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

Submission date 11/03/2009	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol
Registration date 23/04/2009	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 13/10/2017	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
RD2007-114

Study information

Scientific Title
Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) assessment of the vascular changes induced with bevacizumab alone and in combination with interferon-alpha in patients with advanced renal cell carcinoma: a phase II, open labelled, randomised, multicentre trial

Study objectives
The trial aims to answer:
1. Whether bevacizumab induced changes in DCE-MRI vascular parameters are significantly enhanced by interferon-alpha
2. To establish whether there is an interferon (IFN) dose response in potentiating bevacizumab induced changes in dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) vascular parameters
3. If the DCE-MRI vascular parameter changes correlate to the tumour response, progression free survival and changes of other biomarkers

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Research Ethics Service, Charing Cross Research Ethics Committee, 19/01/2009, ref: 09/H0711/6

Study design
Phase II open labelled randomised multicentre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Advanced or metastatic renal cell carcinoma

Interventions
Patients will be randomised to one of the following:
Arm A: Bevacizumab 10 mg/kg every 2 weeks
Arm B: Bevacizumab 10 mg/kg every 2 weeks + interferon alpha 2a (IFN-a2a) 3MU three times per week (t.i.w.)
Arm C: Bevacizumab 10 mg/kg every 2 weeks + IFN-a2a 9 MU t.i.w.

All patients will continue on their randomised treatment regimen until the first tumour assessment at week 8. At this point the decision to introduce or modify the IFN dosage will be at the discretion of the investigator. Treatment with both study drugs will continue until disease progression, unacceptable toxicity, or consent is withdrawn. Patients in all arms will undergo two baseline DCE-MRI scans in the week pre-treatment and then further scans at weeks 2, and 6 weeks post-commencement of bevacizumab. Tumour response will be assessed by RECIST criteria via computed tomography (CT) scans at baseline, 8 weeks and three-monthly thereafter.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Bevacizumab, interferon alpha 2a

Primary outcome measure
DCE-MRI defined changes in Ktrans after 6 weeks of bevacizumab monotherapy or bevacizumab and low or standard dose IFN-alpha.

Secondary outcome measures
1. Vascular endpoints: intra-arm change in vascular permeability (Ktrans) and tumour hypoxia at 2 and 6 weeks post-commencement of treatment
2. Efficacy endpoints: best overall response, progression free survival, time to progression, measured during follow up analyses
3. Safety endpoints: treatment duration of bevacizumab and IFN, treatment withdrawal, dose modification, incidence of adverse events, measured during follow up analyses
4. Surrogate biomarker analysis: peripheral blood analysis of circulating endothelial cells (CEC), circulating endothelial progenitors (CEP) and proangiogenic monocytic cells; angiogenic factors (e.g. vascular endothelial growth factor [VEGF]) and hypoxia regulated markers, measured during follow up analyses
5. Correlation of DCE-MRI defined changes in Ktrans with clinical response, measured during follow up analyses
6. Correlation of DCE-MRI defined changes in Ktrans with surrogate biomarkers, measured during follow up analyses
7. Analysis of Diffusion MRI and BOLD MRI changes and comparison with other pharmacodynamic markers, measured during follow up analyses

Overall study start date
06/04/2009

Completion date
28/02/2010

Eligibility

Key inclusion criteria
1. Male or female subjects greater than or equal to 18 years
2. Patients with previously untreated metastatic (stage IV) or locally advanced (inoperable stage III) renal cell carcinoma (RCC)
3. Subject with histologically and/or cytologically confirmed advanced RCC, of which a majority component of conventional clear-cell type is mandatory. Tumours of mixed histology should be categorised by the predominant cell type.
4. Good or intermediate prognosis disease as defined by Motzer score
5. Response Evaluation Criteria In Solid Tumors (RECIST) measurable lesion(s), which must be amenable to DCE-MRI scanning
6. Life expectancy of at least 12 weeks
7. Eastern Co-operative Oncology Group (ECOG) performance status 0 - 2
8. Adequate haematological function:
8.1. Absolute neutrophil count (ANC) greater than or equal to 1.5 x 10^9/l, and
8.2. Platelet count greater than or equal to 100 x 10^9/l, and
8.3. Haemoglobin greater than or equal to 8 g/dl (may be transfused to maintain or exceed this level)
9. Adequate liver function:
9.1. Total bilirubin less than 1.5 x upper limit of normal (ULN), and
9.2. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) less than 2.5 x ULN in patients without liver metastases; less than 5 x ULN in patients with liver metastases
10. Adequate renal function:
10.1. Serum creatinine less than or equal to 1.5 x ULN, and
10.2. Urine dipstick for proteinuria less than 2+. Patients discovered to have greater than or equal to 2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate less than 1 g of protein in 24 hours
11. International normalised ratio (INR) less than or equal to 1.5 within 7 days prior to enrolment. Anticoagulation is allowed if target INR is less than 3 and INR is therapeutic on a stable dose of coumarin-type anticoagulation, or if subject is on a stable dose of low molecular weight (LMW) heparin for greater than 2 weeks at time of enrolment
12. Women of childbearing age must have a negative pregnancy test and must use adequate contraception during the treatment phase of the study and for 9 months afterwards. Women who wish to breastfeed are not eligible for the study

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
30 patients, 10 in each arm

Key exclusion criteria
1. Diagnosis of brain metastasis
2. Major surgery (including open biopsy) or radiation therapy within 28 days prior to enrolment (palliative radiotherapy to painful bone lesions is allowed within 14 days prior to enrolment). Subjects must have recovered from prior surgery (greater than 28 days) and radiation (greater than 28 days - 14 days if palliative radiotherapy to painful bone lesions)
3. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to enrolment
4. Significant cardiovascular disease defined as congestive heart failure (New York Heart Association [NYHA] class II, II or IV), unstable angina pectoris, or myocardial infarction within 6 months prior to enrolment
5. Inadequately controlled hypertension (defined as a blood pressure of greater than 150 mmHg systolic and/or greater than 100 mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy
6. History of stroke or transient ischaemic attack within 6 months prior to enrolment
7. Significant vascular disease (e.g., aortic aneurysm, aortic dissection), or symptomatic peripheral vascular disease
8. Evidence or history of recurrent thromboembolism (more than one episode of deep vein thrombosis [DVT]/pulmonary embolism [PE]) during the past 6 months, bleeding diathesis or coagulopathy
9. Chronic daily intake of aspirin greater than 325 mg/day or clopidogrel greater than 75 mg/day, or steroids (prednisone greater than 12.5 mg/day or dexamethasone greater than 2 mg/day), excluding inhaled steroids
10. History of abdominal or tracheo-oesophagel fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrolment
11. Serious, non-healing wound, ulcer, or bone fracture
12. Pregnant or breast-feeding mothers
13. No contraindication to MRI scanning e.g. no history of claustrophobia, metal fragment implantation
14. Current active second malignancy other than non-melanoma skin cancers and post-treatment for localised prostate cancer. Patients are not considered to have a currently active malignancy if they are in complete remission for greater than 3 years prior to study
15. Patients with a history of allergic reactions to contrast agents
16. Patients with gross ascites
17. Seizure disorder requiring medication
18. Human immunodeficiency virus (HIV)/hepatitis B/hepatitis C/other infection greater than common toxicity criteria grade 2 (CTC 2); active clinically serious bacterial or fungal infections (greater than CTC 2)
19. Other investigational drug during trial or within 30 days
20. Any other significant medical illness or medically significant abnormal laboratory finding that would, in the investigator's judgment, make the patient inappropriate for this study, or would increase the risk associated with the patients' participation in the study

Date of first enrolment
06/04/2009

Date of final enrolment
28/02/2010

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Mount Vernon Cancer Centre
Middlesex
United Kingdom
HA6 2RN

Sponsor information

Organisation
East and North Hertfordshire NHS Trust (UK)

Sponsor details
Research and Development Department
The Clock Tower
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Sponsor type
Hospital/treatment centre

Website
http://www.enherts-pct.nhs.uk/

ROR
https://ror.org/02ryc4y44

Funder(s)

Funder type
Industry

Funder Name
Roche - educational grant and free IMP supply

Alternative Name(s)
F. Hoffmann-La Roche Ltd, F. Hoffmann-La Roche & Co, F. Hoffmann-La Roche AG, Roche Holding AG, Roche Holding Ltd, Roche Holding, Roche Holding A.G., Roche Holding, Limited, F. Hoffmann-La Roche & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No