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COSAK trial: cediranib and saracatanib/placebo in relapsed clear cell renal cancer

Submission date	Recruitment status	[X] Prospectively registered
14/01/2010	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
05/02/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
25/10/2022	Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-cediranib-and-saracatanib-kidney-cancer-spread-cosak

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2009-018014-20

Protocol serial number
N/A

Study information

Scientific Title
A randomised phase II study evaluating cediranib versus cediranib and saracatanib in patients with relapsed metastatic clear cell renal cancer

Acronym
COSAK

Study objectives
Sunitinib has become standard therapy for first line therapy for metastatic clear cell renal cancer and received NICE approval in March 2008. Although the results are impressive, patients ultimately relapse and die of their disease. Therefore an improvement in this area is required.

At progression on sunitinib further targeted therapy is not clearly defined although clinical benefit occurs with others forms of targeted therapy supporting the investigation of sequential therapy in this setting. There is no clear consensus on standard second line therapy in this setting. Pre-clinical studies have indicated beneficial combination activity for saracatanib with cediranib.

A randomised phase II study is therefore proposed to identify whether the combination of cediranib and saracatanib are more potent than cediranib alone in relapsed clear cell renal cancer after vascular endothelial growth factor (VEGF) targeted therapy. If this regimen is more potent it will be taken into phase III against standard care in this setting.

Ethics approval required
Old ethics approval format

Ethics approval(s)
King's College Hospital Research Ethics Committee, 28/01/2010, MREC ref: 10/H0808/14

Study design
Phase II randomised active-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Clear cell renal cancer

Interventions
Eligible patients will be randomised to one of two treatments arms - arm A or arm B.

Arm A is cediranib 30 mg + saracatanib 175 mg. Both are experimental drugs that come in tablet form. Patients will take the tablets orally once daily for as long as they are receiving clinical benefit.

Arm B is cediranib 30 mg + matching placebo to saracatanib. Both are in tablet form. Patients will take the tablets orally once daily for as long as they are receiving clinical benefit.

The median amount of time that we expect patients to be taking the tablets is about 4 - 6 months. Once patients stop taking the drugs due to progression or withdrawal they will be followed up for life. Unfortunately the prognosis for this group of patients is poor (they will have to have relapsed clear cell renal cancer to be eligible for the study) so this period of follow up is not expected to be longer than 2 years. Follow-up will be every 8 weeks.

There is scope in the protocol for patients to continue on their study drugs even after they have progressed at the discretion of their treating clinician. However cross-over of treatment is not permitted, so patients will have to continue on whatever combination they were originally randomised to.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cediranib, saracatanib

Primary outcome(s)
Progression free survival on the combination of cediranib and saracatanib versus cediranib alone.

CT scans to determine progression free survival will be carried out at baseline, 4 and 8 weeks after commencement of study drugs and every 8 weeks thereafter.

Key secondary outcome(s))
1. Toxicity of the single agent cediranib and the combination
2. Overall survival for both groups
3. Response rate (by Response Evaluation Criteria In Solid Tumors [RECIST] v1.1 criteria)
4. Translational endpoints (this is optional for specific sites) with the exception of collection of original tissue

Secondary outcomes will be measured via blood tests at baseline, 2 and 4 weeks after commencement of study drugs and every 4 weeks thereafter.

Completion date
31/08/2012

Eligibility

Key inclusion criteria
1. Histopathologically confirmed renal cell carcinoma with measurable metastases on computed tomography (CT)/magnetic resonance imaging (MRI)
2. Radiological progressive disease on first line VEGF targeted therapy. First line VEGF targeted therapy must consist of pazopanib, sunitinib, sorafenib, or bevacizumab. Patients treated with initial interferon prior to tyrosine kinase inhibitors (TKI) exposure, or in combination with bevacizumab, are acceptable.
3. Evidence of measurable disease (i.e., greater than or equal to one malignant tumour mass that can be accurately measured in at least one dimension greater than or equal to 20 mm with conventional CT scan or MRI, or greater than or equal to 10 mm with spiral CT scan using a 5 mm

or smaller contiguous reconstruction algorithm). Bone lesions, ascites, peritoneal carcinomatosis or miliary lesions, pleural or pericardial effusions, lymphangitis of the skin or lung, cystic lesions, or irradiated lesions are not considered measurable.
4. Adequate organ function as defined by the following criteria:
4.1. Total serum bilirubin less than or equal to 1.5 x upper limit of normal (ULN) (patients with Gilbert's disease exempt)
4.2. Serum transaminases less than 2.5 x ULN (x 5 in the presence of liver metastasis)
4.3. Serum creatinine less than or equal to 1.5 x ULN
4.4. Absolute neutrophil count (ANC) greater than or equal to 1000/mm^3 without growth factor support
4.5. Platelets greater than or equal to 100,000/mm^3
5. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrolment
6. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study procedures
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2
8. Life expectancy greater than 12 weeks
9. At least 2 weeks since the end of prior systemic treatment (sunitinib, pazopanib, sorafenib), radiotherapy, or surgical procedure with resolution of all treatment-related toxicity to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 grade less than or equal to 1 or back to baseline except for alopecia or hypothyroidism. A 4 week gap between bevacizumab and interferon (INF) should exist.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
138

Key exclusion criteria
1. Congestive heart failure, myocardial infarction or coronary artery bypass graft in the previous six months, ongoing severe heart disease
2. Pregnancy or breastfeeding. Patients must be surgically sterile, post-menopausal, or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate. Male patients must be surgically sterile or agree to use effective contraception.
3. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormally that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study
4. Untreated unstable brain or meningeal metastases or tumour. Patients with radiological

evidence of stable brain metastases are eligible providing that they are asymptomatic and either do not require corticosteroids or have been treated with corticosteroids, with clinical and radiological evidence of stabilisation at least 10 days after discontinuation of steroids.
5. Greater than +1 proteinuria on two consecutive dipsticks taken no less than 1 week apart unless urinary protein less than 1.5 g in a 24 hour period or protein/creatinine ratio less than 1.5
6. History of significant gastrointestinal impairment, as judged by the investigator, that would significantly affect the absorption of cediranib
7. Patients with a recent history of poorly controlled hypertension with resting blood pressure greater than 150/100 mmHg in the presence or absence of a stable regimen of anti-hypertensive therapy, or patients who are requiring maximal doses of calcium channel blockers to stabilise blood pressure
8. Any evidence of severe of uncontrolled diseases, e.g., unstable or uncompensated respiratory, hepatic or renal disease
9. Mean QTc with Bazetts correction greater than 480 msec in screening electrocardiogram (ECG) or history of familial long QT syndrome
10. Any evidence of interstitial lung disease (bilateral, diffuse, parenchymal lung disease)
11. Significant haemorrhage (greater than 30 ml bleeding/episode in previous 3 months) or haemoptysis (greater than 5 ml fresh blood in previous 4 weeks)
12. Recent (less than 14 days) major thoracic or abdominal surgery prior to entry into the study, or a surgical incision that is not fully healed
13. Unresolved toxicity greater than or equal to Common Terminology Criteria (CTC) grade 2 (except alopecia) from previous anti-cancer therapy
14. History of other malignancies (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ or localised controlled prostate cancer) within 5 years, unless the patient has been disease free for 2 years and there is a tissue diagnosis of the primary cancer of interest from a target lesion
15. Known inherited or acquired immunodeficiency
16. Known risk of the patient transmitting human immunodeficiency virus (HIV), hepatitis B or C via infected blood
17. Involvement in the planning and conduct of the study
18. Previous enrolment or randomisation of treatment in the present study
19. Treatment with an investigational (not including VEGF TKIs such as pazopanib) drug within 30 days prior to the first dose of cediranib
20. Other concomitant anti-cancer therapy (including luteinising hormone-releasing hormone [LHRH] agonists) except steroids
21. Previous bone marrow transplant
22. Study drugs should be permanently discontinued in patients with the following conditions:
22.1. Gastrointestinal perforation or wound dehiscence requiring medical intervention
22.2. Serious haemorrhage, i.e., requiring medical intervention
22.3. Severe hypertension (see hypertension management protocol)
22.4. Nephrotic syndrome
22.5. Severe arterial thromboembolic event
22.6. Disease progression (unless, in the investigator's opinion, the patient is receiving benefit from treatment with cediranib)

Date of first enrolment
02/09/2010

Date of final enrolment
26/01/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Barts and the London School of Medicine and Dentistry
London
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Sponsor information

Organisation
Common Services Agency (UK)

ROR
https://ror.org/04za2st18

Funder(s)

Funder type
Research council

Funder Name
Cancer Research UK (CRUK) (UK) - Clinical Trials Advisory and Awards Committee (CTAAC) grant

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Not provided at time of registration

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2016		Yes	No
HRA research summary			28/06/2023	No	No
Plain English results			25/10/2022	No	Yes