Clinical trial results:
A clinicopathological phase II study of axitinib in patients with advanced angiosarcoma and other soft tissue sarcomas

Summary

EudraCT number	2008-006007-23
Trial protocol	GB
Global end of trial date	08 January 2019

Results information

Result version number	v1 (current)
This version publication date	11 August 2022
First version publication date	11 August 2022

Trial information

Trial identification

Sponsor protocol code	STH15195

Additional study identifiers

ISRCTN number	ISRCTN60791336
ClinicalTrials.gov id (NCT number)	NCT01140737
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Trust Headquarters, 11 Broomfield Road, Sheffield, United Kingdom, S10 2SE
Public contact	Mrs Ana Hughes, Cancer Research UK Clinical Trials Unit (University of Birmingham), +44 0121 414 3793, a.i.hughes@bham.ac.uk
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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	24 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to evaluate the therapeutic activity, safety and tolerability of axitinib in patients with advanced soft tissue sarcoma which is incurable by surgery or radiotherapy and unsuitable or unresponsive to standard chemotherapy. The therapeutic activity will be separately assessed in the eligible subtypes.

Protection of trial subjects:

Patients were monitored once weekly for cycle 1, then at 4 week intervals. Toxicity (including hypertension) was closely monitored.

The following treatment-specific measures were put in place to help protect subjects from unacceptable toxicities:

In the event of any grade 3 toxicity or worse, axitinib treatment should be discontinued until the toxicity has recovered to grade 1 or better, when axitinib can be reintroduced at a lower dose of 3 mg twice daily. Treatment may be interrupted for a maximum of 2 weeks. If the toxicity has not improved sufficiently within this time, the patient should be withdrawn from the trial.

Similar criteria for dose modification/withdrawal were detailed in the protocol for the following adverse events: Hypertension, Haemoptysis, Cavitating lung metastases, Proteinuria, Thrombocytopenia.

As Hypertension is very common toxicity for axitinib, and should be actively managed with medication. An angiotensin converting enzyme inhibitor (eg. Ramipril 1.25 mg) or calcium channel blocker (eg, amlodipine 5 mg) is recommended as initial treatment.

Background therapy:

Patients may have received prior anticancer treatment (surgery, radiotherapy and systemic therapies), however this could not be within 4 weeks of eligibility.

As hypertension is very common toxicity for axitinib, an angiotensin converting enzyme inhibitor or calcium channel blocker was recommended as initial treatment. As such , patients are likely to have been treated with an angiotensin converting enzyme inhibitor.

Evidence for comparator:

The objective of this single arm study was to evaluate the therapeutic activity, safety and tolerability of axitinib in patients with advanced/metastatic soft tissue sarcoma who have relapsed after standard chemotherapy. The analysis of progression-free survival rate (PFR) in phase II trials of active and inactive agents by the EORTC Soft Tissue & Bone Sarcoma Group (van Glabbeke et al, 2002) showed that for second-line therapy, a 3-month PFR of >=40% suggests drug activity, and <=20% suggests inactivity. Therefore, the primary outcome measure for this trial was chosen as progression-free survival rate at 12 weeks after the start of treatment – with disease being assessed by comparing CT/MRI scans on (or up to 4 weeks prior to) trial entry with CT/MRI scans taken 12 weeks after entry. Patients with stable or responding disease at 12 weeks are defined as a success.

For each stratum, success in 40% or more (P1) is considered worthwhile for further study, whereas success in 20% or less (P0) is considered unacceptable. The trial is designed such that there is a 5% chance of incorrectly accepting axitinib as worthy of further investigation (significance level) and 80% chance of correctly detecting that axitinib is worthy of further investigation (power).

Therapeutic activity is assessed separately in the eligible subtypes - Angiosarcoma, Synovial sarcoma, Leiomyosarcoma (uterine, skin or non organ origin), and other types of eligible soft tissue sarcoma.

Actual start date of recruitment	31 August 2010
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: 145
Worldwide total number of subjects	145
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)	106
From 65 to 84 years	39
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was open to recruitment during the following periods:
August 2010 - January 2011 (sites across the UK)
October 2011 - January 2016 (sites across the UK)

Recruitment closure to specific arms:
Other - February 2012
Leiomyosarcoma - September 2012
Angiosarcoma - August 2015
Synovial - January 2016

Pre-assignment

Screening details:

Pathologically confirmed soft tissue sarcoma that meets trial inclusion/exclusion criteria. Disease assessment by CT or MRI scan within previous 4 weeks (for evaluable disease and evidence of disease progression in the 6 months prior to trial entry). Age >= 16 yrs.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Angiosarcoma

Arm description:

Patients with pathologically confirmed Angiosarcoma, including intermediate and malignant vascular tumours (WHO classification, 2002) and Kaposi's sarcoma.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	Inlyta
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg Axitinib (oral tablets) twice daily, continuously for the duration of the trial. In the occurrence of certain adverse events, dose may have been reduced to 3 mg if certain conditions were met (as outlined in the 'protection of trial subjects' section).

Arm title	Leiomyosarcoma

Arm description:

Patients with pathologically confirmed Leiomyosarcoma, including uterine, skin or non organ origin.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	Inlyta
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg Axitinib (oral tablets) twice daily, continuously for the duration of the trial. In the occurrence of certain adverse events, dose may have been reduced to 3 mg if certain conditions were met (as outlined in the 'protection of trial subjects' section).

Arm title	Synovial Sarcoma

Arm description:

Patients with pathologically confirmed Synovial Sarcoma.

Arm type	Experimental
Investigational medicinal product name	Axitinib
Investigational medicinal product code	AG-013736
Other name	Inlyta
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg Axitinib (oral tablets) twice daily, continuously for the duration of the trial. In the occurrence of certain adverse events, dose may have been reduced to 3 mg if certain conditions were met (as outlined in the 'protection of trial subjects' section).

Arm title	Other Sarcoma

Arm description:

Patients with eligible subtypes of pathologically confirmed soft tissue sarcoma other than Angiosarcoma, Leiomyosarcoma
or Synovial sarcoma.

Other eligible subtypes of soft tissue sarcoma were of Trojani intermediate or high grade, including fibroblastic, fibrohistiocytic, adipocytic, rhabdomyosarcoma, malignant peripheral nerve sheath, and NOS. Ineligible subtypes that were not included in this arm were: Osteosarcoma, Ewings/PNET sarcomas, Chondrosarcoma, Gastrointestinal stromal tumours (GIST), Dermatofibrosarcoma protuberans (DFSP), Malignant mesothelioma and Mixed mesodermal tumours of uterus.

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

Dosage and administration details:

5 mg Axitinib (oral tablets) twice daily, continuously for the duration of the trial. In the occurrence of certain adverse events, dose may have been reduced to 3 mg if certain conditions were met (as outlined in the 'protection of trial subjects' section).

Number of subjects in period 1	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma
Started	39	36	36
Started Cycle 1 Treatment	38	35	34
Completed	33	33	30
Not completed	6	3	6
Ineligible	1	1	1
Consent withdrawn by subject	-	-	1
Physician decision	-	-	-
Adverse event, non-fatal	2	-	2
Treatment delay over 14 days	1	1	-
Non-disease related illness	-	-	-
Disease Progression	2	1	2

Number of subjects in period 1	Other Sarcoma
Started	34
Started Cycle 1 Treatment	31
Completed	27
Not completed	7
Ineligible	2
Consent withdrawn by subject	-
Physician decision	1
Adverse event, non-fatal	1
Treatment delay over 14 days	1
Non-disease related illness	2
Disease Progression	-

Baseline characteristics

Reporting groups	
Reporting group title	Angiosarcoma
Reporting group description:	
Patients with pathologically confirmed Angiosarcoma, including intermediate and malignant vascular tumours (WHO classification, 2002) and Kaposi's sarcoma.	
Reporting group title	Leiomyosarcoma
Reporting group description:	
Patients with pathologically confirmed Leiomyosarcoma, including uterine, skin or non organ origin.	
Reporting group title	Synovial Sarcoma
Reporting group description:	
Patients with pathologically confirmed Synovial Sarcoma.	
Reporting group title	Other Sarcoma
Reporting group description:	
Patients with eligible subtypes of pathologically confirmed soft tissue sarcoma other than Angiosarcoma, Leiomyosarcoma or Synovial sarcoma. Other eligible subtypes of soft tissue sarcoma were of Trojani intermediate or high grade, including fibroblastic, fibrohistiocytic, adipocytic, rhabdomyosarcoma, malignant peripheral nerve sheath, and NOS. Ineligible subtypes that were not included in this arm were: Osteosarcoma, Ewings/PNET sarcomas, Chondrosarcoma, Gastrointestinal stromal tumours (GIST), Dermatofibrosarcoma protuberans (DFSP), Malignant mesothelioma and Mixed mesodermal tumours of uterus.	

Reporting group values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma
Number of subjects	39	36	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	29	31
From 65-84 years	18	7	5
85 years and over	0	0	0
Age continuous Units: years			
median	64	59	44
full range (min-max)	27 to 82	29 to 79	20 to 73
Gender categorical Units: Subjects			
Female	25	26	18
Male	14	10	18
Primary Tumour Location Units: Subjects			
Liver	2	1	0
Lymph	1	0	0

Lung	2	0	4
Bone	1	0	0
Other soft tissue	1	1	1
Upper limb	1	1	2
Lower limb	5	9	16
Shoulder girdle	0	0	2
Pelvic girdle	0	2	1
Breast	9	0	0
Head & Neck	7	0	1
Other intraabdominal	2	8	5
Other trunk	4	0	3
Uterus	0	12	0
Other	4	2	1
Trojani Grade Units: Subjects			
Grade 1	3	2	0
Grade 2	9	12	11
Grade 3	20	16	20
Not supplied	0	0	0
Not known	7	6	5
WHO Performance Status Units: Subjects			
Grade 0	18	10	16
Grade 1	18	22	18
Grade 2	3	3	2
Grade 3	0	0	0
Grade 4	0	0	0
Not Known	0	1	0
Urine Dipstick Result Units: Subjects			
Negative or 1+	36	33	34
2+	0	0	0
Not known	3	3	2
ECG result Units: Subjects			
Normal	35	30	35
Abnormal	4	4	1
Not Applicable	0	2	0
Con. Med. - Anti-Hypertensives			
Patients reported as taking Anti-hypertensives - defined to be concomitant medication taken for Hypertension or Diuretic indications.			
Units: Subjects			
No	29	31	27
Yes	10	5	9
Con. Med. - Nausea/Vomiting			
Patients at baseline reported as taking concomitant medication for nausea and/or vomiting.			
Units: Subjects			
No	34	35	34
Yes	5	1	2
Con. Med. - Dyspepsia			
Patients at baseline reported as taking concomitant medication for Dyspepsia.			
Units: Subjects			

No	32	28	31
Yes	7	8	5
Con. Med. - Pain			
Patients at baseline reported as taking concomitant medication for Pain.			
Units: Subjects			
No	18	21	18
Yes	21	15	18
Con. Med. - Anxiety/Depression			
patients at baseline reported as taking concomitant medication for Anixiety or Depression.			
Units: Subjects			
No	29	33	27
Yes	10	3	9
Time from first diagnosis to registration			
Units: Years			
median	2	2	2
full range (min-max)	0 to 9	0 to 11	0 to 11
Height			
Units: meters			
arithmetic mean	1.7	1.7	1.7
standard deviation	± 0.1	± 0.1	± 0.1
Weight			
Units: kg			
arithmetic mean	79.8	73.4	76.3
standard deviation	± 19.2	± 14.6	± 18.5
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	127.3	124.5	120.4
standard deviation	± 17.8	± 12.6	± 16.9
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	78.3	78.2	74.4
standard deviation	± 11.9	± 6.0	± 11.2
Pulse Rate			
Units: BPM			
arithmetic mean	84.9	84.9	86.6
standard deviation	± 15.0	± 16.2	± 14.5
Creatine Clearance			
Units: ml/min			
arithmetic mean	99.6	93.7	106.8
standard deviation	± 42.1	± 30.4	± 31.5
Urea			
Units: mmol/L			
arithmetic mean	5.2	4.7	4.4
standard deviation	± 1.7	± 1.4	± 1.4
Albumin			
Units: g/L			
arithmetic mean	40.1	40.8	43.0
standard deviation	± 5.1	± 5.3	± 5.6
Total Protein			
Units: g/L			
arithmetic mean	70.2	71.0	71.4

standard deviation	± 4.6	± 5.1	± 7.6
Bilirubin			
Units: umol/L			
arithmetic mean	9.2	8.4	9.3
standard deviation	± 5.0	± 3.1	± 4.3
Aspartate Aminotransferase (AST)			
Units: IU/L			
arithmetic mean	27.0	29.3	21.1
standard deviation	± 13.7	± 11.8	± 4.0
Alanine Aminotransferase (ALT)			
Units: IU/L			
arithmetic mean	20.5	25.2	20.8
standard deviation	± 11.0	± 10.8	± 10.9
Gamma-GT			
Units: IU/L			
arithmetic mean	38.5	143.1	68.2
standard deviation	± 29.9	± 237.1	± 88.6
Alkaline Phosphate			
Units: IU/L			
arithmetic mean	91.6	167.2	100.2
standard deviation	± 42.9	± 203.0	± 51.5
Haemoglobin			
Units: g/dL			
arithmetic mean	13.0	12.4	12.9
standard deviation	± 1.7	± 1.9	± 1.8
White Blood Cell Count			
Units: x10^9/L			
arithmetic mean	8.1	7.8	7.2
standard deviation	± 2.4	± 3.6	± 3.6
Neutrophils			
Units: x10^9/L			
arithmetic mean	5.5	5.5	5.2
standard deviation	± 2.2	± 3.2	± 3.2
Platelets			
Units: x10^9/L			
arithmetic mean	293.4	310.7	292.4
standard deviation	± 99.8	± 117.6	± 103.1
International Normalized Ratio (INR)			
Units: ratio			
arithmetic mean	1.0	1.0	1.1
standard deviation	± 0.1	± 0.1	± 0.2
Thyroid Stimulating Hormone (TSH)			
Units: mIU/L			
arithmetic mean	2.4	2.0	2.5
standard deviation	± 2.3	± 1.5	± 2.4
Free Thyroxine (FT4)			
Units: pmol/L			
arithmetic mean	14.4	15.6	15.5
standard deviation	± 3.5	± 2.7	± 2.9
Left ventricular ejection fraction (LVEF)			
Units: percent			
arithmetic mean	62.6	63.2	61.3

standard deviation	± 8.1	± 4.9	± 6.2

Reporting group values	Other Sarcoma	Total	
Number of subjects	34	145	
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)	25	106	
From 65-84 years	9	39	
85 years and over	0	0	
Age continuous Units: years			
median	50		
full range (min-max)	21 to 80	-	
Gender categorical Units: Subjects			
Female	13	82	
Male	21	63	
Primary Tumour Location Units: Subjects			
Liver	1	4	
Lymph	0	1	
Lung	4	10	
Bone	2	3	
Other soft tissue	0	3	
Upper limb	1	5	
Lower limb	9	39	
Shoulder girdle	1	3	
Pelvic girdle	5	8	
Breast	1	10	
Head & Neck	0	8	
Other intraabdominal	4	19	
Other trunk	3	10	
Uterus	2	14	
Other	1	8	
Trojani Grade Units: Subjects			
Grade 1	2	7	
Grade 2	7	39	
Grade 3	16	72	
Not supplied	1	1	
Not known	8	26	
WHO Performance Status			

Units: Subjects			
Grade 0	7	51	
Grade 1	25	83	
Grade 2	2	10	
Grade 3	0	0	
Grade 4	0	0	
Not Known	0	1	
Urine Dipstick Result Units: Subjects			
Negative or 1+	27	130	
2+	1	1	
Not known	6	14	
ECG result Units: Subjects			
Normal	31	131	
Abnormal	3	12	
Not Applicable	0	2	
Con. Med. - Anti-Hypertensives			
Patients reported as taking Anti-hypertensives - defined to be concomitant medication taken for Hypertension or Diuretic indications.			
Units: Subjects			
No	24	111	
Yes	10	34	
Con. Med. - Nausea/Vomiting			
Patients at baseline reported as taking concomitant medication for nausea and/or vomiting.			
Units: Subjects			
No	32	135	
Yes	2	10	
Con. Med. - Dyspepsia			
Patients at baseline reported as taking concomitant medication for Dyspepsia.			
Units: Subjects			
No	27	118	
Yes	7	27	
Con. Med. - Pain			
Patients at baseline reported as taking concomitant medication for Pain.			
Units: Subjects			
No	20	77	
Yes	14	68	
Con. Med. - Anxiety/Depression			
patients at baseline reported as taking concomitant medication for Anixiety or Depression.			
Units: Subjects			
No	30	119	
Yes	4	26	
Time from first diagnosis to registration Units: Years			
median	2		
full range (min-max)	0 to 22	-	
Height Units: meters			
arithmetic mean	1.7		
standard deviation	± 0.1	-	

Weight Units: kg arithmetic mean standard deviation	 79.3 ± 14.9	 -	
Systolic Blood Pressure Units: mmHg arithmetic mean standard deviation	 124.2 ± 13.6	 -	
Diastolic Blood Pressure Units: mmHg arithmetic mean standard deviation	 75.6 ± 9.0	 -	
Pulse Rate Units: BPM arithmetic mean standard deviation	 83.3 ± 16.2	 -	
Creatine Clearance Units: ml/min arithmetic mean standard deviation	 115.2 ± 51.6	 -	
Urea Units: mmol/L arithmetic mean standard deviation	 5.0 ± 1.2	 -	
Albumin Units: g/L arithmetic mean standard deviation	 39.8 ± 5.4	 -	
Total Protein Units: g/L arithmetic mean standard deviation	 71.6 ± 5.7	 -	
Bilirubin Units: umol/L arithmetic mean standard deviation	 9.5 ± 3.5	 -	
Aspartate Aminotransferase (AST) Units: IU/L arithmetic mean standard deviation	 23.5 ± 8.8	 -	
Alanine Aminotransferase (ALT) Units: IU/L arithmetic mean standard deviation	 26.4 ± 23.0	 -	
Gamma-GT Units: IU/L arithmetic mean standard deviation	 70.8 ± 97.9	 -	
Alkaline Phosphate Units: IU/L arithmetic mean standard deviation	 143.6 ± 93.8	 -	

Haemoglobin Units: g/dL arithmetic mean standard deviation	 12.1 ± 2.1	 -	
White Blood Cell Count Units: x10^9/L arithmetic mean standard deviation	 6.9 ± 2.8	 -	
Neutrophils Units: x10^9/L arithmetic mean standard deviation	 4.8 ± 2.4	 -	
Platelets Units: x10^9/L arithmetic mean standard deviation	 284.1 ± 140.6	 -	
International Normalized Ratio (INR) Units: ratio arithmetic mean standard deviation	 1.0 ± 0.1	 -	
Thyroid Stimulating Hormone (TSH) Units: mIU/L arithmetic mean standard deviation	 2.1 ± 2.2	 -	
Free Thyroxine (FT4) Units: pmol/L arithmetic mean standard deviation	 15.7 ± 2.4	 -	
Left ventricular ejection fraction (LVEF) Units: percent arithmetic mean standard deviation	 61.1 ± 5.4	 -	

End points

End points reporting groups

Reporting group title	Angiosarcoma
Reporting group description:	
Patients with pathologically confirmed Angiosarcoma, including intermediate and malignant vascular tumours (WHO classification, 2002) and Kaposi's sarcoma.	
Reporting group title	Leiomyosarcoma
Reporting group description:	
Patients with pathologically confirmed Leiomyosarcoma, including uterine, skin or non organ origin.	
Reporting group title	Synovial Sarcoma
Reporting group description:	
Patients with pathologically confirmed Synovial Sarcoma.	
Reporting group title	Other Sarcoma
Reporting group description:	
Patients with eligible subtypes of pathologically confirmed soft tissue sarcoma other than Angiosarcoma, Leiomyosarcoma or Synovial sarcoma. Other eligible subtypes of soft tissue sarcoma were of Trojani intermediate or high grade, including fibroblastic, fibrohistiocytic, adipocytic, rhabdomyosarcoma, malignant peripheral nerve sheath, and NOS. Ineligible subtypes that were not included in this arm were: Osteosarcoma, Ewings/PNET sarcomas, Chondrosarcoma, Gastrointestinal stromal tumours (GIST), Dermatofibrosarcoma protuberans (DFSP), Malignant mesothelioma and Mixed mesodermal tumours of uterus.	

Primary: 12 Week PFS Rate

End point title	12 Week PFS Rate[1]
End point description:	
Progression-free survival (PFS) rate at 12 weeks after starting treatment, defined according to the RECIST criteria version 1.1. Disease was assessed by CT/MRI scans 12 weeks after entry to the trial and was compared to disease measured by CT/MRI on entry or within 4 weeks prior to entry. Progressive disease could also be confirmed by non-CT/MRI means.	
End point type	Primary
End point timeframe:	
12 weeks after trial entry	

Notes:

[1] - 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: No statistical analyses were conducted in relation to this primary outcome as this was a single arm trial and as such the interpretation of the primary outcome was made in relation to what had been deemed clinically relevant. The trial design for each sarcoma subtype is a single-arm Simons 2-stage design which is an evaluation of a proportion against a design specified threshold to meet the criteria for success and as such no hypothesis testing is performed.

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	33	30	27
Units: percent				
number (confidence interval 90%)	42 (29 to 57)	45 (32 to 60)	57 (42 to 70)	33 (21 to 49)

Statistical analyses

No statistical analyses for this end point

Primary: 12 Week PFS

End point title	12 Week PFS[2]

End point description:

This end point entry exists as a supplement to 12 Week PFS rate. It provides a breakdown of patient status that was used to calculate the 12 week PFS rate.

End point type	Primary

End point timeframe:

12 after trial entry

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: No statistical analyses were conducted in relation to this primary outcome as this was a single arm trial and as such the interpretation of the primary outcome was made in relation to what had been deemed clinically relevant. The PFS rates and confidence intervals are reported for each sarcoma subtype from Kaplan-Meier determinations.

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	33	30	27
Units: patients				
Alive and Progression Free	13	15	17	9
Death	2	1	4	2
Not Evaluable	3	1	1	1
Progressive Disease	13	16	8	15

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Response Rate

End point title	Tumour Response Rate

End point description:

The number of patients who achieved complete or partial response at 12 weeks, assessed by CT/MRI scans or clinical photography and in accordance with the RECIST criteria.

End point type	Secondary

End point timeframe:

12 weeks after trial entry

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	33	30	26
Units: percent				
number (confidence interval 95%)	6 (2 to 21)	0 (0 to 10)	10 (3 to 26)	4 (1 to 18)

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFS

End point title	Median PFS
End point description: Progression Free Survival (PFS)	
End point type	Secondary
End point timeframe: 12 months after trial entry	

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: months				
median (confidence interval 95%)	3.0 (2.4 to 6.8)	2.8 (2.6 to 5.1)	3.1 (2.2 to 5.4)	2.8 (2.5 to 3.8)

Statistical analyses

No statistical analyses for this end point

Secondary: 12 Month PFS Rate

End point title	12 Month PFS Rate
End point description: Progression Free Survival (PFS)	
End point type	Secondary
End point timeframe: 12 Months after trial entry	

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: percent				
number (confidence interval 95%)	19 (9 to 34)	6 (1 to 17)	12 (4 to 25)	10 (2 to 23)

Statistical analyses

No statistical analyses for this end point

Secondary: Median PFI

End point title	Median PFI
End point description: Progression Free Interval (PFI)	
End point type	Secondary
End point timeframe: Trial entry to date of first observed disease progression	

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: months				
median (confidence interval 95%)	3.0 (2.4 to 6.8)	2.8 (2.6 to 5.1)	3.2 (2.4 to 5.4)	2.8 (2.5 to 3.8)

Statistical analyses

No statistical analyses for this end point

Secondary: 12 Month PFI Rate

End point title	12 Month PFI Rate
End point description: Progression Free Interval (PFI)	
End point type	Secondary
End point timeframe: Trial entry to date when disease progression first observed	

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: percent				
number (confidence interval 95%)	22 (10 to 36)	6 (1 to 17)	12 (4 to 26)	10 (2 to 23)

Statistical analyses

No statistical analyses for this end point

Secondary: Median OS

End point title	Median OS

End point description:

Overall Survival (OS)

End point type	Secondary

End point timeframe:

Trial entry to death from any cause or date last seen for patients who were still alive at the time of analysis

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: months				
median (confidence interval 95%)	8.6 (5.3 to 17.8)	11.4 (9.2 to 12.6)	9.7 (7.5 to 17.6)	9.9 (6.7 to 14.1)

Statistical analyses

No statistical analyses for this end point

Secondary: 12 Month OS Rate

End point title	12 Month OS Rate

End point description:

Overall Survival (OS)

End point type	Secondary

End point timeframe:

Trial entry to death from any cause or date last seen for patients who were still alive at the time of analysis

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: percent				
number (confidence interval 95%)	40 (24 to 56)	40 (24 to 56)	47 (30 to 63)	34 (18 to 50)

Statistical analyses

No statistical analyses for this end point

Secondary: Change In Performance Status

End point title	Change In Performance Status

End point description:

Performance status change compared to baseline.

End point type	Secondary

End point timeframe:

Trial entry to the end of cycle 3 (12 weeks)

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: patients				
Improvement (1 point)	2	3	0	2
No Change	12	19	18	14
Worsened (1 point)	6	4	5	4
Worsened (2 points)	1	0	0	0
Not Known	15	9	11	11

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity Rate

End point title	Toxicity Rate

End point description:

Toxicity rate has been calculated as the number of patients experiencing at least one grade 3 or 4 adverse event or a serious adverse reaction at any grade divided by the number of patients who started treatment, as per the population definition. Adverse events were grading using NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

End point type	Secondary

End point timeframe:

Time on trial treatment

End point values	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma	Other Sarcoma
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	36	35	34	31
Units: percent				
number (confidence interval 95%)	72 (56 to 84)	60 (44 to 74)	68 (51 to 81)	65 (47 to 79)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time in trial.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Angiosarcoma
Reporting group description:	
Patients with pathologically confirmed Angiosarcoma, including intermediate and malignant vascular tumours (WHO classification, 2002) and Kaposi's sarcoma.	
Reporting group title	Leiomyosarcoma
Reporting group description:	
Patients with pathologically confirmed Leiomyosarcoma, including uterine, skin or non organ origin.	
Reporting group title	Synovial Sarcoma
Reporting group description:	
Patients with pathologically confirmed Synovial Sarcoma.	
Reporting group title	Other Sarcoma
Reporting group description:	
Patients with eligible subtypes of pathologically confirmed soft tissue sarcoma other than Angiosarcoma, Leiomyosarcoma or Synovial sarcoma. Other eligible subtypes of soft tissue sarcoma were of Trojani intermediate or high grade, including fibroblastic, fibrohistiocytic, adipocytic, rhabdomyosarcoma, malignant peripheral nerve sheath, and NOS. Ineligible subtypes that were not included in this arm were: Osteosarcoma, Ewings/PNET sarcomas, Chondrosarcoma, Gastrointestinal stromal tumours (GIST), Dermatofibrosarcoma protuberans (DFSP), Malignant mesothelioma and Mixed mesodermal tumours of uterus.	

Serious adverse events	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 36 (47.22%)	9 / 35 (25.71%)	20 / 34 (58.82%)
number of deaths (all causes)	29	35	30
number of deaths resulting from adverse events	2	4	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Disease progression			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Cerebral metastasis with intrametastatic bleed			

subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (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
Surgical and medical procedures			
Pump Re-Dosing			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracotomy			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	0 / 1	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumothorax			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	2 / 2	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lrti			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Chest pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusion			

subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vascular disorder			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
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			
Abdominal pain			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			

subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (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
Stomach pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic obstruction			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Diarrhoea			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Vomiting			

subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Skin and subcutaneous tissue disorders			
Bleeding			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (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
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Renal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Musculoskeletal and connective tissue disorders			
Chest wall pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	0 / 34 (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
Bone pain			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness lower limb			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Other Sarcoma		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 31 (32.26%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Disease progression			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral metastasis with intrametastatic bleed			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Pump Re-Dosing			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracotomy			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fever			

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Bronchopulmonary haemorrhage				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lrti				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusion				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Platelet count decreased				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Wound complication				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Sinus bradycardia				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal vascular disorder				

subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal perforation				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomach pain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colonic obstruction				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Bleeding				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Dysuria				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal haemorrhage				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Chest wall pain				
subjects affected / exposed	1 / 31 (3.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	0 / 31 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Bone pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscle weakness lower limb			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anorectal infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchial infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hypercalcaemia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 31 (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: 5 %

Non-serious adverse events	Angiosarcoma	Leiomyosarcoma	Synovial Sarcoma
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 36 (100.00%)	35 / 35 (100.00%)	34 / 34 (100.00%)
Vascular disorders			
Haemorrhage			
subjects affected / exposed	5 / 36 (13.89%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	8	0	0
Hypertension			
subjects affected / exposed	26 / 36 (72.22%)	28 / 35 (80.00%)	21 / 34 (61.76%)
occurrences (all)	163	142	77
Hot flashes			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	0	3	3
Thromboembolic event			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	31 / 36 (86.11%)	27 / 35 (77.14%)	28 / 34 (82.35%)
occurrences (all)	279	187	195
Non-cardiac chest pain			
subjects affected / exposed	6 / 36 (16.67%)	2 / 35 (5.71%)	8 / 34 (23.53%)
occurrences (all)	14	3	11
Pain			

subjects affected / exposed	12 / 36 (33.33%)	13 / 35 (37.14%)	12 / 34 (35.29%)
occurrences (all)	30	30	33
Edema limbs			
subjects affected / exposed	1 / 36 (2.78%)	4 / 35 (11.43%)	1 / 34 (2.94%)
occurrences (all)	1	8	2
Fever			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	3 / 34 (8.82%)
occurrences (all)	1	5	4
Flu like symptoms			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	4
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 36 (30.56%)	15 / 35 (42.86%)	16 / 34 (47.06%)
occurrences (all)	46	50	65
Dyspnoea			
subjects affected / exposed	18 / 36 (50.00%)	16 / 35 (45.71%)	21 / 34 (61.76%)
occurrences (all)	103	57	72
Haemoptysis			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Hoarseness			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	3	1	5
Voice alteration			
subjects affected / exposed	18 / 36 (50.00%)	11 / 35 (31.43%)	19 / 34 (55.88%)
occurrences (all)	126	39	81
Epistaxis			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 34 (5.88%)
occurrences (all)	1	4	5
Sore throat			

subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	3 / 34 (8.82%)
occurrences (all)	0	3	5
Laryngeal haemorrhage			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Pneumothorax			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	3 / 34 (8.82%)
occurrences (all)	2	0	6
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	3
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 36 (5.56%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	12	8	1
Insomnia			
subjects affected / exposed	6 / 36 (16.67%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	14	3	1
Anxiety			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight loss			
subjects affected / exposed	13 / 36 (36.11%)	15 / 35 (42.86%)	12 / 34 (35.29%)
occurrences (all)	38	57	45
Alanine aminotransferase increased			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	7	2	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	4	2	12
Cardiac disorders			
Chest pain	Additional description: Cardiac		
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	4	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	4 / 36 (11.11%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	8	4	0
Dysgeusia			
subjects affected / exposed	5 / 36 (13.89%)	3 / 35 (8.57%)	1 / 34 (2.94%)
occurrences (all)	13	17	3
Headache			
subjects affected / exposed	12 / 36 (33.33%)	14 / 35 (40.00%)	12 / 34 (35.29%)
occurrences (all)	25	35	56
Paresthesia			
subjects affected / exposed	2 / 36 (5.56%)	3 / 35 (8.57%)	2 / 34 (5.88%)
occurrences (all)	6	3	2
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	2 / 34 (5.88%)
occurrences (all)	1	11	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	1	6	5
Ear and labyrinth disorders			
Blocked ears			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Eye pain			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	2	0	0
Glaucoma			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 36 (19.44%)	11 / 35 (31.43%)	8 / 34 (23.53%)
occurrences (all)	30	29	25
Constipation			
subjects affected / exposed	14 / 36 (38.89%)	15 / 35 (42.86%)	10 / 34 (29.41%)
occurrences (all)	36	60	30

Diarrhoea			
subjects affected / exposed	16 / 36 (44.44%)	17 / 35 (48.57%)	17 / 34 (50.00%)
occurrences (all)	98	70	98
Dry mouth			
subjects affected / exposed	2 / 36 (5.56%)	5 / 35 (14.29%)	3 / 34 (8.82%)
occurrences (all)	4	11	5
Dysphagia			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	4	0	0
Mucositis oral			
subjects affected / exposed	21 / 36 (58.33%)	19 / 35 (54.29%)	13 / 34 (38.24%)
occurrences (all)	74	68	46
Nausea			
subjects affected / exposed	21 / 36 (58.33%)	20 / 35 (57.14%)	15 / 34 (44.12%)
occurrences (all)	54	71	53
Vomiting			
subjects affected / exposed	11 / 36 (30.56%)	10 / 35 (28.57%)	7 / 34 (20.59%)
occurrences (all)	25	23	17
Dyspepsia			
subjects affected / exposed	1 / 36 (2.78%)	7 / 35 (20.00%)	3 / 34 (8.82%)
occurrences (all)	2	16	11
Flatulence			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 34 (5.88%)
occurrences (all)	3	6	12
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	2	2	0
Oral pain			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	2 / 34 (5.88%)
occurrences (all)	4	2	2
Oral sensitivity			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	1	7	0
Stomach pain			
subjects affected / exposed	1 / 36 (2.78%)	3 / 35 (8.57%)	0 / 34 (0.00%)
occurrences (all)	1	3	0

Dental caries			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Toothache			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	1	3	0
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 36 (5.56%)	3 / 35 (8.57%)	1 / 34 (2.94%)
occurrences (all)	8	4	4
Dry skin			
subjects affected / exposed	3 / 36 (8.33%)	5 / 35 (14.29%)	3 / 34 (8.82%)
occurrences (all)	24	9	5
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	8 / 36 (22.22%)	8 / 35 (22.86%)	8 / 34 (23.53%)
occurrences (all)	24	29	26
Pruritus			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	1 / 34 (2.94%)
occurrences (all)	2	2	7
Rash acneiform			
subjects affected / exposed	5 / 36 (13.89%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	11	0	5
Hyperhidrosis			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	0	1	6
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	9 / 36 (25.00%)	16 / 35 (45.71%)	7 / 34 (20.59%)
occurrences (all)	16	42	37
Urinary frequency			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 36 (2.78%)	1 / 35 (2.86%)	6 / 34 (17.65%)
occurrences (all)	4	1	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 36 (33.33%)	15 / 35 (42.86%)	9 / 34 (26.47%)
occurrences (all)	48	44	71
Back pain			
subjects affected / exposed	5 / 36 (13.89%)	4 / 35 (11.43%)	1 / 34 (2.94%)
occurrences (all)	9	9	2
Chest wall pain			
subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	22	5	0
Pain in extremity			
subjects affected / exposed	8 / 36 (22.22%)	5 / 35 (14.29%)	5 / 34 (14.71%)
occurrences (all)	20	17	13
Bone pain			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	1	6	5
Cramp			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	3	10	0
Myalgia			
subjects affected / exposed	1 / 36 (2.78%)	4 / 35 (11.43%)	1 / 34 (2.94%)
occurrences (all)	2	12	3
Neck pain			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Infections and infestations			
Bronchial infection			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	2 / 34 (5.88%)
occurrences (all)	2	1	2
Eye infection			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	0 / 34 (0.00%)
occurrences (all)	3	0	0

Skin infection			
subjects affected / exposed	3 / 36 (8.33%)	1 / 35 (2.86%)	0 / 34 (0.00%)
occurrences (all)	6	1	0
Upper respiratory infection			
subjects affected / exposed	3 / 36 (8.33%)	2 / 35 (5.71%)	2 / 34 (5.88%)
occurrences (all)	6	2	2
Urinary tract infection			
subjects affected / exposed	4 / 36 (11.11%)	6 / 35 (17.14%)	3 / 34 (8.82%)
occurrences (all)	6	10	4
Mucosal infection			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	3	2	0
Viral cold			
subjects affected / exposed	0 / 36 (0.00%)	2 / 35 (5.71%)	1 / 34 (2.94%)
occurrences (all)	0	2	1
Lung infection			
subjects affected / exposed	0 / 36 (0.00%)	0 / 35 (0.00%)	3 / 34 (8.82%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	13 / 36 (36.11%)	20 / 35 (57.14%)	15 / 34 (44.12%)
occurrences (all)	38	79	51
Hyperglycaemia			
subjects affected / exposed	1 / 36 (2.78%)	2 / 35 (5.71%)	0 / 34 (0.00%)
occurrences (all)	1	7	0

Non-serious adverse events	Other Sarcoma		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	19 / 31 (61.29%)		
occurrences (all)	90		
Hot flashes			

subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Thromboembolic event			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	28 / 31 (90.32%)		
occurrences (all)	175		
Non-cardiac chest pain			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	59		
Edema limbs			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Fever			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Flu like symptoms			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 31 (45.16%)		
occurrences (all)	41		
Dyspnoea			
subjects affected / exposed	14 / 31 (45.16%)		
occurrences (all)	36		

Haemoptysis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Hoarseness subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Voice alteration subjects affected / exposed occurrences (all)	8 / 31 (25.81%) 36		
Epistaxis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Sore throat subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 8		
Laryngeal haemorrhage subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 6		
Pneumothorax subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 2		
Bronchopulmonary hemorrhage subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 4		
Insomnia subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1		
Anxiety subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Investigations			

Weight loss			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	29		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	7		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	8		
Cardiac disorders			
Chest pain	Additional description: Cardiac		
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	10		
Headache			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	21		
Paresthesia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	20		
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Blocked ears			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	13		
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Glaucoma			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 31 (32.26%)		
occurrences (all)	29		
Constipation			
subjects affected / exposed	13 / 31 (41.94%)		
occurrences (all)	35		
Diarrhoea			
subjects affected / exposed	12 / 31 (38.71%)		
occurrences (all)	28		
Dry mouth			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	6		
Dysphagia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Mucositis oral			
subjects affected / exposed	15 / 31 (48.39%)		
occurrences (all)	44		
Nausea			
subjects affected / exposed	16 / 31 (51.61%)		
occurrences (all)	41		
Vomiting			
subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	11		
Dyspepsia			

subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	11		
Flatulence			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Oral pain			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	6		
Oral sensitivity			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Stomach pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	12		
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	9 / 31 (29.03%)		
occurrences (all)	42		
Pruritus			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Rash acneiform			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	16		
Hyperhidrosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	6 / 31 (19.35%)		
occurrences (all)	17		
Urinary frequency			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	7		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	21		
Back pain			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	10		
Chest wall pain			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	10		
Bone pain			

subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	7		
Cramp			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Skin infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Upper respiratory infection			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	4		
Mucosal infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Viral cold			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	2		
Lung infection			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences (all)	1		

Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	 16 / 31 (51.61%) 39 0 / 31 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2010	Since the AXI-STS study was proposed and the protocol written there was a standardisation of the requirements for safety measurements during all axitinib studies. Amendments: Inclusion criteria: Added: No evidence of preexisiting uncontrolled hypertension as documented by 2 baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be <=140 mm Hg, and the baseline diastolic blood pressure readings must be <=90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible. Added: Urinary protein <2+ by urine dipstick. If dipstick is >=2+ then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours. Exclusion criteria: Deleted: "Uncontrolled or poorly controlled hypertension: systolic BP >=150 mmHg or diastolic BP >=90 mmHg. Hypertension may be treated prior to trial entry, but 3 consecutive readings less than 150/90 must be obtained, at least 24h apart prior to trial entry." Expected tocivity: Added "proteinuria" Dose and Schedule modifications: Updated instructions on how to manage dose reductions for to patients with hypertension Added instructions on how to manage dose reductions for related to patients with proteinuria Concomitant medication: Added instructions on how to manage patients on chronic antacid therapy Patient assessments: Added instructions on blood pressure monitoring (patients to self-monitor blood pressure at home)
02 August 2011	Following halt to recruitment the following was implemented into the protocol: Excluding patients at high risk of pulmonary haemorrhage with previous significant haemoptysis, cavitating lung metastases or any metastasis abutting or invading a major pulmonary blood vessel. Additional imaging to monitor patients for possible cavitation of lung metastases and any patients developing such cavitation or significant haemoptysis should stop study treatment. Exclusion of patients taking antiplatelet drugs, including aspirin (>325mg/day) and NSAIDs. Monitoring of platelet counts Additional amendments to the protocol: Updated information about potential toxicities and their management. A study radiologist has been appointed to review patient imaging

30 September 2011	Protocol synopsis - Secondary outcomes measures: Added: Tumour response rate (using Choi criteria) Deleted: 'Estimated start date October 2009 and end date October 2011' Protocol synopsis - Exclusion criteria: Changed: 'within the past 3 months' to 'within the past 12 months' Added: Patients with cavitating lung metastases or any metatstasis abutting or invading a major pulmonary blood vessel on baseline CT or MRI scan. Added: History of bleeding diathesis or coagulopathy within 12 months of study entry Added: History of haemoptysis > 2.5 ml (½ teaspoonful) of blood in any 24-hour period within 6 months of enrolment. Added: Regular treatment with antiplatelet medication, including aspirin >325 mg/day or NSAIDs. Secondary outcomes: Added: 'Tumour response rate (using Choi criteria)' Exclusion criteria: Added: Patients with cavitating lung metastases or any metastasis abutting or invading a major pulmonary blood vessel on baseline CT or MRI scan.Added: History of bleeding diathesis or coagulopathy within 12 months of study entry Added: History of haemoptysis > 2.5 ml (½ teaspoonful) of blood in any 24-hour period within 6 months of enrolment. Added: Regular treatment with antiplatelet medication, including aspirin >325 mg/day or NSAIDs. Updated expected toxicities. Dose and schedule modifications: Updated text on managing patients with hypertension. Added Cavitating lung metastases section Added Thrombocitopenia section Concomitant medication: Added Patients should not take antiplatelet drugs, including aspirin (>325mg/day) and NSAIDs Updated patient assessments section to include Urinary protein, and amend Chest x-ray and CT/MRI information
07 May 2014	Expected toxicity: Updated in line with new data, including the addition of cardiac failure events information. Concomitant medication: Amended instructions on how to manage patients who need to be on chronic antacid therapy with histamine H2 antagonists, proton-pump inhibitors or locally acting antacids .
12 December 2014	Treatment details: Changes to labelling/packaging/formulation and drug supply/distribution to reflect the change in name of distribution company and a change in how the drugs will be the supply and labelled.
25 April 2016	Protocol synopsis - Biological measures: Added: Assessment of CT scan based tumour texture as a biomarker of treatment response. Biological measures: Added: Information regarding the analysis of CT scan based tumour texture as a biomarker of treatment response.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 January 2011	Two fatal SUSARs were reported in which haemoptysis was implicated. In the first case pulmonary haemorrhage was recorded as the cause of death while in the second infection was the primary cause of death but haemoptysis was listed as a symptom. Subsequently an additional SAE has been reported for haemoptysis. Following discussions with Pfizer it was decided to temporarily halt recruitment until these events could be properly investigated. DMC reviewed clinical narratives and imaging for all the SAE patients. They recommended a number of precautions in order to mitigate the risk of further haemorrhagic adverse events. In particular, excluding patients at high risk of pulmonary haemorrhage with previous significant haemoptysis, cavitating lung metastases or any metastasis abutting or invading a major pulmonary blood vessel. They mandated additional imaging to monitor patients for possible cavitation of lung metastases and demanded that any patients developing such cavitation or significant haemoptysis should stop study treatment. Advice was also taken advice from the study drug manufacturer, Pfizer Ltd., including the exclusion of patients taking antiplatelet drugs, including aspirin (>325mg/day) and NSAIDs. They also requested that platelet counts should be monitored.	07 October 2011

Notes:

Limitations and caveats

None reported