Clinical trial results:
A Phase II Trial of Nilotinib in the Treatment of Patients with c-KIT Mutated Advanced Acral and Mucosal Melanoma (NICAM)

Summary

EudraCT number	2009-012945-49
Trial protocol	GB
Global end of trial date	12 December 2016

Results information

Result version number	v1 (current)
This version publication date	25 March 2018
First version publication date	25 March 2018

Trial information

Trial identification

Sponsor protocol code	CCR3261

Additional study identifiers

ISRCTN number	ISRCTN39058880
ClinicalTrials.gov id (NCT number)	NCT01395121
WHO universal trial number (UTN)	-
Other trial identifiers	Cancer Research UK: CRUK/09/028 , MHRA CTA: 15983/0226/001 , Main REC Reference: OXFORDSHIRE C 09/H0606/103, ICR-CTSU Protocol Number: ICR-CTSU/2009/10020

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, Sutton, United Kingdom, SM2 5NG
Public contact	NICAM Trial Manager, The Institute of Cancer Research, nicam-icrctsu@icr.ac.uk
Scientific contact	NICAM Trial Manager, The Institute of Cancer Research, nicam-icrctsu@icr.ac.uk
Sponsor organisation name	The Royal Marsden Hospital Foundation Trust
Sponsor organisation address	Downs Road, Sutton, United Kingdom, SM2 5PT
Public contact	NICAM Trial Manager, The Royal Marsden Hospital Foundation Trust, nicam-icrctsu@icr.ac.uk
Scientific contact	NICAM Trial Manager, The Royal Marsden Hospital Foundation Trust, nicam-icrctsu@icr.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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2016
Global end of trial reached?	Yes
Global end of trial date	12 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and effectiveness of the drug nilotinib in the treatment of acral and mucosal melanomas which have mutations in a cell surface protein known as c-KIT.

Protection of trial subjects:

For cKIT mutation status testing, trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. Those providing the verbal explanation and discussion had training and experience in dealing with patients with advanced acral or mucosal melanoma. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.

The patients were given as much time as they needed to come to a decision about screening for the trial prior to giving consent for registration and cKIT screening. It took at least 3 weeks for the results of the cKIT test to be returned to the specialist centre during which time the patient had further opportunity to consider the trial. Once eligibility had been confirmed, patients were given as much time as they needed to come to a decision about trial entry, as long as they remained eligible.

The patient information sheet, which was provided to the patient prior to obtaining consent for screening and discussed again with the patient prior to consent for trial entry, described fully which parties would have access to their identifiable personal information and patients were asked to give their consent to this.

The trial treatment was less onerous than standard treatment with intravenous DTIC chemotherapy given every 3 weeks (i.e. less frequent visits and blood tests and orally administered treatment). Some medications interact with nilotinib and advice was given in both the patient information sheet and protocol on which medications should be avoided.

As the trial continued any relevant information was conveyed to the patient via the patient's oncologist. The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2009
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: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initial consent was obtained from patients for registration into the screening stage of the trial. Screening evaluations, including c-KIT sequencing, were performed to confirm eligibility for trial entry. Once confirmed, consent was obtained from patients for entry into the treatment stage of the trial.

Pre-assignment

Screening details:

Initial consent for c-kit mutation determination and screening was obtained for 219 patients. c-kit mutation status could be determined for 191 patients, with 39 being identified as c-kit positive. Ten patients did not enter study due to: death (2), metastases (3), pt choice/responding on current treatment (2), too ill (3).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Nilotinib
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	L01XE08
Other name	Tasigna
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

800 mg daily (2 x 200 mg capsules twice a day) administered to the patient for as long as patient is gaining clinical benefit.

Number of subjects in period 1	Nilotinib
Started	29
Completed	28
Not completed	1
Relapsed prior to start treatment	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All patients enrolled in this single stage phase II trial	

Reporting group values	Overall Trial	Total	
Number of subjects	29	29	
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			
arithmetic mean	67.1		
standard deviation	± 9.1	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	9	9	

End points

End points reporting groups

Reporting group title	Nilotinib
Reporting group description: -	
Subject analysis set title	Evaluable population
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients enrolled into the study evaluable for the primary endpoint (eligible and possible to establish RECIST assessment by 6 months or prior progression or death).	
Subject analysis set title	Evaluable population (as planned)
Subject analysis set type	Per protocol
Subject analysis set description:	
This phase II trial was planned on 24 patients, but due to replacement of unevaluable patients, the trial over-recruited to 26 evaluable patients.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received at least 1 dose of study treatment.	

Primary: Proportion alive and progression free at 6 months

End point title	Proportion alive and progression free at 6 months[1]
End point description:	
The primary endpoint of NICAM is the proportion of patients alive and progression free according to RECIST criteria (as assessed locally at the participating site) at 6 months. Under a 2-stage design, the trial was planned with 24 overall patients: if 7 or more out of 24 were alive and progression free at 6 months, nilotinib would have shown worthwhile activity to pursue further investigation. Because more than 24 patients were recruited to replace non-evaluable patients, the primary endpoint was assessed in the first 24 evaluable patients and in the overall 26 evaluable patients. The SAP specified that a one-sided binomial test would be used to disprove the null hypothesis that 6 month proportion alive and free of progression is <=15%.	
End point type	Primary
End point timeframe:	
6 months from 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: This is a single arm study and no comparative analysis is performed, but the system expects at least 2 groups to be identified. All methods and options specified in analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one-group inference and summary values without triggering an error or reporting inaccurate information.

End point values	Evaluable population	Evaluable population (as planned)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	24		
Units: Patients				
Alive and progression free	6	6		
Progressed <6 months	11	10		
Died <6 months & no progression	1	1		
Progressed and died <6 months	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion alive and progression free at 6 months (central review)

End point title	Proportion alive and progression free at 6 months (central review)

End point description:

Proportion of patients alive and progression free according to RECIST criteria as assessed by central review at 6 months. Central review of the CT on trial scans was performed for all evaluable patients. A single independent reviewer assessed centrally all available scans. In case of discrepancy between local and central review, a 3rd independent reviewer assessed the scans to resolve the discrepancy. The SAP specified that a one-sided binomial test would be used to disprove the null hypothesis that 6 month proportion alive and free of progression is <=15%.

End point type	Secondary

End point timeframe:

6 months from trial entry

End point values	Evaluable population	Evaluable population (as planned)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	24		
Units: Patients				
Alive and progression free	7	7		
Progressed <6 months	10	9		
Died <6 months (no progression)	1	1		
Progressed and died <6 months	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate at 12 weeks as assessed locally

End point title	Response rate at 12 weeks as assessed locally

End point description:

Response at 12 weeks is defined as partial or complete response, as assessed using RECIST criteria, at the 12 week assessment. As for the primary endpoint, the analysis is performed in the first 24 patients entered and evaluable, and repeated in all 26 evaluable patients. The proportion of patients with CR or PR at 12 weeks is reported with 95% confidence intervals.

End point type	Secondary

End point timeframe:

12 weeks from trial entry

End point values	Evaluable population	Evaluable population (as planned)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	26	24		
Units: Patients				
Complete response	1	1		
Partial response	4	4		
Stable disease	9	8		
Progressive disease	12	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival at 12 months

End point title	Overall survival at 12 months

End point description:

Time from trial entry to death is summarised by overall survival, estimated by Kaplan-Meier. The timepoint of interest (12 months) is reported with 95% confidence intervals.

End point type	Secondary

End point timeframe:

12 months

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	28			
Units: percentage survival				
number (confidence interval 95%)	46.5 (26.9 to 63.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From trial entry to 30 days after last dose of trial treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Safety population

Reporting group description:

Patients who received at least 1 dose of experimental treatment.

In the non-serious adverse events section we report all serious and non-serious adverse events reported with grade 3 or 4 according to the CTCAE grading, that were present in more than 5% of patients.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 28 (35.71%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	0		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Liver function test abnormal			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Oedema peripheral			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chest pain			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Cellulitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 28 (42.86%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Cellulitis			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Lower respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 February 2010	Eligibility criteria updated to change from at least 28 days from major surgery to 14 days and to remove the stipulation regarding time since biopsy (since patients have a biopsy whilst on study medication at days 1 and 15). Updated assessment schedule as follows: further clarification of the screening evaluation demographic details explicitly to include smoking history, family history of melanoma and Fitzpatrick skin classification and physical evaluation to include pulse; baseline assessments on day 1 updated to remove 'physical examination' (this would have been conducted at screening); assessment of height, weight, ECOG performance status, pulse and blood pressure added to all visits; adverse event reporting has been removed from day 1 since this was not applicable; and follow up schedule changed from every 4 weeks to every 4 weeks in year 1 and 8 weekly thereafter with tumour re-staging every 3 months. RECIST guidelines updated to include the addition of malignant lymph nodes must be ≥15 mm in the short axis when assessed by CT scan to be considered measurable under evaluation of measurable and non-measurable lesions. As requested by REC the date of birth was removed from the circulating tumour cells (CTCs) label details.
25 May 2010	Removal of the measurement of circulating tumours cells (CTCs) as recent data suggested that collection of CTCs in melanoma was not that useful therefore CTC analysis will not be performed. Inclusion criteria updated to include measurement of AST or ALT. Trial Steering Committee and the Independent Data Monitoring Committee combined into one committee. Removal of genomic analysis carried out on normal skin and addition of genomic DNA extraction from blood samples for analysis and comparison with tumour DNA. Removal of instruction relating to processing of bloods at local site, all processing to be conducted in the central research laboratory.
03 December 2010	Addition of blood test for amylase and lipase added to the schedule of assessments for consistency with screening requirements plus administrative updates due to study personnel changes.
27 May 2011	Schedule of assessments table updated to clarify the requirements for lipase and amylase blood tests and advise on requirement for blood tests to be repeated if there was clinical indication to do so.
30 July 2012	Expected rate of c-KIT mutation in advanced acral and mucosal melanoma updated from 20% to 10-20% based on current literature and subsequent clarification that at least 120 patients would need to be screened in order to identify 24 patients eligible for the trial. Update made to allow accredited c-KIT laboratories to determine the c-KIT status of their own patients without the need to send for central confirmation at The Royal Marsden NHS Foundation Trust. Update to the study end date deemed to be the date of last data capture changed in line with the current regulatory requirements. Administrative updates due to study personnel changes.
05 June 2013	Addition of further clarification regarding the testing process for patients from regional centres who may have their samples processed at a regional accredited laboratory without the need to send for central testing at the Royal Marsden NHS Foundation Trust. Summary of product information provided by the drug company no longer included proton pump inhibitors as recent research showed that these drugs were no longer thought to compromise the absorption of nilotinib therefore reference to proton pump inhibitors was removed from protocol.

20 January 2015	Change to schedule for restaging CT scans to be performed every 4 months after the patient has remained on study for 3 years to reduce the burden of clinic visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported