTP was computed from the date of start of treatment to the first documented date of progression (measured according to the RECIST v1.1, as assess by local reviewers) or death due to progressive disease, whichever occurs first.

End point values	Cabazitaxel	Per protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40[6]	38[7]		
Units: Months				
median (confidence interval 95%)	7.4 (2.8 to 12.1)	7.4 (2.8 to 12.1)		

Notes:

[6] - This is a single arm assessment. Two arms were provided due to EUDRACT reporting system limitation.

[7] - This is a single arm assessment and TTP was performed only in the per protocol population.

Statistical analyses

Statistical analysis title	TTP- Per protocol population

Statistical analysis description:

Time to progression (TTP) was computed from the date of start of treatment to the first documented date of progression or death due to progressive disease, whichever occurs first. Patients free from progression at the time of analysis will be censored at the date of last follow-up. TTP was estimated by the Kaplan-Meier (KM) method. Median TTP was provided with its 95% confidence interval.

Comparison groups	Cabazitaxel v Per protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Median TTP estimate
Point estimate	7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.8
upper limit	12.1

Notes:

[8] - This is a single arm assessment. TTP was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation.

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis will be censored at the date of last follow-up.

End point type	Secondary

End point timeframe:

OS was computed from the date of start of treatment to the date of death (due to any cause).

End point values	Cabazitaxel	Per protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40[9]	38[10]		
Units: Months				
median (confidence interval 95%)	21.1 (14.8 to 33.5)	21.1 (14.8 to 33.5)		

Notes:

[9] - This is a single arm assessment. Two arms were provided due to EUDRACT reporting system limitation.
[10] - This is a single arm assessment and OS analysis was performed only in the per protocol population.

Statistical analyses

Statistical analysis title	OS- Per protocol population

Statistical analysis description:

Overall survival (OS) was computed from the date of start of treatment to the date of death (due to any cause). Patients alive at the time of analysis were censored at the date of last follow-up. OS was estimated by the Kaplan-Meier (KM) method. Median PFS was provided with its 95% confidence interval.

Comparison groups	Cabazitaxel v Per protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[11]
Method	Kaplan-Meier
Parameter estimate	Median OS estimate
Point estimate	21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.8
upper limit	33.5

Notes:

[11] - This is a single arm assessment and OS was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation

Secondary: Objective tumor response (Local investigator)

End point title	Objective tumor response (Local investigator)

End point description:

Objective tumor response (CR + PR) was measured according to RECIST v1.1(by local investigators). Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

End point type	Secondary

End point timeframe:

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and –together with other lesions that are denoted as non-target lesions – followed until disease progression.

End point values	Cabazitaxel	Per protocol population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	40[12]	38[13]		
Units: Subjects				
No	35	35		
Yes	3	3		

Notes:

[12] - This is a single arm study. Objective tumor response was assessed in the per-protocol population

[13] - Objective tumor response was only assessed in the per-protocol population

Statistical analyses

Statistical analysis title	Objective response (CR+PR)

Statistical analysis description:

The rate of objective tumor response (CR+PR) was computed with its 95% confidence interval (from the exact binomial distribution). Patients in response categories progression, early death or unknown were considered as failures.

Comparison groups	Cabazitaxel v Per protocol population
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[14]
Method	exact binomial
Parameter estimate	proportion estimate
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	21.4

Notes:

[14] - This is a single arm assessment. The rate of objective tumor response (CR+PR)was performed only in the per protocol population. Two arms were provided due to EUDRACT reporting system limitation.

Secondary: Best overall response (Local investigator)

End point title	Best overall response (Local investigator)

End point description:

Response was measured according to RECIST v1.1 (performed by local investigator). Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression. Each patient was assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

End point type	Secondary

End point timeframe:

Patients' best overall response was based on assessments from start of treatment until the end of treatment or until clinical cut-off for this analysis (for patients still on treatment).

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Subjects				
Complete response	1			
Partial response	2			
Stable disease	22			
Progressive disease	11			
Early death	1			
Not evaluable	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective tumor response (Central review)

End point title	Objective tumor response (Central review)

End point description:

Objective tumor response (CR + PR) was measured according to RECIST v1.1 (via central review). Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

End point type	Secondary

End point timeframe:

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and –together with other lesions that are denoted as non-target lesions – followed until disease progression.

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Subjects				
No	36			
Yes	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response (Central review)

End point title	Best overall response (Central review)

End point description:

Response was measured according to RECIST v1.1 (central review). Response criteria are essentially

based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression. Each patient was assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death or not evaluable.

End point type	Secondary

End point timeframe:

Patients' best overall response was based on assessments from start of treatment until the end of treatment or until clinical cut-off for this analysis (for patients still on treatment).

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Subjects				
Complete response	0			
Partial response	2			
Stable disease	20			
Progressive disease	10			
Early death	1			
Not evaluable	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of response

End point title	Time to onset of response

End point description:

At the time of clinical cut-off for this analysis, objective response (CR/PR) was observed in 3 out of the 38 eligible patients.

End point type	Secondary

End point timeframe:

Time to onset of response was measured from the date of start of treatment until the criteria for CR/PR (whichever is first recorded) are met.

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Months				
median (full range (min-max))	8 (5.1 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Only one of the three eligible patients who experience objective response had progressed at the time of clinical cut-off for this analysis.

End point type	Secondary

End point timeframe:

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that progressive disease is objectively documented.

End point values	Per protocol population			
Subject group type	Subject analysis set			
Number of subjects analysed	38			
Units: Months				
number (not applicable)	2.9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, laboratory and physical abnormalities were collected till three months after the end of treatment. Afterwards, only treatment related AE are collected. For SAEs: all SAEs till 30 days after end of treatment; afterwards, only related SAEs

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. AEs are evaluated using CTC grading, SAEs using MedDra.
AEs are tabulated for safety population, i.e. all patients starting Cabazitaxel.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Arm 1

Reporting group description:

This was based on the safety population, i.e. all 40 patients who started Cabazitaxel

Serious adverse events	Arm 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 40 (35.00%)		
number of deaths (all causes)	21		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
INFUSION RELATED REACTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	4 / 40 (10.00%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
NEUTROPENIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
CONDITION AGGRAVATED				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
FATIGUE				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PAIN				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PYREXIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
alternative dictionary used: MedDRA 24.1				

subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COLITIS				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
NAUSEA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
VOMITING				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
URINARY RETENTION				
alternative dictionary used: MedDRA 24.1				

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ENTEROCOLITIS INFECTIOUS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ERYSIPELAS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PNEUMONIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 40 (95.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOR PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Vascular disorders			
FLUSHING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
EDEMA LIMBS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
FATIGUE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	19 / 40 (47.50%)		
occurrences (all)	37		
FEVER			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	8		
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
INFUSION RELATED REACTION			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	5		
INJECTION SITE REACTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
MALAISE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Reproductive system and breast disorders			
VAGINAL DISCHARGE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
COUGH			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
DYSPNEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
EPISTAXIS			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
POSTNASAL DRIP			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Psychiatric disorders			
ANXIETY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
DEPRESSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
INSOMNIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	5		
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
BLOOD BILIRUBIN INCREASED			

alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
CREATININE INCREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	8		
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	21 / 40 (52.50%)		
occurrences (all)	42		
PLATELET COUNT DECREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	7		
WEIGHT GAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	13		
WEIGHT LOSS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	11 / 40 (27.50%)		
occurrences (all)	17		
Injury, poisoning and procedural complications			
FRACTURE			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Cardiac disorders			
MYOCARDITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Nervous system disorders			
CONCENTRATION IMPAIRMENT			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
DIZZINESS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
DYSGEUSIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	8		
HEADACHE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
NEURALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	42		
FEBRILE NEUTROPENIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	10 / 40 (25.00%)		
occurrences (all)	11		
Eye disorders			
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Gastrointestinal disorders			
BLOATING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
ABDOMINAL DISTENSION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	9		
COLITIS			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	2			
CONSTIPATION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	4			
DIARRHEA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	17 / 40 (42.50%)			
occurrences (all)	31			
DYSPEPSIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	6 / 40 (15.00%)			
occurrences (all)	6			
DYSPHAGIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
FLATULENCE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
GASTROESOPHAGEAL REFLUX DISEASE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
HEMORRHOIDS				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
MUCOSITIS ORAL				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences (all)	3			

NAUSEA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	17 / 40 (42.50%)		
occurrences (all)	24		
STOMACH PAIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
VOMITING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
DRY SKIN			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
PRURITUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
NAIL RIDGING			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
Renal and urinary disorders			

CHRONIC KIDNEY DISEASE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
CYSTITIS NONINFECTIVE				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
HEMATURIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
URINARY RETENTION				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
URINARY TRACT PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences (all)	2			
Musculoskeletal and connective tissue disorders				
ARTHRALGIA				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	4 / 40 (10.00%)			
occurrences (all)	5			
CHEST WALL PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences (all)	1			
BACK PAIN				
alternative dictionary used: CTCAE 4.0				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences (all)	3			
FLANK PAIN				
alternative dictionary used: CTCAE				

4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	3		
MYALGIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Infections and infestations			
BLADDER INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	5		
RHINITIS INFECTIVE			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
ENTEROCOLITIS INFECTIOUS			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
SKIN INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
SMALL INTESTINE INFECTION			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	16		
HYPOALBUMINEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	5		
DEHYDRATION			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
HYPOKALEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4.0			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	2		
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4.0			

subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2015	This study was originally designed to evaluate two different chemotherapy regimes in second line, in two independent Simon 2-stage phase II trials run in parallel, one addressing cabazitaxel, the other addressing prolonged infusional ifosfamide (described in previous versions 1.0 and 2.0 of the protocol). On the 05/03/2015 there was a protocol amendment (1.0 to 2.0), and the rationale for the amendment and its classification were: Upon the release of the Investigator's brochure for Cabazitaxel, the patient information sheet had to be amended for side effects. In addition, the protocol was updated for the following sections: • Background section : new information from Cabazitaxel's IB • Eligibility section based on German Ethics committee request • Drug information section: information about Baxter pump (pharmacy Royal Marsden), capping the dose for ifosfamide to a maximum of Body Surface Area of 2 m² (request study coordinator), new data about drug-drug interactions (Cabazitaxel's IB). • End of study definition (Section 8.4) to ensure the safety reporting of all patients while on treatment • List of Reference pathologists (Pathologist reviewer added for German sites, and changed for Italy [from the UK to the French lab]).
26 October 2016	Recruitment issues led to a further amendment. On the 26/10/2016, the EORTC Board decided to move on with a phase 2 design with single agent cabazitaxel. They suspected that the amended protocol would attract more patients than had been the case before. The protocol (current version 3.0) was amended as well as the patient information sheet to remove the ifosfamide arm. In addition, changes have been implemented: • Changes to eligibility criteria based upon study coordinator 's suggestions and based on the current reference safety document : • Age 18-75 years old • Hepatic: Bilirubin < 1.5 times upper limit of normal (1.5xULN) of institutional limits, ALT and/or AST< 1.5 x ULN. If isolated elevated bilirubin <2 x ULN and Gilberts syndrome suspected, suggest repeating bloods after food. If bilirubin improves to meet the criteria above this is acceptable. • Renal: creatinine clearance (CrCl) * > 30 ml/min; • No inflammation of the urinary bladder (cystitis); • Change to adverse events/ side-effects associated with the drugs based on the current reference safety document. • Phase 2 design with single agent cabazitaxel o All reference to ifosfamide removed o All references to randomization removed or changed appropriately (eg. registration) o All references to recruited removed or changed appropriately (eg. screened) o Removal of the Stratification factors, o Plural reference to treatment or arms changed to singular etc • Change in number of subjects planned for trial and for each participating country due to a change in design. o Up to 50 patients will be enrolled. • Change in duration of trial o At the time of submission of the amendment (v3.0) to the protocol, 1 patient had started treatment o The duration of accrual was expected to vary between 10 months and 20 months (30-40 months from first patient in (FPI)). • Changes to reporting procedures and FU of SAEs

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported