ISRCTN96787846 https://doi.org/10.1186/ISRCTN96787846

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Dr Paul Nathan

Contact details
Mount Vernon Hospital
Northwood
Middlesex
United Kingdom
HA6 2RN
+44 (0)1923 84 4729
nathan.pd@gmail.com

Additional identifiers

ClinicalTrials.gov (NCT)
NCT00395434

Protocol serial number

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

Study type(s)
Treatment

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(s)
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.

Key secondary outcome(s))
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

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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

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
United Kingdom

England

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

Sponsor information

Organisation

OXiGENE, Inc. (USA)

ROR
https://ror.org/00cj7p033

Funder(s)

Funder type
Industry

Funder Name
OXiGENE, Inc. (USA)

Results and Publications

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