Clinical trial results:
A randomised phase II study of sunitinib versus dacarbazine in the treatment of patients with metastatic uveal melanoma

Summary

EudraCT number	2008-008794-55
Trial protocol	GB
Global end of trial date	17 March 2014

Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	RDD299

Additional study identifiers

ISRCTN number	ISRCTN75033520
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Clatterbridge Cancer Centre NHS Foundation Trust
Sponsor organisation address	Clatterbridge Road, Wirral, United Kingdom, CH63 4JY
Public contact	Ms Charlotte Rawcliffe, Liverpool Cancer Trials Unit, University of Liverpool, 0151 794 8167, C.Rawcliffe@liverpool.ac.uk
Scientific contact	Dr Victoria Shaw, GCLP Labs, University of Liverpool, 0151 706 4180, Victoria.Shaw@liverpool.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2012
Global end of trial reached?	Yes
Global end of trial date	17 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Can the progression free survival time of patients with metastatic Uveal Melanoma be extended by treatment with Sunitinib, compared with the treatment by Dacarbazine?

Protection of trial subjects:

Consent should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. The right of patients to refuse their consent to participate in the trial without providing a reason must be respected.

Verification of appropriate informed consent will be enabled by the provision of copies of participants" signed informed consent form being supplied to the LCTU by recruiting centres. This requires that name data will be transferred to the LCTU, which is explained in the PIS. The LCTU will preserve the confidentiality of participants taking part in the study and the University of Liverpool is a Data Controller registered with the Information Commissioners Office.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. CRFs will be labelled with patient initials and unique trial screening and/or randomisation number. Blood and paraffin blocks will be transferred to the LECMC GCLP laboratory and will be identifiable by unique trial randomisation number only. Consent forms sent to the LCTU as part of the randomisation process may contain patient identifiers for the purpose of monitoring as described in the trial risk assessment. Such information will be stored in secure, locked cabinets.
The LCTU will request consent from all patients to obtain information from the NHS Information Centre (Medical Research Information Service) to follow patient progress if this is not available from their hospital or General Practitioner (GP).

Background therapy: -

Evidence for comparator:

Relapsed uveal melanoma carries a dismal prognosis and to date no systemic or regional therapy has shown a survival advantage over best supportive care. As a consequence there is an urgent need to investigate novel therapies in this disease. Presently, patients with metastatic uveal melanoma have few treatment options given the limited available evidence base for systemic therapy. In the UK, the majority of patients are managed with symptomatic measures, DTIC chemotherapy or entry into phase I clinical programmes.

Preliminary evidence suggests that C-Kit and angiogenesis may both play a role in disease progression and that Imatinib may have limited activity irrespective of C-Kit expression.

Sunitinib is a multi-targeted TKI which has shown significant activity both in Imatinib resistant GIST but also in a range of malignancies by virtue of its anti-angiogenic effects. A preliminary report of efficacy in uveal melanoma requires confirmation in a larger randomised controlled setting.

The heterogeneous nature of the disease and variable prognosis according to tumour volume at relapse limit the utility of further small single arm pilot phase II studies.

Currently, DTIC represents a standard of care in the absence of evidence based protocols and thus Sunitinib will be investigated in a randomised phase II setting with the opportunity for cross-over on first progression. For the purposes of this trial and potential future phase III comparison, DTIC will be administered at an internationally recognised standard dose of 1000mg/m2.

Actual start date of recruitment	22 October 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: 84
Worldwide total number of subjects	84
EEA total number of subjects	84

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)	48
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

UK; First patient randomised: 22/10/2010; Last patient randomised: 07/08/2012;
Cut off date: 30/11/2012;
Total number randomised to Cutoff date: 84
Total number withdrawn from study to Cutoff date: 75/84 before crossover (62 due to progression); 19/35 after crossover (12 due to progression)
Total number of deaths to Cutoff date: 54

Pre-assignment

Screening details:

ECOG performance status (see Appendix B); Physical Examination (including weight); Urine pregnancy test; 12 lead ECG; Vital Signs; Haematology; Biochemistry; CT scan; Additional MRI Scan; Identification of target lesions; CT Scan; Blood Sample
Cutoff date: 30/11/2012 - Total number screened to Cutoff date: 110

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dacarbazine

Arm description:

Patients will receive 1000mg/m2 every 21 days by IV until progression or unacceptable toxicity

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dacarbazine will be administered as an open-label by IV infusion 1000mg/m2 over 30 to 60 minutes, starting on Week 1 and repeated every 3 weeks until disease progression or unacceptable toxicity.

Arm title	Sunitinib

Arm description:

Sunitinib 50mg to be taken orally once a day for 28 days followed by 14 day break, until progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Individual patients will receive 28 days supply, dispensed at every other 3-weekly clinic visit (i.e. every 6 weeks) according to locally defined policy.
50mg of Sunitinib to be taken by mouth once a day for 28 days followed by a 14 day break (4/2 schedule) until progression or unacceptable toxicity.

Number of subjects in period 1	Dacarbazine	Sunitinib
Started	40	44
Cross Over	24	11
Completed	24	11
Not completed	16	33
Withdrew between cross-over of treatments	16	33

Baseline characteristics

Reporting groups	
Reporting group title	Dacarbazine
Reporting group description:	
Patients will receive 1000mg/m2 every 21 days by IV until progression or unacceptable toxicity	
Reporting group title	Sunitinib
Reporting group description:	
Sunitinib 50mg to be taken orally once a day for 28 days followed by 14 day break, until progression or unacceptable toxicity.	

Reporting group values	Dacarbazine	Sunitinib	Total
Number of subjects	40	44	84
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	62.6	66.6	
inter-quartile range (Q1-Q3)	53.1 to 68.1	59.4 to 71.9	-
Gender categorical			
Units: Subjects			
Female	26	20	46
Male	14	24	38
ECOG Performance			
ECOG Performance Status			
Units: Subjects			
ECOG 0	22	27	49
ECOG 1	18	14	32
ECOG 2	0	3	3

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for: a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process	

c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation.

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received any trial treatment.

Reporting group values	Full Analysis Set	Safety Set	
Number of subjects	84	84	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female	46	46	
Male	38	38	
ECOG Performance			
ECOG Performance Status			
Units: Subjects			
ECOG 0	49	49	
ECOG 1	32	32	
ECOG 2	3	3	

End points

End points reporting groups

Reporting group title	Dacarbazine
Reporting group description:	
Patients will receive 1000mg/m2 every 21 days by IV until progression or unacceptable toxicity	
Reporting group title	Sunitinib
Reporting group description:	
Sunitinib 50mg to be taken orally once a day for 28 days followed by 14 day break, until progression or unacceptable toxicity.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
In order to follow the Intention to Treat (ITT) principle this will consist of all randomised patients excepting for: a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation.	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received any trial treatment.	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description:	
Progression will be defined according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 (see Appendix C) and will be captured by 12 weekly imaging, or imaging in the event of a clinical deterioration. Patients still alive with no evidence of progression at the time of their last visit are censored at the time of the most recent information. That is, PFS (months) = (min(censoring date, date of death) – date of randomisation)/30.4. The protocol specified that the analysis would take place once all patients have been followed up for at least 3 months. Because of the early termination (which might affect willingness to switch treatments) a common administrative) censoring date was taken as the date of the TSC letter suspending randomisation (referred to as the "cutoff" date). Time to progression on firstline treatment (TTP1) will be compared to time to progression on secondline treatment (TTP2) for patients who receive crossover therapy	
End point type	Primary
End point timeframe:	
Measured as days from randomisation to progression or death.	

End point values	Dacarbazine	Sunitinib	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	44	84	
Units: Subjects				
median (confidence interval 95%)	2.8 (2.6 to 2.9)	2.8 (2.6 to 3.5)	2.8 (2.6 to 2.9)	

Statistical analyses

Statistical analysis title	PFS Analysis
Comparison groups	Dacarbazine v Sunitinib
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7658
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.39

Secondary: AEs

End point title	AEs

End point description:

Classified using the NCI CTCAE version 4. Measured as the number of patients to experience at least 1 grade 3 adverse event.

End point type	Secondary

End point timeframe:

AEs experienced following randomisation

End point values	Dacarbazine	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: Subjects	27	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival of Crossover Patients

End point title	Progression Free Survival of Crossover Patients

End point description:

Time to progression on first-line treatment (TTP1) compared to time to progression on second-line treatment (TTP2) for patients who receive cross-over therapy

End point type	Secondary

End point timeframe:

Measured as days from randomisation to progression or death

End point values	Dacarbazine	Sunitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	44		
Units: Subjects				
median (full range (min-max))	2.5 (0 to 12)	2.5 (0 to 12)		

Statistical analyses

Statistical analysis title	Second-line PFS
Comparison groups	Dacarbazine v Sunitinib
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Cox proportional hazard
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.28

Secondary: Overall survival to death from any cause

End point title	Overall survival to death from any cause

End point description:

Patients known to have survived past the cutoff date (eg have attended for assessment after the cutoff date) will be censored at the cutoff date. Patients not known to have died but who have no record of attendance after the cutoff date will censored at the last visit date before the cutoff date.

End point type	Secondary

End point timeframe:

Overall survival measured as months from randomisation to death from any cause

End point values	Dacarbazine	Sunitinib	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	44	84	
Units: Subjects				
median (confidence interval 95%)	7.4 (6.2 to 11.1)	6.3 (3.3 to 8.4)	7.4 (6.1 to 8.4)	

Statistical analyses

Statistical analysis title	OS Analysis
Comparison groups	Dacarbazine v Sunitinib
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.61

Secondary: Overall response according to RECIST

End point title	Overall response according to RECIST

End point description:

Overall response rate on first-line treatment (RR1) compared to overall response rate on second-line treatment (RR2) for patients who receive cross-over therapy

End point type	Secondary

End point timeframe:

From randomisation until cut-off date

End point values	Dacarbazine	Sunitinib	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	40	44	84	
Units: Subjects	3	0	3	

Statistical analyses

Statistical analysis title	Difference in ORR
Comparison groups	Dacarbazine v Sunitinib
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.108
Method	Fisher exact
Parameter estimate	Difference in Proportions
Point estimate	-0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.01

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events were reported from first patient first visit until 28 days after the last study treatment was administered.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCTAE
Dictionary version	4

Reporting groups

Reporting group title	Dacarbazine

Reporting group description:

Patients will receive 1000mg/m2 every 21 days by IV until progression or unacceptable toxicity
This reporting group also includes patients who have crossed over to Dacarbazine from the original Sunitinib Arm

Reporting group title	Sunitinib

Reporting group description:

Sunitinib 50mg to be taken orally once a day for 28 days followed by 14 day break, until progression or unacceptable toxicity.
This also includes patients who have cross over from Dacarbazine

Serious adverse events	Dacarbazine	Sunitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 51 (29.41%)	10 / 68 (14.71%)	
number of deaths (all causes)	26	28	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	2 / 51 (3.92%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	7 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Pain			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleuritic Pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
infections and infestations - Other			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infection			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alkaline phospate increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine Increased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count increased			
subjects affected / exposed	2 / 51 (3.92%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell decreased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate Phosphotase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			

subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Dacarbazine	Sunitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 51 (78.43%)	55 / 68 (80.88%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 51 (5.88%)	10 / 68 (14.71%)	
occurrences (all)	4	16	
Thromboembolic event			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	2 / 51 (3.92%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
FATIGUE			
subjects affected / exposed	23 / 51 (45.10%)	34 / 68 (50.00%)	
occurrences (all)	43	50	
FEVER			
subjects affected / exposed	4 / 51 (7.84%)	2 / 68 (2.94%)	
occurrences (all)	10	2	
Flu like symptoms			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Localized edema			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
PAIN			
subjects affected / exposed	7 / 51 (13.73%)	9 / 68 (13.24%)	
occurrences (all)	7	10	
General disorders and administration			

site conditions - Other, specify			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
Irregular menstruation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Vaginal hemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 51 (3.92%)	4 / 68 (5.88%)	
occurrences (all)	2	6	
DYSPNEA			
subjects affected / exposed	4 / 51 (7.84%)	8 / 68 (11.76%)	
occurrences (all)	5	10	
Epistaxis			
subjects affected / exposed	2 / 51 (3.92%)	4 / 68 (5.88%)	
occurrences (all)	2	5	
Hiccups			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders - Other, specify			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	

Nasal congestion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	3	
Restlessness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Agitation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Alanine Aminotransferase increased			
subjects affected / exposed	4 / 51 (7.84%)	5 / 68 (7.35%)	
occurrences (all)	4	8	
Alkaline Phosphatase Increased			
subjects affected / exposed	6 / 51 (11.76%)	7 / 68 (10.29%)	
occurrences (all)	6	9	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 51 (11.76%)	10 / 68 (14.71%)	
occurrences (all)	8	15	
Creatinine Increased			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	3	
GGT increased			
subjects affected / exposed	16 / 51 (31.37%)	16 / 68 (23.53%)	
occurrences (all)	21	22	
Haemoglobin increased			

subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Investigations - Other, specify			
subjects affected / exposed	2 / 51 (3.92%)	4 / 68 (5.88%)	
occurrences (all)	5	4	
Lymphocyte count decreased			
subjects affected / exposed	5 / 51 (9.80%)	6 / 68 (8.82%)	
occurrences (all)	8	9	
neutrophil count decreased			
subjects affected / exposed	12 / 51 (23.53%)	6 / 68 (8.82%)	
occurrences (all)	22	9	
platelet count decreased			
subjects affected / exposed	9 / 51 (17.65%)	10 / 68 (14.71%)	
occurrences (all)	16	22	
WEIGHT LOSS			
subjects affected / exposed	1 / 51 (1.96%)	4 / 68 (5.88%)	
occurrences (all)	1	5	
white blood cell decreased			
subjects affected / exposed	10 / 51 (19.61%)	6 / 68 (8.82%)	
occurrences (all)	13	10	
Blood Bilirubin Increased			
subjects affected / exposed	0 / 51 (0.00%)	6 / 68 (8.82%)	
occurrences (all)	0	7	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	2 / 51 (3.92%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Wound complication			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Venous injury			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
dysgeusia			
subjects affected / exposed	3 / 51 (5.88%)	13 / 68 (19.12%)	
occurrences (all)	3	16	
Headache			
subjects affected / exposed	2 / 51 (3.92%)	2 / 68 (2.94%)	
occurrences (all)	2	3	
Lethargy			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 51 (3.92%)	2 / 68 (2.94%)	
occurrences (all)	2	6	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	9 / 51 (17.65%)	6 / 68 (8.82%)	
occurrences (all)	13	10	
Blood and lymphatic system disorders - Other, specify			
subjects affected / exposed	3 / 51 (5.88%)	4 / 68 (5.88%)	
occurrences (all)	7	5	
Febrile neutropenia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 68 (0.00%)	
occurrences (all)	2	0	
Thrombotic thrombocytopenic purpura			

subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Eye disorders			
Eye disorders - Other, specify			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
photophobia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	3 / 51 (5.88%)	6 / 68 (8.82%)	
occurrences (all)	3	7	
CONSTIPATION			
subjects affected / exposed	7 / 51 (13.73%)	7 / 68 (10.29%)	
occurrences (all)	15	8	
DIARRHEA			
subjects affected / exposed	7 / 51 (13.73%)	12 / 68 (17.65%)	
occurrences (all)	8	13	
Dry mouth			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
dyspepsia			
subjects affected / exposed	1 / 51 (1.96%)	10 / 68 (14.71%)	
occurrences (all)	1	10	
Flatulence			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Gastrointestinal disorders - Other, specify			

subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Gastrointestinal pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Mucositis oral			
subjects affected / exposed	2 / 51 (3.92%)	11 / 68 (16.18%)	
occurrences (all)	3	15	
NAUSEA			
subjects affected / exposed	8 / 51 (15.69%)	19 / 68 (27.94%)	
occurrences (all)	8	25	
VOMITING			
subjects affected / exposed	6 / 51 (11.76%)	8 / 68 (11.76%)	
occurrences (all)	8	9	
Oral pain			
subjects affected / exposed	0 / 51 (0.00%)	5 / 68 (7.35%)	
occurrences (all)	0	5	
Bloating			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	3	
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	2 / 51 (3.92%)	1 / 68 (1.47%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	3	
Erythema multiforme			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Pain of skin			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Palmar-plantar erythrodysesthesia syndrome			

subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Photosensitivity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Scalp pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Skin atrophy			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Dry skin			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders - Other, specify			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Nail discoloration			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Skin hypopigmentation			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 51 (0.00%)	3 / 68 (4.41%)	
occurrences (all)	0	3	
skin hyperpigmentation			
subjects affected / exposed	0 / 51 (0.00%)	4 / 68 (5.88%)	
occurrences (all)	0	8	
Renal and urinary disorders			
urinary tract pain			

subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 68 (0.00%)	
occurrences (all)	4	0	
Bone pain			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	2	2	
Flank pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Muscle weakness lower limb			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 51 (1.96%)	3 / 68 (4.41%)	
occurrences (all)	1	3	
Buttock pain			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Infections and infestations			
Infections and infestations - Other, specify			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
lung infection			

subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
Rhinitis infective			
subjects affected / exposed	1 / 51 (1.96%)	1 / 68 (1.47%)	
occurrences (all)	1	1	
urinary tract infection			
subjects affected / exposed	1 / 51 (1.96%)	3 / 68 (4.41%)	
occurrences (all)	1	3	
Mucosal infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Upper respiratory infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Bladder infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	4 / 51 (7.84%)	8 / 68 (11.76%)	
occurrences (all)	6	10	
HYPOALBUMINEMIA			
subjects affected / exposed	4 / 51 (7.84%)	2 / 68 (2.94%)	
occurrences (all)	5	3	
Hypokalemia			
subjects affected / exposed	1 / 51 (1.96%)	2 / 68 (2.94%)	
occurrences (all)	1	2	
HYPONATREMIA			
subjects affected / exposed	3 / 51 (5.88%)	5 / 68 (7.35%)	
occurrences (all)	4	6	
HYPOPHOSPHATEMIA			
subjects affected / exposed	2 / 51 (3.92%)	1 / 68 (1.47%)	
occurrences (all)	2	1	

Dehydration			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Hyperkalemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
Hypocalcemia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	3	
Hypercalcemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
HYPOMAGNESEMIA			
subjects affected / exposed	0 / 51 (0.00%)	1 / 68 (1.47%)	
occurrences (all)	0	1	
HYPERNATREMIA			
subjects affected / exposed	0 / 51 (0.00%)	2 / 68 (2.94%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2010	AMENDMENT 1 (Substantial 01) - Addition of sites (Beatson, Royal Devon & Exeter, Southampton, The Christie) - Change in PI (Royal Marsden) - Change of Institution (Hillingdon to East & North Hertfordshire)
02 November 2010	AMENDMENT 2 (Substantial 02) - Update to protocol (Version 1 to 2) * Inclusion criteria changes: to refer to randomisation correct units for platelets (Section 2 pages 12-13, Section 6 24-25) * Exclusion criteria changes: typographical error corrected reference to Coumadin removed (Section 2 pages 12-13, Section 6 24-25) * Trial Schematic updated: to reflect protocol changes (Section 2 15-16) * Clarification of withdrawal process (section 6.3 page 25, section 6.3.2 page 26) * Enrolment and randomisation details clarified (section 7, page 27-28)
17 May 2011	AMENDMENT 3 (Substantial 03) - Addition of New Site (Queen Elizabeth, Birmingham)
07 June 2012	AMENDMENT 4 (Substantial 04) - Addition of New Site (Velindre)
30 August 2012	AMENDMENT 5 (Substantial) - Change of Sponsor name (Clatterbridge Centre for Oncology NHS Foundation Trust to The Clatterbridge Cancer Centre NHS Foundation Trust
14 December 2012	AMENDMENT 6 (Substantial 05) - Protocol update (Version 2 to Version 3) * Administrative updates to trial management (adding new contacts, clearer instructions for dose modification and RECIST 1.1) * Expansion of window for Tumour Assessments (+/- 2 weeks rather than +/- 1 week) * Updated central monitoring procedures (closer monitoring of our primary endpoint of PFS by requesting CT scan reports be sent in to LCTU at all time points as previously only requested at Crossover) * Allowance for Dacarbazine administration in elderly patients (at PI discretion, can start at 850 mg/m2 rather than 1000mg/m2) * Updating inclusion criteria from transaminases < 5 x ULN to AST and ALT < 5 x ULN - PIS update (Version 2 to Version 3) - GP Letter update (Version 2 to Version 3) - Addition of New Site (St Barts)
07 January 2013	AMENDMENT 8 (Substantial 06) - Cessation to recruitment - Addendum to ICF Version 1 and Addendum to PIS Version 1 (explaining cessation of recruitment)
02 July 2013	AMENDMENT 9 (Substantial 07) - Update from Protocol Version 3 to Version 4 * Addition of a specific reference to the RSI to the Pharmacovigilance section - Changes in PI (Leicester and Weston Park)
05 September 2013	AMENDMENT 11 (Substantial 08) - Update to the Sunitinib SmPC Version 4 to Version 5

04 February 2014	AMENDMENT 12 (Substantial 09) - Update to Protocol Version 4 to Version 5 (update to the End of Trial definition - 'If trial recruitment ends early due to harm or futility the end of trial will be 28 days after the first progression of the last patient currently treated with sunitinib, or 28 days after the second progression of the last patient currently treated with Sunitinib, whichever is later.') - End date changed to 01/11/2014 (The study end date was amended to 22/10/2013. That date passed and there were still some patients receiving Sunitinib, therefore an extension to the study end date was required for patient to reach the end of trial under the definition above.)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported