A phase I study of the safety, tolerability, and antitumor activity of escalating doses of combretastatin A4 phosphate given in combination with bevacizumab to subjects with advanced solid tumors

Submission date	Recruitment status No longer recruiting	Prospectively registered		
30/10/2006		☐ Protocol		
Registration date	Overall study status	Statistical analysis plan		
21/12/2006	Completed	[X] Results		
Last Edited	Condition category	Individual participant data		
13/11/2013	Cancer			

Plain English summary of protocol

Not provided at time of registration

Contact information

Type(s)

Scientific

Contact name

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

NCT00395434

Secondary identifying numbers

OXC4P1-105

Study information

Scientific Title

Study objectives

- 1. To determine the safety and tolerability of three dose levels of Combretastatin A4 Phosphate (CA4P) given IntraVenously (IV) in combination with bevacizumab every 14 days in subjects with advanced solid tumours. The Maximum Tolerated Dose (MTD) will be defined if it is at one of the three dose levels under study
- 2. To obtain preliminary information on the anti-tumour activity of CA4P when administered in combination with bevacizumab
- 3. To assess the pharmacodynamic anti-tumour activity of CA4P in combination with bevacizumab utilising Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) for those patients with suitable lesions
- 4. To obtain pharmacokinetic information on the combination of CA4P and bevacizumab
- 5. To assess the effect of CA4P alone and the combination of CA4P and bevacizumab on circulating Endothelial Progenitor Cells (EPCs)

Please note that the anticipated end recruitment date of this trial has been extended to September 2007. The previous anticipated end date of this trial was 30/06/2007.

Ethics approval required

Old ethics approval format

Ethics approval(s)

NHS Leeds (East) Research Ethics Committee, 27/06/2006, REC reference number: 06/Q1206/89

Study design

Open-label multi-centre ascending-dose single-arm study

Primary study design

Interventional

Secondary study design

Multi-centre

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

Advanced solid tumours

Interventions

CA4P will be given IV as a single agent therapy on day one and then once every 14 days in combination with bevacizumab beginning on day eight. Three subjects will be evaluated at each dose level (three dose levels). If a Dose-Limiting Toxicity (DLT) is seen in one subject, the cohort will be expanded to six subjects. If two or more subjects experience a DLT, the cohort at the preceding level will be expanded to six subjects. If the MTD is not found to be at one of the three dose levels under study, no further dose escalation will be performed. At the end of the treatment schedule, if a subject is showing clinical benefit, the subject may continue to receive additional cycles at the discretion of the Principal Investigator (PI) and agreement of the sponsor.

Intervention Type

Drug

Phase

Phase I

Drug/device/biological/vaccine name(s)

Combretastatin A4 Phosphate (CA4P) and bevacizumab.

Primary outcome measure

To determine the safety and tolerability of three dose levels of CA4P given IV in combination with bevacizumab every 14 days in subjects with advanced solid tumors. The MTD will be defined if it is at one of the three dose levels under study.

Secondary outcome measures

- 1. To obtain preliminary information on the antitumor activity of CA4P when administered in combination with bevacizumab
- 2. To assess the pharmacodynamic anti-tumor activity of CA4P in combination with bevacizumab utilising DCE-MRI for those patients with suitable lesions
- 3. To obtain pharmacokinetic information on the combination of CA4P and bevacizumab
- 4. To assess the effect of CA4P alone and the combination of CA4P and bevacizumab on circulating EPCs

Overall study start date

15/09/2006

Completion date

01/09/2007

Eligibility

Key inclusion criteria

- 1. Histopathologically or cytologically confirmed malignant solid tumours that have failed standard therapy or for which no life prolonging treatment exists
- 2. Measurable disease as defined by the Response Evaluation Criteria In Solid Tumours (RECIST) criteria
- 3. At least four weeks since any prior immunotherapy, chemotherapy or radiation therapy prior to first dose of study drug (six weeks for therapy known to be associated with delayed toxicity such as nitrosoureas or mitomycin-C)
- 4. Age more than or equal to 18 years old
- 5. Adequate bone marrow function:
- a. Absolute granulocyte count (neutrophils and bands) more than 1500 cells/mm^3
- b. Platelet count more than 100,000 cells/mm^3
- c. Haemoglobin more than 9 g/dL
- 6. Adequate renal function (Glomerular Filtration calculated by Cockcroft/Gault formula or measure urine creatinine clearance more than 50 mL/minute)
- 7. Adequate hepatic function:
- a. Bilirubin less than 1.5 mg/dL
- b. Aspartate Transaminase (AST) and Alanine Transaminase (ALT) less than 2.5 times the institutional Upper Limit of Normal (ULN) (or less than five times ULN if liver metastases are present)
- 8. Eastern Cooperative Oncology Group (ECOG) performance status zero to two
- 9. Life expectancy of more than or equal to 12 weeks
- 10. Written, signed, dated, and witnessed (if applicable as per International Conference on Harmonisation [ICH] guidelines) Independent Ethics Committee (IEC) approved informed consent form before any study specific screening procedures are performed
- 11. Fertile subjects must abstain from sexual intercourse or use effective birth control
- 12. All Women Of Child-Bearing Potential (WOCBP) must have a negative serum pregnancy test within 72 hours of first dose

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

~12 (3-6 per dose group)

Key exclusion criteria

- 1. Contraindications, allergies or sensitivity to the use of the study medications or any other products required for participation in this study (i.e. contrast agents)
- 2. Presence of Central Nervous System (CNS) metastases
- 3. Diagnosed Squamous Non-Small Cell Lung Cancer (NSCLC)
- 4. History of Gastrointestinal Perforations
- 5. Surgery within 28 days of screening visit or a surgical incision that is not fully healed. Any

surgery planned during the study period

- 6. Proteinuria more than 1 g/24 hours by 24 hour urine collection (perform 24 hour urine collection if more than 1+ on dipstick)
- 7. Recent haemoptysis (occurrence within the past three months)
- 8. Prior therapy with CA4P or bevacizumab, or other agents which target Vascular Endothelial Growth Factor (VEGF) or Vascular Endothelial Growth Factor Receptor (VEGFR) signalling such as Sorafenib and Sutent
- 9. Prior radiation involving more than 30% of the bone marrow
- 10. Radical radiotherapy to the thorax or abdomen at any time or post-operative radical radiotherapy to the pelvis. Palliative radiotherapy treatments are acceptable. Subjects with rectal primaries who have received pre-operative pelvic radiotherapy or chemoradiation are eligible if the small bowel was mobile and not stuck to the tumour
- 11. Active autoimmune disorder(s)
- 12. Immuno-compromised, including subjects known to be Human Immunodeficiency Virus (HIV) positive
- 13. Active infection requiring antibiotic therapy or any other serious intercurrent illness
- 14. History of angina (stable or severe, even if controlled with medications), myocardial infarction, Congestive Heart Failure (CHF), non-controlled atrial arrhythmias or clinically significant arrhythmias including conduction abnormality, nodal junctional arrhythmias and dysrhythmias, sinus bradycardia or tachycardia, supraventricular arrhythmias, atrial fibrillation or flutter, syncope or vasovagal episodes
- 15. Electrocardiogram (ECG) with evidence of prior myocardial infarction (e.g., significant Q waves), QTc more than 450 msec or other clinically significant abnormalities
- 16. Taking any drug(s) known to prolong the QTc interval, which cannot be interrupted for at least four days during each treatment cycle
- 17. Known significant heart wall abnormality or heart muscle damage as evidenced on Multiple Gated Acquisition (MUGA) scan or echocardiogram (this is not a required screening investigation)
- 18. Uncontrolled hypertension (defined as blood pressure consistently greater than 150/100 irrespective of medication), or controlled hypertension requiring use of more than two classes of anti-hypertensives
- 19. Uncontrolled hypokalemia and/or hypomagnesemia
- 20. Symptomatic peripheral vascular disease or cerebrovascular disease
- 21. Psychiatric disorders or other conditions rendering subjects incapable of complying with the requirements of the protocol
- 22. Receiving concurrent hormonal therapy with exception of gonadotropin-Releasing Hormone (GnRH) agonists in subjects with hormone refractory prostate cancer, Hormone Replcaement Therapy (HRT), oral contraceptive, and megestrol acetate used for anorexia/cachexia
- 23. Receiving anticoagulation with warfarin, heparin or low molecular weight heparin other than low dose (1 mg) warfarin for maintenance of central line patency
- 24. Women who are currently pregnant, nursing, or planning a pregnancy; or women who have a positive pregnancy test
- 25. Receiving concurrent antineoplastic therapy (radiation therapy, cytotoxic or biologic therapy)
- 26. Participation in an investigational drug or device trial within 30 days of entering the study

Date of first enrolment

15/09/2006

Date of final enrolment

01/09/2007

Locations

Countries of recruitment

England

United Kingdom

Study participating centre Mount Vernon Hospital Middlesex United Kingdom HA6 2RN

Sponsor information

Organisation

OXiGENE, Inc. (USA)

Sponsor details

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Sponsor type

Industry

Website

http://www.oxigene.com

ROR

https://ror.org/00cj7p033

Funder(s)

Funder type

Industry

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?
Results article	results	15/06/2012		Yes	No