



## Clinical trial results: A Phase II Study of Neoadjuvant Sunitinib in Metastatic Renal Cell Carcinoma Summary

EudraCT number	2005-004502-82
Trial protocol	GB
Global end of trial date	22 December 2015

### Results information

Result version number	v1 (current)
This version publication date	17 December 2016
First version publication date	17 December 2016
Summary attachment (see zip file)	NeoSun SAE Listing (List of all SAE.docx)

### Trial information

#### Trial identification

Sponsor protocol code	SUN1972
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
Public contact	Chief Investigator - Prof Tim Eisen, Cambridge University Hospitals NHS Foundation Trust, tgqe2@medschl.cam.ac.uk
Scientific contact	Chief Investigator - Prof Tim Eisen, Cambridge University Hospitals NHS Foundation Trust, tgqe2@medschl.cam.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	07 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2015
Global end of trial reached?	Yes
Global end of trial date	22 December 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To determine the anti-tumour activity of sunitinib when given before and after nephrectomy to previously untreated patients with metastatic renal cell carcinoma

Protection of trial subjects:

The study was approved by Research Ethics Committee and received authorisation from the Medicines and Healthcare Products Regulatory Authority. Patients received verbal and written information prior consenting to the trial, and had time to consider their participation and opportunity to ask questions. Consenting patients had a series of screening tests and exams to ensure they were suitable for the study and it was safe to proceed. Enrolment into the trial did not affect any aspect of the surgical treatment plan and each patient was treated according to local practice. On registration to the trial patients were allocated a unique reference number to be used on all data and samples sent to the sponsor, which allowed their personal data to remain anonymous. Only the patients direct care team had access to their recruited participants personal data during the trial. Patients could be withdrawn at any time, at the patient's request or at the clinician's decision, if the patient would benefit from alternative treatment. Adverse events were monitored on an ongoing basis, with end of study/withdrawal assessments performed 28 days after last study drug administration. Collection of follow-up and survival data continued after this time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	5
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial originally planned to recruit 35 patients: 18 in stage 1 and 17 in stage 2. The study proved extremely slow to recruit due to changes in the clinical criteria for cytoreductive nephrectomy. The trial was stopped early with 16 patients enrolled from a single site (first patient was enrolled 29Oct2010, last patient was enrolled 15Jan2014).

### Pre-assignment

Screening details:

Key inclusion criteria included: presumed metastatic (stage IV) renal cell carcinoma (RCC), aged  $\geq 18$  years, ECOG 0/1 & no prior systemic therapy for RCC. A total of 22 patients were screened with 16 enrolled. Reasons for non-enrollment were: family circumstances (1), cardiac history (1), not well enough (2), inoperable (1), RCC not confirmed (1).

### Pre-assignment period milestones

Number of subjects started	22 <sup>[1]</sup>
Number of subjects completed	16

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Family Circumstances: 1
Reason: Number of subjects	Not well enough: 2
Reason: Number of subjects	Cardiac History: 1
Reason: Number of subjects	Inoperable: 1
Reason: Number of subjects	Inadequate biopsy, could not confirm RCC: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 22 screened, 16 enrolled

### Period 1

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

### Arms

Arm title	Sunitinib
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Arm description:

Sunitinib was administered orally at 50mg once daily starting 14 days before nephrectomy was scheduled. It was to be taken for 12 days, with a 2 day break prior to surgery. Patients then recommenced sunitinib when the investigator felt the patient had recovered enough, but not sooner than 15 days post-operatively, continuing on a 4 week on, 2 week off repeating 6 week cycle. This was continued until the patient was no longer gaining benefit from the drug, judged by progressive disease as per RECIST criteria or unacceptable toxicity from sunitinib.

Arm type	Experimental
Investigational medicinal product name	Sunitinib malate
Investigational medicinal product code	EU/1/06/347/001-008
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

50 mg gelatin capsule, orally, once daily.

<b>Number of subjects in period 1</b>	Sunitinib
Started	16
Registered	16
Pre-Surgery Study Treatment Received	14
Nephrectomy	14
Post-Surgery Study Treatment Received	13
Completed	13
Not completed	3
All target lesions resected, no post-surgery trt	1
Developed pulmonary embolism, did not start trt	1
AE, withdrew before starting treatment	1

## Baseline characteristics

### Reporting groups

Reporting group title	On-Study
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Reporting group description: -

Reporting group values	On-Study	Total	
Number of subjects	16	16	
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)	11	11	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	60.8		
full range (min-max)	50.4 to 73.8	-	
Gender categorical			
Units: Subjects			
Female	1	1	
Male	15	15	
ECOG Performance Status			
Units: Subjects			
0 - Asymptomatic	12	12	
1 - Symptomatic but completely ambulatory	4	4	

## End points

### End points reporting groups

Reporting group title	Sunitinib
Reporting group description:	
Sunitinib was administered orally at 50mg once daily starting 14 days before nephrectomy was scheduled. It was to be taken for 12 days, with a 2 day break prior to surgery. Patients then recommenced sunitinib when the investigator felt the patient had recovered enough, but not sooner than 15 days post-operatively, continuing on a 4 week on, 2 week off repeating 6 week cycle. This was continued until the patient was no longer gaining benefit from the drug, judged by progressive disease as per RECIST criteria or unacceptable toxicity from sunitinib.	
Subject analysis set title	Full analysis
Subject analysis set type	Full analysis
Subject analysis set description:	
All registered subjects planned to receive sunitinib prior to and following nephrectomy	

### Primary: Objective response rate (by RECIST criteria)

End point title	Objective response rate (by RECIST criteria) <sup>[1]</sup>
End point description:	
The primary analysis is defined as the proportion of patients with confirmed RECIST response of CR or PR during the treatment period. The Evaluable population (defined as those patients who completed at least Cycle 2 of treatment and had their disease re-evaluated) with measurable disease at Day 1 Cycle 2 is used for the primary analysis. A total of 4 registered subjects are excluded from the primary analysis: 3 subjects did not complete at least cycle 2 of treatment, and 1 further subject is excluded as although they received post-surgery study treatment they did not have measurable disease at Day 1 Cycle 2.	
This is a single-arm study. 58.3% (7/12) subjects achieved confirmed RECIST response (95% CI: 27.7%, 84.8%).	

End point type	Primary
End point timeframe:	
The primary analysis is based on all evaluable patients with measurable disease at Day 1 Cycle 2. Baseline for response is the assessment done prior to Day 1 Cycle 1, and excludes the primary renal cell carcinoma (RCC) target lesion.	
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 therefore there are no statistical comparisons.	

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
CR or PR	7			
Not CR or PR	5			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective Clinical Benefit rate of sunitinib

End point title	Objective Clinical Benefit rate of sunitinib
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End point description:

This includes all evaluable patients with measurable disease at Day 1 Cycle 2.

This is a single-arm study. 91.7% (11/12) subjects achieved objective clinical benefit (95% CI: 61.5%, 99.8%).

End point type	Secondary
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End point timeframe:

Defined as proportion of subjects with a RECIST response (CR / PR) or stable disease for at least 3 months

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
CR or PR or SD (3 months)	11			
Not CR or PR or SD (3 months)	1			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate
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End point description:

This includes all evaluable patients with measurable disease at Day 1 Cycle 2.

End point type	Secondary
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End point timeframe:

Best response (not confirmed) during the treatment period.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
Complete Response	2			
Partial Response	7			
Stable Disease	3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall Survival

End point title	Overall Survival
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End point description:

This includes all evaluable patients, that is patients who completed at least cycle 2 of drug treatment and had their disease re-evaluated.

This is a single arm study. Median survival with 95% CI has been presented (Note: Upper limit of 95% CI not reached, maximum follow-up of 45m has been entered). For the 13 subjects, 6 events were observed and 7 are censored.

End point type	Secondary
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End point timeframe:

Overall survival is the time between the date of registration and death, whatever the cause; surviving patients, and those who discontinued/lost-to-follow-up, are censored at the date last known alive.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
median (confidence interval 95%)	33.7 (22.4 to 45)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Progression

End point title	Time to Progression
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End point description:

This includes all evaluable patients, that is all patients who completed at least cycle 2 of drug treatment and had their disease re-evaluated.

This is a single arm study. Median PFS with 95% CI has been presented. For the 13 subjects, 11 events were observed and 2 are censored.

End point type	Secondary
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End point timeframe:

Progression-Free Survival is calculated from date of registration to date of clinical/radiological progression or death from any cause, whichever occurs first; surviving patients without progression are censored at date of their last clinical follow-up.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
median (confidence interval 95%)	15.7 (9.5 to 29.6)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Response Duration

End point title	Response Duration
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End point description:

This includes all evaluable patients (completed at least cycle 2 of drug treatment and had their disease re-evaluated) with measurable disease at Day 1 Cycle 2 who achieve PR or CR.

This is a single arm study. Median response duration with 95% CI has been presented (Note: Upper limit of 95% CI not reached, maximum follow-up of 45m has been entered). For the 9 subjects, 6 events were observed and 3 are censored.

End point type	Secondary
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End point timeframe:

Response Duration is calculated from the date of first CR/PR response to the date of clinical/radiological progression (PD); patients without progression are censored at the date of their last clinical follow-up.

End point values	Sunitinib			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Months				
median (confidence interval 95%)	8.7 (2.6 to 45)			

## Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

From patient registration until 28 days after the last study drug administration, whether observed by the investigator or reported by the patient during the study period, regardless of whether or not they are considered related to the drug.

Adverse event reporting additional description:

Serious Adverse Events are reported in the file found in the uploaded attachment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	3
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Frequency threshold for reporting non-serious adverse events: 0 %

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#### Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Hypertension was an AE of special interest, with 6 events reported at CTCAE grade  $\geq 3$ . No other clinically significant AEs of special interest were reported. A listing of all SAE's has been provided.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2011	Update to the patient information sheet (PIS) with the side effects profile of the investigational medicinal product (IMP).
21 June 2012	<p>Change the study from multi-centre to single-centre. Typographical errors were corrected and other minor amendments were included to clarify:</p> <ul style="list-style-type: none"><li>- The inclusion criteria: patients with presumed metastatic renal cell carcinoma are included in the study following a referral from their treating physician. The diagnosis is confirmed after study entry and before treatment starts. The patients would be made aware of this presumed diagnosis by their treating physician prior to their referral and before they are approached about this study.</li><li>- The treatment changes required when a patient's surgery is delayed</li><li>- The conditions for patients' withdrawals</li><li>- The registration process</li><li>- The update of the IMP label, as required by the MHRA</li></ul>
14 August 2013	<ul style="list-style-type: none"><li>- Change the supply of IMP from clinical trials stock to commercial stock</li><li>- Remove the need to send a pathological confirmation of renal cell carcinoma as part of the registration process as this confirmation is required post registration. In order to be eligible for the trial the patient must have presumed renal cell carcinoma.</li><li>- Introduce a patient ID card</li><li>- Update the Protocol and PISICF to reflect the current Sunitinib SmPC dated 03/2013 (updated on EMC 03/05/2013)</li><li>- Notify the Ethics committee of a revised trial end date of 28/03/2014</li></ul>
31 January 2014	Update the Protocol and PISICF to reflect the current Sunitinib SmPC dated 03/2013 (updated on EMC 03/05/2013). In the last substantial amendment in July we omitted in error the rare event cholecystitis from the PIS/ICF. This amendment is to add in the original omission.
30 April 2014	<p>To the protocol</p> <ul style="list-style-type: none"><li>- Add new secondary end points</li><li>- Add a new co-Investigator</li><li>- Update the coordinators fax number and address</li><li>- Removal of the term ICH from statements including ICH/GCP</li></ul> <p>To the PISICF</p> <ul style="list-style-type: none"><li>- Update the PISICF to reflect the current Sunitinib SmPC dated 28/02/2014 and a letter from Pfizer dated 24th March 2014 with updated adverse event details.</li><li>- Addition of a statement to inform the patient that some side effects can be mild where as others can be life threatening.</li><li>- Update to site contact details</li><li>- Clarification that sponsor and doctors can stop the trial.</li></ul>
29 September 2015	Update the PISICF to reflect updated safety information in Section 4.8 of the Sunitinib SmPC, currently dated July 2015 (updated on EMC 28/07/2015). Additions to the PISICF include the wording 'worsening of pre-existing angina, and rarely heart attacks' as possible common side effects'.

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported