

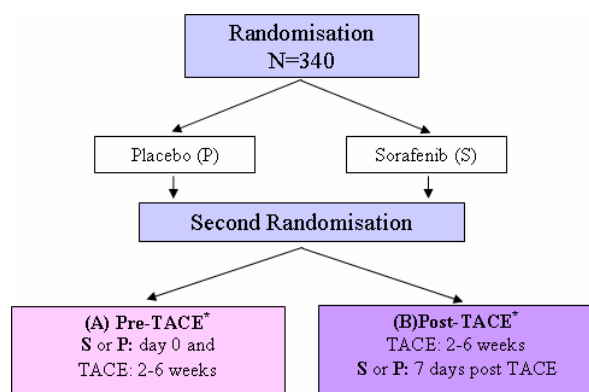
Trial Development Group: Dr Tim Meyer (Chief Investigator), Dr Dawn Brant, Dr Andrew Burroughs, Prof James Garden, Prof. P. Johnson, Dr Daniel Palmer, Prof J. Primrose, Ms Deborah Stocken.

Rationale: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the incidence of HCC in Europe is increasing. For 20-30% patients with HCC the best treatment option is transarterial chemoembolisation which has been shown in two randomised trials and one meta-analysis to improve survival over best supportive care. Unfortunately patients inevitably relapse with re-growth of the original tumour or the development of new tumours. Until recently no systemic therapy had been shown to improve survival in HCC however a large randomised placebo controlled trial of sorafenib has now reported a 44% improvement in median overall survival from 7.9 to 10.7 months in patients with advanced HCC. Sorafenib is a small molecular inhibitor of Raf kinase, PDGF (platelet-derived growth factor), VEGF receptor 2 & 3 kinases and c Kit. There is a clear rationale for combining embolisation, which causes acute tumour necrosis with sorafenib which appears to prevent tumour progression and may inhibit the angiogenic response that occurs as a consequence of embolisation. We therefore propose to perform a randomised placebo-controlled phase III to test the hypothesis that sorafenib will prolong time to progression in patients treated with chemoembolisation.

Study Design

TACE performed using doxorubicin loaded DCBead™ TACE performed TACE will be performed 2-6 weeks after randomisation and further TACE only performed if felt clinically indicated upon review of follow-up imaging assessment.

Sorafenib (400mg/m²) twice daily until progression



Endpoints

Phase II Primary Objective: Toxicity
 Secondary Objective: Disease control

Phase III Primary Objective: Progression free survival
 Secondary Objectives: Overall survival; Toxicity; QoL; number TACE performed; Health Economics

Translational Research Objectives: -Serum/Plasma Proteomics; Circulating tumour/endothelial cell biomarkers; To fresh frozen establish a tissue bank for genomic and proteomic analysis.

Prior Randomisation

Up to 2 wks before randomisation:-

- Confirmation of disease by histology or EASL criteria
- Physical exam & Full history
- ECOG & Child-Pugh status
- Laboratory investigations: to check adequate haematological function, adequate clotting, and adequate hepatic and renal function
- QoL baseline assessment.

Up to 4 weeks before randomisation:-

Chest X-ray or CT Scan & CT scan of abdomen and pelvis to exclude metastatic disease

For Further information

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 Version 1.3 date 23 Aug 2007

Recruitment

- 340 patients in the UK and Europe over 3 years with 1 year follow-up
- Estimated start of recruitment April 2008. Expected closure April 2011

Inclusion & Exclusion Criteria

Inclusion Criteria

- Histological or cytological meet the EASL criteria for diagnosis of HCC and at least one uni-dimensional lesion measurable according to the RECIST criteria by CT-scan or MRI.
- Not a candidate for surgical resection.
- Aged ≥ 18 years and estimated life expectancy >3 months
- ECOG performance status ≤ 2
- Adequate haematological function Hb ≥ 9g/L, Absolute neutrophil count ≥ 1.5x10⁹/L, platelet count ≥ 60x10⁹/L
- Bilirubin ≤ 50 µmol/L, AST and ALT ≤ 5 x ULN
- Adequate renal function; Cockcroft and Gault estimation ≥ 50ml/min
- INR ≤ 1.5
- Modified Child-Pugh A or B
- Women of child-bearing potential should have a negative pregnancy test prior to study entry AND be using an adequate contraception method, which must be continued for 3 months after completion of treatment
- Written informed consent

Exclusion Criteria

- Extra-hepatic metastasis (this should not exclude patients if small volume lung nodules ≤ 1cm and if embolisation is regarded as the optimum treatment by the treating clinician)
- Prior embolisation, systemic or radiation therapy for HCC.
- Investigational therapy or major surgery within 4 weeks of the study.
- Any ablative therapy (RFA or PEI) for HCC (this should not exclude patients if target lesion(s) have not been treated and occurred >6 weeks prior study entry)
- History of bleeding within the past 2 weeks.
- Child Pugh C cirrhosis
- Hepatic encephalopathy
- Ascites refractory to diuretic therapy
- Documented occlusion of the hepatic artery or main portal vein
- Hypersensitivity to intravenous contrast agents
- Active clinically serious infection (> grade 2 NCI-CTC version 3.0)
- Pregnant or lactating women
- History of second malignancy except those treated with curative intent more than three years previously without relapse and non-melanotic skin cancer or cervical carcinoma in situ.
- Evidence of severe or uncontrolled systemic diseases, congestive cardiac failure >NYHA class 2, MI within 6 months or laboratory finding that in the view of the investigator makes it undesirable for the patient to participate in the trial
- Psychiatric or other disorder likely to impact on informed consent
- Symptomatic brain metastases
- Patient is unable and/or unwilling to comply with treatment and study instructions or patient unable to swallow oral medications