**TACE-2: A randomised placebo-controlled, double blinded, phase III trial of sorafenib in combination with transarterial chemoembolisation in hepatocellular cancer**

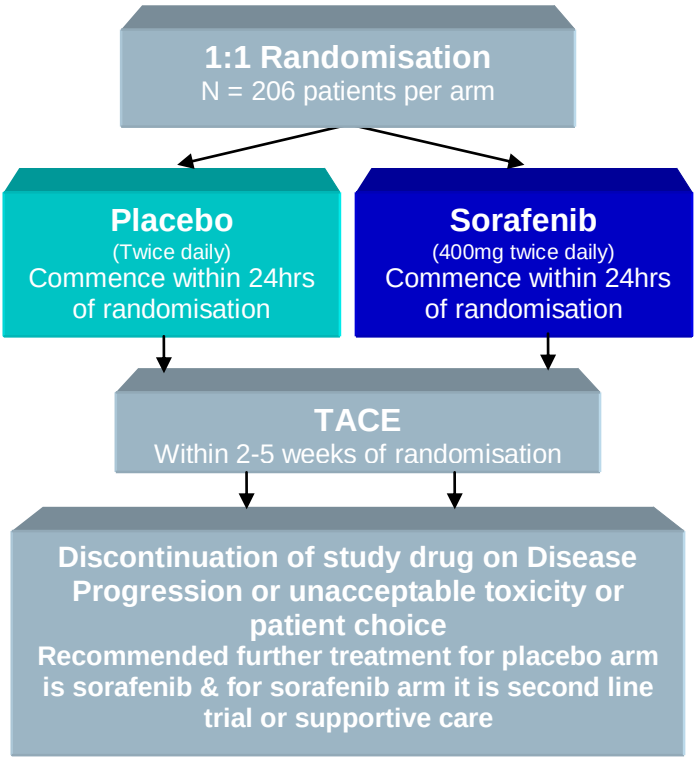
Trial Development Group: Dr Tim Meyer (Chief Investigator), Dr Deborah Stocken, Dr Andrew Burroughs, Prof James Garden, Prof. P. Johnson, Dr Daniel Palmer, Prof J. Primrose, Dr Jenny Barnwell, Ms Deborah Bird
Lead Co-investigator in Italy (to be confirmed), Lead Co-investigator in France (to be confirmed).

## Trial Objectives

To determine whether the addition of sorafenib to TACE (performed according to a standardised protocol with doxorubicin eluting beads) is superior to TACE alone in the treatment of HCC

## Sample Size

The trial will aim to recruit 206 patients per arm (412 in total)




## Trial Duration

It is anticipated that recruitment will take approximately three years and the study will continue for a further year after the last patient has been recruited. The start for recruitment was Autumn 2010. All patients will be followed up for one year after the last administration of sorafenib/placebo and flagged with the Medical Research Information Service until death.

## Outcome Measures

Primary: Progression Free Survival

Secondary: Overall Survival; Time to Progression; Toxicity; Disease Control (CR+PR+SD); QoL and number of TACE procedures performed during 12 months following randomisation.

## Eligibility Criteria

### Inclusion Criteria

- Histological or cytological diagnosis or meet the AASLD 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 or liver transplant
- Aged ≥18 years and estimated life expectancy >3 months
- ECOG performance status ≤1
- Adequate haematological function Hb ≥9g/L, absolute neutrophil count ≥1.5x$10^9$/L, platelet count ≥60x$10^9$/L
- Bilirubin ≤50 µmol/L, AST or ALT ≤5 x ULN, ALP <4 x ULN
- Adequate renal function; Creatinine ≤1.5x ULN
- INR ≤1.5
- Amylase and lipase <2 x ULN
- Child-Pugh cirrhosis A (score must be ≤6)
- Left Ventricular Ejection fraction ≥45%
- Women of child-bearing potential should have a negative pregnancy test prior to study entry. Both men and women must be using an adequate contraception method, which must be continued for 3 months after completion of treatment
- Written informed consent

### Exclusion Criteria

- Extrahepatic metastasis
- Prior embolisation, systemic or radiation therapy for HCC
- Any contraindications for hepatic embolisation procedures including portosystemic shunt, hepatofugal blood know, known serve atheromatosis
- Investigational therapy or major surgery within 4 weeks of trial entry
- 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 to study entry)
- History of bleeding within the past 4 weeks
- Child-Pugh cirrhosis C and B with score ≥7
- 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
- Known history of HIV infection
- 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, cardiac arrhythmias (requiring anti-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
- Patient is unable and/or unwilling to comply with treatment and study instructions
- Patient is unable to swallow oral medications

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