



## Clinical trial results:

### A Phase II Trial of Metformin and Axitinib in BRAF Mutated Advanced Melanoma

#### Summary

EudraCT number	2011-001793-26
Trial protocol	GB
Global end of trial date	29 July 2015

#### Results information

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

#### Trial information

##### Trial identification

Sponsor protocol code	3590
-----------------------	------

##### Additional study identifiers

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

Notes:

##### Sponsors

Sponsor organisation name	The Royal Marsden NHS Foundation Trust
Sponsor organisation address	Fulham Road, London, United Kingdom, SW36JJ
Public contact	Lyra Del Rosario, The Royal Marsden NHS Foundation Trust, +44 2078082710, Lyra.DelRosario@rmh.nhs.uk
Scientific contact	Lyra Del Rosario, The Royal Marsden NHS Foundation Trust, +44 2078082710, Lyra.DelRosario@rmh.nhs.uk

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2015
Global end of trial reached?	Yes
Global end of trial date	29 July 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of metformin and axitinib in BRAF mutated advanced melanoma.

The secondary objectives of the study are to evaluate response rate at 12 weeks, overall survival and toxicity of treatment.

Protection of trial subjects:

Patients are closely monitored during the study by the investigator and other delegated clinical members of the research team. Conducting regular tests and procedures to assess clinical status of the patient are written into the protocol to detect adverse events early on, minimising worsening of symptoms.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	3
EEA total number of subjects	3

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)	1
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Potential patients were identified by the Principal Investigator, Sub-Investigators and research nurses during out-patient clinics. Patients were given trial information and adequate time (>24hrs) to consider study entry. Recruitment duration was 2 years from study opening.

### Pre-assignment

Screening details:

Screening evaluations were performed to confirm eligibility. Seven (7) patients consented into the trial and 4 were screen failures. This analysis includes patients consent into the trial and had at least one dose of trial drugs. Screen failures were not included.

### Period 1

Period 1 title	Baseline and study treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

### Arms

Arm title	Single arm
-----------	------------

Arm description:

This study is single-arm. All patients received metformin and axitinib, treatment continued for as long as patients are judged to be gaining clinical benefit by their clinician.

Arm type	Experimental
Investigational medicinal product name	Axitinib and Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Axitinib - 5mg BD daily

Metformin - 500mg bd and increased after 2 weeks to 850mg bd and after 2 further weeks to a dose of 850mg three times daily

<b>Number of subjects in period 1</b>	Single arm
Started	3
Completed	3

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline and study treatment
-----------------------	------------------------------

Reporting group description: -

Reporting group values	Baseline and study treatment	Total	
Number of subjects	3	3	
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)	1	1	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Units: years			
median	66		
full range (min-max)	60 to 73	-	
Gender categorical			
Units: Subjects			
Male	3	3	
Pre-treatment with BRAF inhibitor			
Patient history were checked if they have received previous BRAF inhibitor treatment.			
Units: Subjects			
Yes	3	3	
No	0	0	
Family history of Melanoma			
Patient history was checked if they had family history of melanoma.			
Units: Subjects			
Yes	0	0	
No	3	3	
Previous Radiotherapy for Melanoma			
Patient history was checked if patients received previous radiotherapy for their melanoma.			
Units: Subjects			
Yes	2	2	
No	1	1	
Previous anti-cancer therapy			
Patient history was checked if they receive previous anti-cancer therapy.			
Units: Subjects			
Yes	3	3	
No	0	0	
ECOG - performance status			

Patients' performance status was assessed at screening according to European Cooperative Oncology Group (ECOG) measurement.			
Units: Subjects			
Score 0	1	1	
Score 1	2	2	
ECG status			
All patients underwent Electrocardiograph (ECG) testing to check their cardiac status.			
Units: Subjects			
Normal	2	2	
Abnormal (not clinically significant)	1	1	

### Subject analysis sets

Subject analysis set title	Entire patients recruited on the study
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients recruited and received treatment is included	
Subject analysis set title	End of study
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The patients who received Axitinib and Metformin treatments	

Reporting group values	Entire patients recruited on the study	End of study	
Number of subjects	3	3	
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)	1		
From 65-84 years	2		
85 years and over	0		
Age continuous			
Units: years			
median	66		
full range (min-max)	60 to 73		
Gender categorical			
Units: Subjects			
Male	3		
Pre-treatment with BRAF inhibitor			
Patient history were checked if they have received previous BRAF inhibitor treatment.			
Units: Subjects			
Yes	3		
No	0		
Family history of Melanoma			
Patient history was checked if they had family history of melanoma.			

Units: Subjects			
Yes	0		
No	3		
Previous Radiotherapy for Melanoma			
Patient history was checked if patients received previous radiotherapy for their melanoma.			
Units: Subjects			
Yes	2		
No	1		
Previous anti-cancer therapy			
Patient history was checked if they receive previous anti-cancer therapy.			
Units: Subjects			
Yes	3		
No	0		
ECOG - performance status			
Patients' performance status was assessed at screening according to European Cooperative Oncology Group (ECOG) measurement.			
Units: Subjects			
Score 0	1		
Score 1	2		
ECG status			
All patients underwent Electrocardiograph (ECG) testing to check their cardiac status.			
Units: Subjects			
Normal	2		
Abnormal (not clinically significant)	1		

## End points

### End points reporting groups

Reporting group title	Single arm
Reporting group description: This study is single-arm. All patients received metformin and axitinib, treatment continued for as long as patients are judged to be gaining clinical benefit by their clinician.	
Subject analysis set title	Entire patients recruited on the study
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients recruited and received treatment is included	
Subject analysis set title	End of study
Subject analysis set type	Intention-to-treat
Subject analysis set description: The patients who received Axitinib and Metformin treatments	

### Primary: Proportion of patients progression free at 6 months

End point title	Proportion of patients progression free at 6 months
End point description:	
End point type	Primary
End point timeframe: 6 months	

End point values	Entire patients recruited on the study	End of study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	3		
Units: Proportion				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)		

### Statistical analyses

Statistical analysis title	Progression free survival at 6 months
Comparison groups	Entire patients recruited on the study v End of study
Number of subjects included in analysis	6
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	Proportion
Point estimate	0



Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[1] - Parameter estimate - Progression free survival at 6 months

### Secondary: Response at 12 weeks

End point title	Response at 12 weeks
-----------------	----------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

The response assessed by the RECIST criteria at 12 weeks.

End point values	Entire patients recruited on the study			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Number responding to treatment				
Complete Response	0			
Partial Response	0			
Stable Disease	0			
Progressive Disease	1			
Unevaluable	2			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

End point title	Overall Survival
-----------------	------------------

End point description:

Kaplan Meier method was used to calculate overall survival time (in months) from date of registration to date of death

End point type	Secondary
----------------	-----------

End point timeframe:

Patients will be followed from date of registration to death from any cause

<b>End point values</b>	Entire patients recruited on the study			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: Overall Survival Time				
median (confidence interval 95%)	3.5 (2.6 to 12.5)			

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events will be collected from the day of consenting to until 30 days after the last administration of the Investigational Medicinal Products.

Adverse event reporting additional description:

Each adverse event will be reported with: onset date, time point and pre-defined expected AE categories including a free-text box for those that does not fall under any of the categories. NCI-CTCAE ver 4 is used to record the severity of each event.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	NCI-CTCAE
-----------------	-----------

Dictionary version	4
--------------------	---

### Reporting groups

Reporting group title	Single arm
-----------------------	------------

Reporting group description:

This study is single-arm. All patients received metformin and axitinib, treatment continued for as long as patients are judged to be gaining clinical benefit by their clinician.

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypertension	Additional description: There SAE was Grade 3 severity and lead to Hospitalisation or Prolongation of existing hospitalisation.		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	Additional description: This SAE was Grade 4 leading to Hospitalisation or prolongation of existing hospitalisation.		
subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: There SAE was Grade 3 severity and lead to Hospitalisation or Prolongation of existing hospitalisation.		

subjects affected / exposed	1 / 3 (33.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue/Lethargy			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	3		
Alopecia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	3 / 3 (100.00%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 3 (66.67%)		
occurrences (all)	2		

Diarrhoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Constipation subjects affected / exposed occurrences (all)	3 / 3 (100.00%) 3		
Anorexia subjects affected / exposed occurrences (all)	2 / 3 (66.67%) 2		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Skin and subcutaneous tissue disorders Acneiform subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		
Psychiatric disorders Mood alteration/anxiety subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2011	The amendment is a recommendation by the MHRA to add amend the exclusion criteria in line with the Investigator Brochure ver 10.
10 May 2012	Change to the protocol and trial design include: participants will consent to BRAF testing prior to screening evaluations; addition of laboratory manual, removal of 'serum lipase and amylase' in inclusion criteria, removal of 'abstinence' as a form of contraception; exclusion criteria on washout period is updated; and administrative changes were also made. Patient information sheet updated to reflect protocol changes. Patient registration form amended.
15 June 2012	New wording added in the protocol for hypertension management guidelines. Patient information sheet updated as per protocol change and a diary card is introduced for the trial.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study did not meet its recruitment target but due to changes in the treatment landscape, it was deemed unethical to continue recruitment.

Notes: