



## Clinical trial results:

### AN OPEN LABEL RANDOMISED PHASE II STUDY COMPARING AZD2014 VERSUS EVEROLIMUS IN PATIENTS WITH ADVANCED METASTATIC RENAL CANCER AND PROGRESSION ON VEGF TARGETED THERAPY

#### Summary

EudraCT number	2012-002874-30
Trial protocol	GB
Global end of trial date	31 January 2015

#### Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	06 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	008424QM
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01793636
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Queen Mary University London
Sponsor organisation address	2-4 Walden Street, , London, United Kingdom, E12EF
Public contact	Marianne Tomsa, Centre for Experimental Cancer Medicine, Queen Mary University London, bci-zebra@qmul.ac.uk
Scientific contact	Thomas Powles, Centre for Experimental Cancer Medicine, Queen Mary University London, bci-zebra@qmul.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	31 January 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	31 January 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to investigate if AZD2014 is associated with an improvement in progression free survival (PFS) compared to everolimus.

Protection of trial subjects:

Side effects were closely monitored during and after the study. Patients were required to attend clinic weekly for the first four weeks and then every 4 weeks whilst they were on study medication where adverse events were recorded. The patient information sheet included details on expected adverse events for patients to look out for and also detailed that unexpected events may occur. The independent data monitoring committee for the trial was in place throughout to closely assess the side effects of the drugs on a regular basis and the trial results to make sure there were no excess risks to patients. On-site monitoring was performed throughout the study to provide real time review of source data to allow for early detection signals.

There were potential risks due to radiation, from additional scans that were carried out as part of this study. A medical physics expert and clinical radiology expert reviewed the associated risks and confirmed that they were within reasonable limits for this patient group.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2013
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: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	31
From 65 to 84 years	18
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Starting in February 2013, patients were randomised (1:1) to AZD2014 or everolimus at 10 centres across the UK. Trial was stopped early in June 2014.

### Pre-assignment

Screening details:

Inclusion criteria included patients with advanced or metastatic ccRCC and progression of disease after exposure to at least 1 VEGF-targeted therapy. 67 patients were assessed for eligibility, however only 49 were randomised. 18 patients were excluded prior to randomised as their screening assessments showed they did not meet inclusion criteria.

### Period 1

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

Blinding implementation details:

NA

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	AZD2014 (50mg twice daily)

Arm description:

AZD2014 (50mg twice daily)

Arm type	Experimental
Investigational medicinal product name	AZD2014
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg twice a day until disease progression.

<b>Arm title</b>	Everolimus (10mg once daily)
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Arm description:

Everolimus (10mg once daily)

Arm type	Active comparator
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg once a day until disease progression.

<b>Number of subjects in period 1</b>	AZD2014 (50mg twice daily)	Everolimus (10mg once daily)
Started	26	23
Completed	26	23

## Baseline characteristics

### Reporting groups

Reporting group title	AZD2014 (50mg twice daily)
Reporting group description:	
AZD2014 (50mg twice daily)	
Reporting group title	Everolimus (10mg once daily)
Reporting group description:	
Everolimus (10mg once daily)	

Reporting group values	AZD2014 (50mg twice daily)	Everolimus (10mg once daily)	Total
Number of subjects	26	23	49
Age categorical			
Units: Subjects			
Adults (18-64 years)	17	14	31
From 65-84 years	9	9	18
85 years and over	0	0	0
Age continuous			
Units: years			
median	58	63	
inter-quartile range (Q1-Q3)	48 to 67	52 to 67	-
Gender categorical			
Units: Subjects			
Female	4	4	8
Male	22	19	41
MSKCC Risk Score			
Units: Subjects			
Good	10	10	20
Intermediate	7	10	17
Poor	9	3	12
Duration of first-line therapy			
Units: Subjects			
≤6 months	6	6	12
≥6 months	20	17	37
Number of prior therapies			
Units: Subjects			
= 1	10	14	24
> 1	16	9	25
Nephrectomy			
Units: Subjects			
Yes	21	18	39
No	5	5	10
Bone/liver/brain metastasis			
Units: Subjects			
Yes	5	8	13
No	21	14	35
Missing	0	1	1
ECOG Performance Status			

Units: Subjects			
1-2	14	14	28
Zero	10	8	18
Missing	2	1	3

## End points

### End points reporting groups

Reporting group title	AZD2014 (50mg twice daily)
Reporting group description:	
AZD2014 (50mg twice daily)	
Reporting group title	Everolimus (10mg once daily)
Reporting group description:	
Everolimus (10mg once daily)	

### Primary: Progression-free survival

End point title	Progression-free survival
End point description:	
End point type	Primary
End point timeframe:	
From randomisation until time of progression	

End point values	AZD2014 (50mg twice daily)	Everolimus (10mg once daily)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: months				
median (confidence interval 95%)	1.8 (1.54 to 1.94)	4.6 (2.92 to 5.82)		

<b>Attachments (see zip file)</b>	Kaplan-Meier Curve - PFS at Interim Analysis/Kaplan-Meier
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### Statistical analyses

<b>Statistical analysis title</b>	Progression-free survival
Comparison groups	Everolimus (10mg once daily) v AZD2014 (50mg twice daily)
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Stratified Log-rank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.8



Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	6.5

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From informed consent to 30 days post last IMP

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4
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### Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 49 (40.82%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 0		
Increased Blood Creatinine			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertriglyceridaemia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Decreased appetite			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 49 (97.96%)		
Blood and lymphatic system disorders			

Increased LFTs			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	19		
Anaemia			
subjects affected / exposed	21 / 49 (42.86%)		
occurrences (all)	35		
Increased blood cholesterol			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	32		
Increased blood creatinine			
subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	34		
Hypercalcaemia			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	11 / 49 (22.45%)		
occurrences (all)	26		
Hypertriglyceridaemia			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	28		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 49 (32.65%)		
occurrences (all)	21		
Lethargy			
subjects affected / exposed	12 / 49 (24.49%)		
occurrences (all)	19		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 49 (22.45%)		
occurrences (all)	12		
Decreased appetite			
subjects affected / exposed	9 / 49 (18.37%)		
occurrences (all)	9		
Diarrhoea			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>8 / 49 (16.33%)</p> <p>10</p> <p>11 / 49 (22.45%)</p> <p>15</p> <p>6 / 49 (12.24%)</p> <p>6</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>11 / 49 (22.45%)</p> <p>15</p> <p>9 / 49 (18.37%)</p> <p>9</p>		
<p>Infections and infestations</p> <p>Infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 49 (14.29%)</p> <p>10</p>		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2013	Change of Principal Investigators and addition of participating sites
14 October 2013	Expansion of details regarding risks of CT scans added to PIS/ICF
13 February 2014	Changes to Principal Investigators and addition of new sites only
31 March 2014	Administrative updates only.
23 June 2014	Notification of recruitment suspension following DMC review
10 July 2014	Notification of early recruitment termination (patients to remain on follow-up)
17 December 2014	Reduction of follow-up period

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 June 2014	The Data Monitoring Committee (DMC) met on the 9th June 2014 and confirmed that there is a statistically significant difference between the two treatment arms showing that the study drug AZD2014 is inferior. The DMC recommended that patients should be returned to standard care as soon as possible, and stated that it would be unethical to continue the study.	-

Notes:

### Limitations and caveats

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

Small numbers precluded meaningful subset analysis, such as the importance of performance status or previous therapies with regard to outcome.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26364551>