

Project Title:	A Phase II randomised clinical trial of conditioning cyclophosphamide and chemoembolisation with or without vaccination with dendritic cells pulsed with HepG2 lysate ex vivo in patients with Hepatocellular Carcinoma: IMMUNOTACE.
Project Ref:	09/160/24
Cost:	£580,846
Lead Applicant & Institution:	Professor David Adams University of Birmingham Medical School
Start Date:	1 September 2012
Plain English Summary:	<p>The incidence of primary liver cancer or hepatocellular carcinoma (HCC) is rising & it is becoming a major health burden in the UK. Current treatment is limited & 5-year survival for all stages combined is less than 5%. Patients who are unsuitable for surgery may derive palliative benefit from a procedure called transarterial chemoembolisation(TACE), which involves direct injection of chemotherapy into the blood vessels supplying the tumour followed by blockage of these vessels to starve the cancer of blood flow.</p> <p>As well as these direct effects, TACE also stimulates anti-tumour immune responses which we propose to boost to establish protective anti-tumour immunity. Dendritic cells (DC) are white blood cells that are highly effective at stimulating immune responses. They can be derived from patients' blood, loaded with proteins from cancer cells and re-infused intravenously to activate immune responses against the cancer. We published a phase II clinical trial of the safety and efficacy of DC vaccination for pts with extensive HCC in 2009. 134 DC infusions were administered with no significant side-effects. In 25 pts who received at least 3 vaccine infusions the radiologically determined disease control rate was 28% associated with anti-tumour immune responses.</p> <p>These data justify further development of this novel therapy. We hypothesise that a vaccination to boost the immune response, in addition to TACE, may improve the clinical outcome. In addition we will combine DC vaccination with low-dose cyclophosphamide which has been shown to deplete regulatory T cells that suppress anti-tumour immunity. DC will be infused directly into the liver blood supply during TACE to maximise immune responses in the liver. We have already piloted this approach in a current phase 0 trial. Eligible pts with HCC will be randomised to TACE with cyclophosphamide pre-conditioning with or without DC vaccination.</p> <p>After initial infusion into the liver at the time of TACE subsequent vaccination will be by monthly intravenous infusions preceded by</p>

	<p>cyclophosphamide.</p> <p><u>Primary objective:</u> To determine whether activity due to the addition of DC vaccine to chemoembolisation and preconditioning warrants further investigation.</p> <p><u>Secondary endpoints:</u> a) characterise immune responses stimulated by vaccination b) determine if responders have a blood protein profile that can be used to select those likely to benefit in future studies c) measure the effect of cyclophosphamide on the immune system d) assess side effects of vaccination e) measure overall survival.</p> <p>This trial will be conducted by the NIHR BRU, CRCTU & NHSBT which brings together oncologists, hepatologists, scientists & statisticians with facilities to produce GMP-grade cells, administer them safely & monitor outcomes.</p> <p>The infrastructure & equipment is in place & we are requesting funds for consumables, running costs & a trials manager.</p>
<p>Abstract:</p>	<p><u>RESEARCH DESIGN</u> Randomised Phase II trial of cyclophosphamide & chemoembolisation with or without vaccination with dendritic cells pulsed with HepG2 lysate in hepatocellular carcinoma.</p> <p><u>INCLUSION</u> 1) HCC with at least 1 lesion measurable by CT/MRI 2) Suitable for TACE but not surgical resection or transplantation 3) Age >18yrs 4) Life expectancy >3 months; ECOG status<1 5) Adequate haematological, liver & renal function 6) Informed consent.</p> <p><u>EXCLUSION</u> 1) Extra-hepatic disease 2) Prior ablative, systemic or radiation therapy 3) Investigational therapy or surgery within 4 wks 4) Child Pugh score >7 5) Hepatic encephalopathy or refractory ascites 6) Hepatic artery or main portal vein occlusion 7) Hypersensitivity to contrast agents 8) Active infection within 2 wks 9) Pregnant or lactating 10) Second cancer except non-melanotic skin or cervical carcinoma in situ 11) Severe systemic disease 12) History of HIV</p> <p><u>INTERVENTIONS</u> Group 1: TACE + low-dose cyclophosphamide to deplete regulatory T cells Group 2: TACE + low-dose cyclophosphamide + infusion of tumor lysate pulsed DCs</p> <p><u>PRIMARY OUTCOME MEASURES</u> Progression free survival (PFS)</p> <p><u>SECONDARY OUTCOME MEASURES</u> 1) Radiological response 2) Rate of change in tumour marker 3) Toxicity 4) Immune response rate 5) Survival</p> <p><u>ASSESSMENT</u> Group 1 Visit 1 Screening Visit 2 Treatment initiation+ clinical assessment, bloods & immune response Visit 3 End of treatment clinical assessment, bloods & immune response Group 2 Visit 1 Screening; Visit 1b Dendritic cell collection via leukopheresis; Visit 2 Treatment initiation, clinical assessment, bloods & immune assessment; Visit 3: End of treatment clinical assessment, bloods & immune assessment. Immune Response Assessment Weekly for first month; monthly thereafter. Tumour</p>

	<p>assessment Day 62+/-3 after randomisation & 3 monthly for 1 year</p> <p><u>PARTICIPANT FOLLOW UP</u> End of treatment follow up at 3 monthly intervals with clinical assessment & bloods + immune response assessment; tumour assessment</p> <p><u>SAMPLE SIZE & STATISTICS</u> The trial design is based on a randomized phase II trial using a Jung design (alpha=0.2, beta=0.2, relevant increase in PFS=20%) requiring 70 patients in total.</p> <p><u>PROJECT TIMETABLES INCLUDING RECRUITMENT RATE</u> Jan 2011 Notification of funding, MHRA & Ethics submission; May 2011 Open to recruitment; June 2011 1st pt, 1st visit; June 2014 Last pt, 1st visit; June 2015 last pt, last visit; Sept 2015 Final analysis. We see >200 new HCC pts/year and an audit of our TACE activity since 2005 confirms 70 procedures/yr. We estimate recruitment of >25 patients/year allowing us to comfortably recruit the required 70 patients.</p>
ISRCTN: (if applicable)	To follow
Project Protocol:	www.eme.ac.uk/projectfiles/0916024protocol.pdf
Project website: (if applicable)	To follow
URL of this Page:	www.eme.ac.uk/projectfiles/0916024info.pdf