



Clinical trial results:

Dynamic contrast enhanced MRI (DCE-MRI) assessment of the vascular changes induced with bevacizumab alone and in combination with interferon- in patients with advanced renal cell carcinoma.

Summary

EudraCT number	2008-006414-19
Trial protocol	GB
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	26 June 2019
First version publication date	26 June 2019
Summary attachment (see zip file)	Interim analysis early termination (2008-006414-19 DCE-MRI_report interim analysis (early termination).pdf)

Trial information

Trial identification

Sponsor protocol code	RD2007-114
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Additional study identifiers

ISRCTN number	ISRCTN08193901
ClinicalTrials.gov id (NCT number)	NCT00873236
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	East and North Hertfordshire NHS Trust
Sponsor organisation address	Coreys Mill Lane, Stevenage, United Kingdom, SG14AB
Public contact	Phillip Smith, Associate Director of Research and Development, East and North Hertfordshire NHS Trust , 0203 826 2075, phillip.smith5@nhs.net
Scientific contact	Dr Paul Nathan, Consultant Oncologist, East and North Hertfordshire NHS Trust , 0203 826 2444, p.nathan@nhs.net

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	Interim
Date of interim/final analysis	22 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No
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Notes:

General information about the trial

Main objective of the trial:

To establish whether bevacizumab induced changes in DCE MRI vascular parameters are significantly enhanced by interferon- α

And if so:

To establish whether there is an IFN dose response in potentiating bevacizumab induced changes in DCE-MRI vascular parameters.

Protection of trial subjects:

Patients had the potential benefit of accessing the trial treatment with proven activity for advanced renal cell carcinoma.

An independent Advisor unrelated to the investigators and sponsors reviewed the safety data once 8 weeks of data had been accrued for 15 patients.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	19 November 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: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	18
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

25 patients were screened for the study between December 2009 and February 2012. The steering committee performed an un-planned interim analysis after 24 months of recruitment to assess for any trends to justify continued recruitment in the trial. At this point, excluding the 4 screen failures, 21 patients were randomised into the three arms

Pre-assignment

Screening details:

Metastatic (stage IV) or locally advanced (inoperable stage III) RCC Male or female patients aged ≥ 18 years with good or intermediate prognosis by Motzer score who were systemic treatment naïve in metastatic setting formed the subjects of this trial.

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:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Bevacizumab 10mg/kg every 2 weeks

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg/2 weeks

Arm title	Arm B
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Arm description:

Bevacizumab 10mg/kg every 2 weeks plus low-dose IFN- α 2a 3MU Three times in a week (t.i.w), commencing on Day 0

Arm type	Experimental
Investigational medicinal product name	Roferon-A
Investigational medicinal product code	PL 0031/0485
Other name	IFN- α
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients in Arm B had a maximum of 3MU of interferon subcutaneously three times a week, commencing on day 0.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg/2 weeks

Arm title	Arm C
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Arm description:

Bevacizumab 10mg/kg every 2 weeks plus standard dose IFN- α 2a 9 MU t.i.w. Patients will commence on IFN- α 3MU t.i.w on Day 0, and escalate dose to 9MU t.i.w on Day 14.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10mg/kg/2 weeks

Investigational medicinal product name	Roferon-A
Investigational medicinal product code	PL 0031/0485
Other name	IFN- α
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients in Arm C had a maximum of 9MU of interferon subcutaneously three times a week.

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	6	9	6
Completed	6	9	6

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	21	21	
Age categorical			
Male and Female subjects \geq 18 years with previously untreated metastatic (stage IV) or locally advanced (inoperable stage III) renal cell carcinoma were recruited. 21 patients were randomised in the following age groups: - 40-50 years - 5 patients - 50-60 years - 5 patients - 60-70 years - 8 patients - 70-75 years - 2 patients - Over 75 years - 1 patient			
Units: Subjects			
40-50 years	5	5	
50 - 60 years	5	5	
60-70 years	8	8	
70-75 years	2	2	
Over 75	1	1	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	19	19	

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: Bevacizumab 10mg/kg every 2 weeks	
Reporting group title	Arm B
Reporting group description: Bevacizumab 10mg/kg every 2 weeks plus low-dose IFN- α 2a 3MU Three times in a week (t.i.w), commencing on Day 0	
Reporting group title	Arm C
Reporting group description: Bevacizumab 10mg/kg every 2 weeks plus standard dose IFN- α 2a 9 MU t.i.w. Patients will commence on IFN- α 3MU t.i.w on Day 0, and escalate dose to 9MU t.i.w on Day 14.	

Primary: Primary

End point title	Primary ^[1]
End point description: Primary objective: To establish whether bevacizumab induced changes in DCE MRI vascular parameters are significantly enhanced by interferon- α And if so: To establish whether there is an IFN dose response in potentiating bevacizumab induced changes in DCE-MRI vascular parameters. Primary endpoint: DCE-MRI defined changes in Ktrans after 6 weeks of bevacizumab monotherapy or bevacizumab and low or standard dose IFN- α	
End point type	Primary
End point timeframe: After 6 weeks of bevacizumab monotherapy or bevacizumab and low or standard dose IFN- α	
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: Statistical analyses available in attached publication	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	4	
Units: Changes in Ktrans	4	7	4	

Attachments (see zip file)	Interim analysis/2008-006414-19 DCE-MRI_report interim
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Statistical analyses

No statistical analyses for this end point

Secondary: Secondary

End point title	Secondary
End point description: Secondary objectives: 1. To correlate changes in DCE-MRI vascular parameters for each treatment group with the following:	

- progression free survival
- tumour response and changes in tumour size
- other surrogate biomarkers

2. To assess the degree of change in baseline Ktrans within each arm of treatment

3. To investigate changes in Diffusion and BOLD MRI and their correlation with other pharmacodynamic endpoints.

4. To assess the efficacy and safety profile of bevacizumab monotherapy or in combination with low or standard doses of IFN

End point type	Secondary
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End point timeframe:

Secondary endpoints: Change in vascular permeability (Ktrans), Response, Treatment duration, withdrawal, dose modification, incidence of AEs and biomarker correlations

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	7	4	
Units: Various	4	7	4	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non-serious adverse events were collected up to 28 days after the last bevacizumab infusion.

Adverse event reporting additional description:

Serious adverse events (SAEs) related to bevacizumab were reported for the duration of the study. Intensity of all adverse events were graded according to the NCI Common Terminology Criteria for Adverse Events v 3.0 (CTCAE) on a five-point scale (Grade 1 to 5).

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm A
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Reporting group description:

Bevacizumab 10mg/kg every 2 weeks

Reporting group title	Arm B
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Reporting group description:

Bevacizumab 10mg/kg every 2 weeks plus low-dose IFN-α2a 3MU Three times in a week (t.i.w), commencing on Day 0

Reporting group title	Arm C
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Reporting group description:

Bevacizumab 10mg/kg every 2 weeks plus standard dose IFN-α2a 9 MU t.i.w. Patients will commence on IFN-α 3MU t.i.w on Day 0, and escalate dose to 9MU t.i.w on Day 14.

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	3 / 5 (60.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Proctitis	Additional description: Rectal Bleed assessed as not related to Avastin although Avastin permanently discontinued.		
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pregnancy of partner	Additional description: Patient's partner conceived while patient was taking Avastin + INFα		

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Infection	Additional description: Chest Infection not related to study drugs		
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis	Additional description: Epistaxis Grade 2 Related to Avastin required cauterization.		
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Bladder obstruction	Additional description: Bladder obstruction caused by clot retention unrelated to study drugs		
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Viral infection	Additional description: Viral Illness with hospitalisation not related to study drugs		
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	5 / 5 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Hypertension			

subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 3	0 / 5 (0.00%) 0	2 / 5 (40.00%) 2
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 5 (20.00%) 2	1 / 5 (20.00%) 1
General disorders and administration site conditions Chills subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1
Fatigue subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	5 / 5 (100.00%) 16	4 / 5 (80.00%) 6
Influenza subjects affected / exposed occurrences (all)	Additional description: Fevers, rigors and/or shivers/flu-like symptoms.		
	2 / 5 (40.00%) 2	1 / 5 (20.00%) 1	1 / 5 (20.00%) 1
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1
Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 5 (60.00%) 4	3 / 5 (60.00%) 5
Mucositis management subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	0 / 5 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 5 (40.00%) 3	2 / 5 (40.00%) 2
Vomiting subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	1 / 5 (20.00%) 1	1 / 5 (20.00%) 1

Respiratory, thoracic and mediastinal disorders	Cough			
	subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
	occurrences (all)	1	1	0
	Epistaxis			
	subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 5 (40.00%)
	occurrences (all)	0	0	3
Throat irritation	Additional description: Hoarse voice			
	subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
	occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders	Alopecia			
	subjects affected / exposed	0 / 5 (0.00%)	3 / 5 (60.00%)	0 / 5 (0.00%)
	occurrences (all)	0	3	0
	Dry skin			
	Additional description: Dry lips			
	subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
	occurrences (all)	0	0	1
	Palmar-plantar erythrodysaesthesia syndrome			
	Additional description: Dry lips and/or stomatitis			
	subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	4 / 5 (80.00%)
Psychiatric disorders	Depression			
	subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	2 / 5 (40.00%)
	occurrences (all)	0	1	2
	Insomnia			
	subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
	occurrences (all)	0	1	0
Renal and urinary disorders				
Haematuria				

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	3 / 5 (60.00%)
occurrences (all)	1	15	3
Musculoskeletal and connective tissue disorders			
Myalgia	Additional description: Muscle aches		
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Appetite disorder	Additional description: Anorexia No. of patients with grad 1 or 2 AE: 6 No. of patients with grad 3 or 4 AE: 2		
subjects affected / exposed	1 / 5 (20.00%)	3 / 5 (60.00%)	3 / 5 (60.00%)
occurrences (all)	1	6	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 March 2010	1. Inclusion criteria - Calculated creatinine clearance > 50ml/min to be used in place of serum creatinine < 1.5 ULN. 2. To include prior adjuvant antiangiogenic treatment in the last 6 months as an exclusion criteria
05 January 2011	Update to the safety information regarding the use of AVASTIN (bevacizumab).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 September 2012	Temporary halt to recruitment to perform an interim futility analysis with current dataset.	-

Notes:

Limitations and caveats

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

5 patients were excluded from the primary DCE-MRI analysis due to technical reasons. 5 patients had to be excluded from the primary DCE-MRI analysis due to technical reasons. Slow recruitment due to inclusion/exclusion criteria.

Notes: