Clinical trial results:
A Phase II Study Of Sunitinib And Low Dose Metronomic Cyclophosphamide In Advanced Renal Cell Cancer

Summary

EudraCT number	2008-008676-13
Trial protocol	GB
Global end of trial date	31 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	3164

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	31 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and toxicity of the combination of sunitinib and low dose cyclophosphamide

To eludicate possible mechanisms of action by measuring serum and angiogenic factors and molecular markers in tumours

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 asses clinical status of the patients 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	28 September 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: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	10

From 65 to 84 years	9
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-patients 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. Nineteen (19) patients were consented and enrolled into the trial. There were no screen failures and this analysis includes all nineteen patients .

Period 1

Period 1 title	Baseline, Study Treatment and Follow-up (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Arm 1

Arm description:

This study is single-arm. All patients received Sunitinib and Cyclophosphamide. Treatment continues for as long as patients are judged to be gaining clinical benefit by their clinician.

Arm type	Experimental
Investigational medicinal product name	Sunitinib
Investigational medicinal product code	LO1XE04
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50mg once daily starting on Day 1 for 4 weeks followed by a 2 week break. This will be defined as one cycle of treatment.

Investigational medicinal product name	Cyclophosphamide (low dose)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50mg daily

Number of subjects in period 1	Arm 1
Started	19
Completed	18
Not completed	1
Adverse event, serious fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
This study is single-arm. All patients received Sunitinib and Cyclophosphamide. Treatment continues for as long as patients are judged to be gaining clinical benefit by their clinician.	

Reporting group values	Arm 1	Total	
Number of subjects	19	19	
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)	10	10	
From 65-84 years	9	9	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	8	8	
Male	11	11	
Histology Units: Subjects			
Clear Cell	18	18	
Papillary	1	1	
Stage at initial diagnosis Units: Subjects			
Stage I	1	1	
Stage II	1	1	
Stage III	8	8	
Stage IV	9	9	
AJCC grading at initial diagnosis Units: Subjects			
G2 (Intermediate grade)	2	2	
G3 (Poorly Differentiated, high grade)	10	10	
G4 (Undifferentiated, high grade)	3	3	
GX (Undifferentiated)	3	3	
Not Known	1	1	
Status of disease at study entry Units: Subjects			
Stage III	1	1	
Stage IV	18	18	
MOTZER category			

Units: Subjects			
High (3 or more risk factors)	1	1	
Intermediate (1 or 2 risk factors)	8	8	
Low (0 risk factors)	10	10	
ECOG Performance status >2 Units: Subjects			
No	16	16	
Yes	3	3	
High Lactate Dehydrogenase (>1.5xULN) Units: Subjects			
No	17	17	
Yes	2	2	
Low Serum Haemoglobin (<LLN) Units: Subjects			
No	14	14	
Yes	5	5	
High Corrected serum Calcium Units: Subjects			
No	19	19	
Yes	0	0	
Absence of prior nephrectomy Units: Subjects			
No	17	17	
Yes	2	2	
Previous Surgery for RCC Units: Subjects			
No	1	1	
Yes	18	18	
Number of RCC surgery Units: Subjects			
One	17	17	
Two	1	1	
None	1	1	

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
This study is single-arm. All patients received Sunitinib and Cyclophosphamide. Treatment continues for as long as patients are judged to be gaining clinical benefit by their clinician.	
Subject analysis set title	Baseline and treatment
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Overall patients recruited and started the experimental drug	
Subject analysis set title	End of study
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Overall subject who received treatment	

Primary: Overall Response Rate

End point title	Overall Response Rate
End point description:	
End point type	Primary
End point timeframe:	
Response rate: CT scans are performed at baseline, Cycle 2 Day 36-42, then every even cycle day 36-42. Response rate will be defined as the percentage of patients with their best response of CR or PR using RECIST 1.1 criteria.	

End point values	Arm 1	Baseline and treatment	End of study	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	19	19	
Units: Number				
Complete Response	0	0	0	
Partial Response	8	8	8	
Stable Disease	9	9	9	
Progressive Disease	1	1	1	
Never started treatment	1	1	1	

Statistical analyses

Statistical analysis title	Overall response rate
Statistical analysis description:	
Proportion of patients responded to treatment (complete or partial response)	
Comparison groups	Arm 1 v Baseline and treatment v End of study

Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Proportion
Point estimate	44
Confidence interval	
level	95 %
sides	2-sided
lower limit	22
upper limit	69

Notes:

[1] - Parameter estimate - Overall response rate

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

End point type	Secondary

End point timeframe:

Cycle 1 until the end of treatment (progression).

End point values	Arm 1	Baseline and treatment	End of study	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	19	19	
Units: Median in months				
median (confidence interval 95%)	16.0 (6.9 to 27.6)	16.0 (6.9 to 27.6)	16.0 (6.9 to 27.6)	

Statistical analyses

Statistical analysis title	Progression free survival

Statistical analysis description:

Progression free survival defined from date of registration to date of progression or death from any cause. Patients who do not progress or die were censored at last follow up. Kaplan Meier methods was used to calculate median PFS with the 95% confidence intervals.

Comparison groups	Arm 1 v End of study v Baseline and treatment
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Median progression free survival
Point estimate	16
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	27.6

Notes:

[2] - Parameter estimate - progression free survival

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Cycle one, first dose of drug until death

End point values	Arm 1	Baseline and treatment	End of study	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19	19	19	
Units: Median in months				
median (confidence interval 95%)	21.0 (11.1 to 31.8)	21.0 (11.1 to 31.8)	21.0 (11.1 to 31.8)	

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

Overall survival defined from date of registration to date of death from any cause. Surviving patients were censored at last follow-up. Kaplan Meier methods was used to calculate median PFS with the 95% confidence intervals.

Comparison groups	Arm 1 v Baseline and treatment v End of study
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Median overall survival
Point estimate	21
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	31.8

Notes:

[3] - Parameter estimate - Overall survival

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from the day of consent until 30 days after the last administration of the Investigational Medicinal Products.

Adverse event reporting additional description:

Each adverse event were 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 3 was used to record the severity of each event.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Single Arm

Reporting group description:

This study is single arm.

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	1		
Investigations			
Disease progression	Additional description: Disease progression and performance status deterioration		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Blurred vision and loss of speech	Additional description: CNS cerebrovascular ischemia		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage, CNS			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematemesis			

subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bowel ischemia				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac ischemia	Additional description: Chest pain			
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Transient ischemic attack				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Hemolysis	Additional description: Patient presented with anaemia			
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia/Granulocytopenia				
subjects affected / exposed	2 / 19 (10.53%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	3 / 19 (15.79%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 19 (5.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

General disorders and administration site conditions			
Syncope	Additional description: Fainting		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Allergic reaction/Hypersensitivity	Additional description: Allergic reaction to Enalopril		
subjects affected / exposed	1 / 19 (5.26%)		
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	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain	Additional description: Secondary to disease progression		
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Chest Infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 19 (5.26%)		
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 %

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	10		
Left ventricular dysfunction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nervous system disorders			
Hand and foot syndrome			
subjects affected / exposed	11 / 19 (57.89%)		
occurrences (all)	11		
Mood disturbance			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	7		
Neurological disorders			
subjects affected / exposed	10 / 19 (52.63%)		
occurrences (all)	10		
Paresthesia			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 19 (89.47%)		
occurrences (all)	17		
Flushing			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Headache			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Mucositis			
subjects affected / exposed	15 / 19 (78.95%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	12 / 19 (63.16%)		
occurrences (all)	12		
Pain			
subjects affected / exposed	15 / 19 (78.95%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Hemorrhage			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	18		
Neutropenia			
subjects affected / exposed	15 / 19 (78.95%)		
occurrences (all)	15		
Thrombocytopenia			
subjects affected / exposed	13 / 19 (68.42%)		
occurrences (all)	13		
Thrombosis/Embolism			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	14 / 19 (73.68%)		
occurrences (all)	14		
Indigestion			

subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	9		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	12 / 19 (63.16%)		
occurrences (all)	12		
Skin rash			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	8		
Musculoskeletal and connective tissue disorders			
Aching muscles and joints			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Bone Pain			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Infections and infestations			
Infection			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2010	Protocol updated to ver 4 dated 29-July-2009, patient facing documents and GP letter were also updated.
09 December 2010	Addition of Mount Vernon Hospital as a site.

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 targets but due to changes in the treatment landscapes, it is not beneficial to continue. At the point of notification to the Ethics Committee (31-July-2015), the study did not have any ongoing patients.

Notes: