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Trial of PAZOpanib with or without FOSbretabulin in advanced recurrent ovarian cancer

Submission date 17/04/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 17/04/2014	**Overall study status** Completed	
Last Edited 11/04/2019	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-pazopanib-fosbretabulin-for-ovarian-cancer-that-has-come-back-pazfos

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2013-005471-40

IRAS number

ClinicalTrials.gov number
NCT02055690

Secondary identifying numbers
16494

Study information

Scientific Title
A Phase Ib and randomised Phase II trial of pazopanib with or without fosbretabulin in advanced recurrent ovarian cancer

Acronym
PAZOFOS

Study objectives
The principal research question for the study is whether combining pazopanib and fosbretabulin is a more effective treatment than giving pazopanib on its own for patients with advanced recurrent ovarian cancer.

On 22/09/2014 the anticipated start date was changed from 23/06/2014 to 17/09/2014.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool Central Ethics Committee, 08/05/2014, ref. 14/NW/0196

Study design
Both; Interventional; Design type: Treatment

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 below to request a patient information sheet

Health condition(s) or problem(s) studied
Topic: Cancer; Subtopic: Gynaecological Cancer; Disease: Ovary/Fallopian tube

Interventions

Fosbretabulin is administered by intravenous infusion. In each cycle/month of treatment patients will receive fosbretabulin once a week for the first 3 weeks of the cycle/month. Patients can receive the drug for up to 6 cycles

Pazopanib is taken orally and comes in the form of a tablet which is taken every day for each cycle. Patients can continue on pazopanib until they are no longer benefitting from the drug.

The phase Ib component of the study is a dose-finding component which involves recruiting patients in cohorts where the dosage is increased until the best dose is found. The dose of fosbretabulin being investigated is 45, 54 and 60 mg/m2 and for pazopanib the dose is 600 or 800 mg.

The phase II component of the study is randomised and patients will receive 800 mg of pazopanib on its own or the combination of the drugs at the dose established during phase Ib.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Pazopanib, Fosbretabulin

Primary outcome measure
Phase Ib: dose-limiting toxicities of dose of pazopanib and fosbretabulin [time point: 4 weeks after starting treatment (1 cycle)]
To determine the dose of pazopanib and fosbretabulin in combination by recording dose-limiting toxicities (DLTs) at each cohort level as categorised by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). Assessment of toxicity will take place over the 4-week period that constitutes one cycle

Phase II: progressive disease [time point: progressive disease (average of 4 months from start of treatment) measured by RECIST]
To determine whether fosbretabulin and pazopanib in combination improves progression-free survival compared to pazopanib alone measured by RECIST
Computed tomography (CT) scans are taken every 8 weeks for the first 6 cycles and evaluated by the Response Evaluation Criteria In Solid Tumours (RECIST) criteria.
After 6 cycles of fosbretabulin and pazopanib patients will receive pazopanib alone and CT scans will be undertaken every 3 months (12 weeks).

Secondary outcome measures
Phase I: biomarker changes on a cohort-by-cohort basis [time point: samples taken within the 4 weeks prior to the first dose of drug and during first cycle (weeks 2 and 3) and then at progressive disease (average of 4 months from start of treatment)]
Circulating markers of angiogenesis: VEGFA (Vascular Endothelial Growth Factor), VEGFR2, Ang1 (Angiopoietin), Ang2 and Tie (tyrosine kinase with immunoglobulin-like and EGF-like domains) 2 will be measured from samples taken pre-treatment and during cycle 1 of treatment

Phase Ib and Phase II: safety and toxicity profile of pazopanib and fosbretabulin in combination [time point: adverse events recorded within the 4 weeks prior to the first dose of drug is

administered and during the first 3 weeks of a 4-week cycle of treatment for 6 cycles, then every month until progressive disease (average of 4 months from start of treatment)]
The Phase Ib component is estimated to last approximately 9 months with the total duration of the trial expected to last 45 months. All adverse events will be recorded and categorised by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
Patients will receive up to six cycles of fosbretabulin and pazopanib after which treatment will be continued with pazopanib alone until progressive disease. It is estimated each patient will be on the trial for approximately 4 months.

Phase II: biomarker signature for progression-free survival [time point: samples taken within the 4 weeks prior to first dose of drug]
To investigate whether the pre-treatment biomarker signature can predict which patients have a response and a longer progression-free survival
Circulating markers of angiogenesis: VEGFA, VEGFR2, Ang1, Ang2 and Tie 2 will be measured by ELISA and compared to progression-free survival data

Phase II: response rates by RECIST and GCIG CA-125 criteria [time point: progressive disease (average of 4 months from start of treatment) measured by RECIST and CA125 biomarkers]
The response rate in the pazopanib and combination arms according to RECIST and Gynaecologic Cancer Intergroup (GCIG) Cancer Antigen 125 (CA-125) criteria
CT scans every every 8 weeks for the first 6 cycles then every 3 months until progressive disease (average of 4 months from start of treatment). CA125 taken twice per cycle for first 6 and then every month until progressive disease

Phase II: biomarker response in combination arm [time point: samples taken within the 4 weeks prior to the first dose of drug, cycle 1 (weeks 2 and 3) and at progression (average of 4 months from start of treatment)]
To investigate whether biomarkers can demonstrate additivity of the combination in comparison with single-agent pazopanib
Circulating markers of angiogenesis: VEGFA, VEGFR2, Ang1, Ang2 and Tie 2 will be measured from samples taken pre-treatment and during cycle 1 of treatment and at progression.
Circulating endothelial progenitor cells (CEPCs) from these samples will be counted.

Overall study start date
17/09/2014

Completion date
31/03/2017

Eligibility

Key inclusion criteria
1. Advanced, progressive, recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma, which has recurred following at least one platinum-containing regimen.
2. Progressive disease according to RECIST 1.1 or GCIG criteria within 312 months of completing platinum-containing therapy, although this need not be the immediately preceding regimen.
3. World Health Organisation (WHO) performance status of 0 or 1 (Appendix 1).
4. Measurable disease (RECIST 1.1 (Appendix 2) or PD according to CA125 GCIG criteria with non-measurable disease on CT scan.
5. Life expectancy of at least 12 weeks.
6. Haematological and biochemical indices within the ranges shown below. These measurements

must be performed within one week (Day 7 to Day 1) before the patient receives the first dose of IMP. Laboratory Test Value required:
6.1. Haemoglobin (Hb) = 90 g/L
6.2. Absolute neutrophil count = 1.5 x 10*9/L
6.3. Platelet count = 100 x 10*9/L
6.4. Serum potassium within normal range
6.5. Bilirubin up to 1.5 x ULN and
6.6. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) = 2.5 x ULN unless raised due to hepatic metastatic disease in which case up to 5 x ULN is permissible
6.7. Calculated creatinine clearance or isotope clearance measurement = 40 mL/min
6.8. Activated partial thromboplastin time (aPTT) = 1.2 x ULN
6.9. Prothrombin Time (PT) or international normalised ratio (INR) = 1.3 x ULN
7. Urine protein dipstick of less than 2+, or if 2+ or greater the patient must have a 24-hour urinary protein value of less than 2 g.
8. Clinically euthyroid
9. Aged 18 years or over at the time of consent
10. Written (signed and dated) informed consent and capable of cooperating with treatment and follow-up
11. Patients can have received bevacizumab prior to trial entry providing that the last dose was administered at least 6 months before the first dose of IMP
Target Gender: Female ; Lower Age Limit 18 years

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 128; UK Sample Size: 128; Description: Phase Ib: 9-18 Phase II: 110

Total final enrolment
33

Key exclusion criteria
1. Radiotherapy, surgery or tumour embolisation within 28 days before the first dose of IMP
2. Endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin C and six weeks for investigational medicinal products) before the first dose of IMP.
3. Ongoing grade = 2 toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1 toxicities, which in the opinion of the Chief and Principal Investigators should not exclude the patient; and grade 1 or 2 neurotoxicity considered to be due to paclitaxel.
4. Female patients who are able to become pregnant (or are already pregnant or lactating). Those who have a negative serum or urine pregnancy test before enrolment and agree to use

two highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom, have an intrauterine device and condom, diaphragm with spermicidal gel and condom) for four weeks before entering the trial, during the trial and for six months afterwards are considered eligible.
5. Major thoracic or abdominal surgery from which the patient has not yet recovered.
6. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.
7. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).
8. History of any of the following cardiovascular conditions within the last six months:
8.1. Coronary revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG])
8.2. Acute coronary syndrome (myocardial infarction [MI], unstable angina)
8.3. Symptomatic peripheral vascular disease
8.4. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (Appendix 4)
9. Patients who have sustained hypertension, defined as a systolic blood pressure (SBP) of > 140 mmHg or diastolic blood pressure (DBP) of > 90 mmHg, on three occasions.
10. ECG with evidence of clinically significant abnormalities.
11. Patients with a QTc > 480 ms or taking any drug known to prolong the QTc interval that cannot be stopped for the duration of the trial (Appendix 4).
12. Patients with pathologic bradycardia (<60 b/m in nonathletes), heart block (excluding first-degree block, being PR interval prolongation only).
13. History of cerebrovascular accident (including transient ischaemic attack [TIA]), pulmonary embolism or untreated deep vein thrombosis (DVT) within the past six months. Patients with recent DVT who have been treated with therapeutic anticoagulant agents for at least six weeks will be eligible, provided their INR (if taking oral anticoagulants) has been stable for this period of time.
14. History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously treated CNS metastases, are asymptomatic and have had no requirement for steroids or anticonvulsant medication for six months prior to the first dose of IMP.
15. Clinically significant abnormalities that may increase the risk of gastrointestinal bleeding or perforation, including but not limited to:
15.1. Bleeding: active peptic ulcer disease, known intraluminal metastatic lesions with risk of bleeding, inflammatory bowel disease (Crohns disease, ulcerative colitis);
15.2. Perforation: history of abdominal fistula or large pelvic mass; gastrointestinal perforation or intra-abdominal abscess within four weeks prior to first dose of IMP; previous bowel surgery which is judged by the investigator to increase significantly the risk of gastrointestinal complications from trial treatment
16. Evidence of active bleeding or bleeding diathesis.
17. Transfusion within one week prior to first dose of IMP.
18. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.
19. Clinically significant haemoptysis, within eight weeks before the first dose of IMP.
20. Previous treatment with pazopanib or fosbretabulin.
21. Any participant that is participating in (or plans to participate in) another interventional clinical trial, whilst taking part in this Phase Ib/II study of fosbretabulin and pazopanib. Participation in an observational trial would be acceptable.
22. Any other condition which in the Investigators opinion would not make the patient a good candidate for the clinical trial.
23. Current malignancies of other types, with the exception of adequately treated conebiopsied in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin and no

evidence of recurrence of other malignancy for at least 2 years.
24. Hypersensitivity to pazopanib/fosbretabulin or any of its excipients

Date of first enrolment
17/09/2014

Date of final enrolment
01/06/2017

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Christie Hospital, 550 Wilmslow Road
Manchester
United Kingdom
M20 4BX

Sponsor information

Organisation
The Christie NHS Foundation Trust (UK)

Sponsor details
Christie Hospital, 550 Wilmslow Road
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type

Industry

Funder Name
GlaxoSmithKline (UK)

Alternative Name(s)
GlaxoSmithKline plc., GSK plc., GSK

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Funder Name
East and North Herts NHS Trust (UK)

Funder Name
Oxigene, Inc. (USA)

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?
Abstract results	conference abstract	01/10/2018		No	No
HRA research summary			28/06/2023	No	No