TACE 2: A randomised placebo-controlled, double-blinded, phase 3 trial evaluating sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma.

Tim Meyer MBBS[1,2], Richard Fox MSc[3], Yuk Ting Ma MBChB [4], Paul J. Ross MBBS [5,6], Martin W. James MBBS [6], Richard Sturgess MBBS [7], Clive Stubbs MSc[3], Deborah D. Stocken PhD[8], Lucy Wall MBBS [9], Anthony Watkinson MD [10], Nigel Hacking MBBS [11], T.R. Jeffry Evans MBBS [12], Peter Collins MBBS [13], Richard A Hubner PhD [14], David Cunningham MD [15], John Neil Primrose MBBS [11], Philip J Johnson MBBS [16,17], Daniel H. Palmer MBBS [16,17].

[1] UCL Cancer Institute, University College London, UK
[2] Royal Free London NHS Foundation Trust, London, UK
[3] Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, UK
[4] Queen Elizabeth Hospital Birmingham, UK
[5] Guy's Hospital, London, UK
[6] King's College Hospital, London, UK
[7] Nottingham University Hospitals NIHR BRC, Nottingham, UK
[8] Aintree University Hospital, Liverpool, UK
[9] Institute of Health and Society, Newcastle University, UK
[10] Western General Hospital, Edinburgh, UK
[11] The Royal Devon and Exeter Hospital, Exeter, UK
[12] Southampton University Hospitals NHS Trust, Southampton, UK
[13] University of Glasgow, Glasgow, UK
[14] Bristol Royal Infirmary, Bristol, UK
[15] Christie Hospital NHS Foundation Trust, Manchester, UK
[16] The Royal Marsden NHS Foundation Trust, Sutton and London Hospital, Surrey, UK
[17] University of Liverpool, Liverpool, UK
[18] Clatterbridge Cancer Centre, Liverpool, UK

Address for Correspondence:

Prof Tim Meyer, UCL Cancer Institute, University College London

72, Huntley Street, London WC1E 6BT, UK

email; t.meyer@ucl.ac.uk Tel; 0207 679 6731, Fax; 0203 108 2025

Running head: The TACE 2 trial

Previous presentations
2012 ASCO Annual Meeting Poster Session, Chicago, USA
2016 ASCO Annual Meeting Poster Discussion Session, Chicago, USA

2016 NCRI Annual Meeting Oral Presentation, Liverpool, UK

ABSTRACT

Background

TACE is the standard-of-care for patients with intermediate stage hepatocellular carcinoma (HCC) whilst the multi-kinase inhibitor sorafenib improves survival in patients with advanced disease. The TACE 2 trial was designed to determine whether TACE + sorafenib improves progression free survival (PFS) compared to TACE + placebo.

Methods

TACE 2 was multicentre, randomised, placebo controlled, phase 3 trial for patients with unresectable, liver-confined HCC, with patent main portal vein, Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 1 and Child-Pugh A liver disease. Patients were randomised 1:1 by computerised minimisation algorithm to continuous oral sorafenib (400mg twice-daily) or matching placebo combined with TACE using drug-eluting beads (DEB-TACE) which was performed 2-5 weeks post-randomisation and according to radiological response and patient tolerance thereafter. Patients were stratified according to randomising centre and serum alpha-fetoprotein levels (AFP) (<400, ≥400 ng/ml). The primary outcome was PFS defined as the interval between randomisation and progression according to RECIST v1.1 or death due to any cause and analysed by intention to treat. The trial has been completed and the final results are reported. The trial is registered at EudraCT, number 2008-005073-36, and ISRCTN, number ISRCTN93375053.

Findings

The trial enrolled between 04 Nov 2010 and 07 Dec 2015, and was terminated after a planned interim futility analysis. Data from 313 randomised patients is presented;

157 randomised to sorafenib and 156 and to placebo. The median (IQR) daily-dose and duration of therapy was 660mg (389.2, 800.0) versus 800mg (758.2, 800.0), and 120.0 days (43.0, 266.0) versus 162.0 days (70.0, 323.5) for sorafenib and placebo respectively. There was no evidence of difference in PFS between sorafenib and placebo-treated patients; HR 0.99 (95%CI 0.77-1.27, p=0.94) with median PFS 238 (95% CI 221, 281) and 235 (95% CI 209, 322) days respectively. The most common grade 3-4 adverse events were fatigue (29 [18.5%] of 157 patients in the sorafenib treated group versus 21 [13.5%] of 156 patients), abdominal pain (20 [12.7%] and 12 [7.7%]), diarrhoea (16 [10.2%] and 4 [2.6%]), gastrointestinal disorders (18 [11.5%] and 12 [7.7%]) and hand foot skin reaction (12 [7.6%] and 0). At least one SAE was reported in 65 (41.4%) of 157 sorafenib and 50 (32%) of 156 placebo-treated patients, and in total 181 SAEs were reported, 95 (52.5%) in the sorafenib and 86 (47.5%) in the placebo-treated groups.

Interpretation

TACE 2 provides no evidence that addition of sorafenib to DEB-TACE improves PFS in European patients with HCC. Alternative systemic therapies need to be evaluated in combination with TACE to improve patient outcomes.

Funding: Bayer PLC and BTG PLC.

Research In Context

Evidence before the study

A search of PubMed between January 2000 and the start of the TACE 2 trial in November 2010 including the search terms, hepatocellular carcinoma and sorafenib yielded two randomised placebo controlled trials evaluating sorafenib as a single agent for the treatment of advanced hepatocellular cancer. These two trials confirmed a survival benefit of 2-3 months for patients in patients with good performance status and Child Pugh A liver function. In addition, there was one phase 1 trial that had demonstrated the feasibility of combining sorafenib with transarterial chemoembolisation in 14 patients with HCC, but no randomised trials including the combination of sorafenib and TACE were available. We therefore initiated the first randomised phase 3 trial of TACE combined with continuous sorafenib to determine if the addition of sorafenib prolonged progression free survival (PFS) in patients treated with TACE. A subsequent search of PubMed between November 2010 and March 2017 including the terms sorafenib, hepatocellular carcinoma, TACE and randomised, resulted in three prospective trials; A phase 3 trial comparing sorafenib with placebo in in Japanese and Korean patients who had achieved ≥25% tumour necrosis following TACE, showed no improvement in TTP for those receiving sorafenib. By contrast, a small randomised trial of 80 HCV infected patients demonstrated a significant improvement in TTP for patients treated with TACE followed by sorafenib compared to placebo. The only randomised trial to evaluate concurrent sorafenib and TACE was the SPACE trial; a global randomised phase 2 trial which demonstrated no improvement in TTP for sorafenib and TACE compared with TACE alone. Follow-up was too short to provide a meaningful comparison of overall survival.

Added value of this trial

The TACE 2 trial is the first Phase 3 trial to compare continuous concurrent, sorafenib combined with TACE versus the combination of placebo and TACE. We found no evidence of an improvement in the primary endpoint, progression free survival or the secondary endpoint, overall survival.

Implications for clinical practice

We believe that this trial now provides definitive evidence that the combination of sorafenib and TACE, while feasible, is not effective, and alternative strategies to improve outcomes for intermediate stage HCC should be explored.

INTRODUCTION

Hepatocellular carcinoma is the 6th most common cancer and the second most common cause of cancer death worldwide[1]. Less than 30% patients are eligible for potentially curative therapies such as transplantation, resection or ablation. For selected patients not suitable for such interventions yet who have liver-confined disease, preserved liver function and good performance status, transarterial chemoembolisation (TACE) is recommended according to international guidelines [2]. The evidence for TACE comes from two small randomised controlled trials and a meta-analysis demonstrating a significant survival benefit for TACE-treated patients compared with those receiving best supportive care [3-5]. In clinical practice, there is wide variation in the application of TACE with regard to embolic particle, chemotherapeutic used, frequency and extent[6]. There is also variation in patient selection in terms of tumour extent, vascular invasion, presence of extrahepatic disease and performance status. Recent data also question the role of chemotherapy, suggesting that outcomes from bland embolisation (TAE) are equivalent to those of TACE [7,8] and a Cochrane Review also questioned the survival benefit attributable to TACE [9]. The introduction of drug-eluting beads (DEB-TACE) has provided a method of embolising tumours with a more controlled local release of chemotherapy. Whilst this approach has not been shown to be superior to conventional TACE (cTACE) in terms of survival, there is less chemotherapy related toxicity due to the lower systemic exposure to chemotherapy [10,11]. Specifically, the extent of transaminitis and alopecia are reduced with DEB-TACE[10,12].

For advanced disease, sorafenib is currently the standard of care based on two large placebo controlled, randomised trials demonstrating a median survival benefit of 2-3 months [13,14]. Sorafenib is a multi-kinase inhibitor targeting, among others, VEGFR

RAF, and PDGFR thereby exerting both anti-angiogenic and direct anti-tumour effect. The use of sorafenib as an adjuvant therapy after resection or ablation has been explored and found to be ineffective [15] and a number of strategies have been explored in the TACE population. TACE causes acute hypoxia leading to upregulation of VEGF which may contribute to revascularisation. As such there is a clear rational to combine TACE with sorafenib, both to inhibit revascularisation and also tumour proliferation. We therefore performed a randomised, placebo controlled trial to evaluate the role of sorafenib combined with standard DEB-TACE.

PATIENTS AND METHODS

Study design and participants

This was a phase 3 multicentre, randomised, double-blind, placebo-controlled study conducted in the United Kingdom, in which patients were randomised 1:1 to receive continuous oral sorafenib 400mg twice-daily or matching placebo starting within 24 hours of randomisation. Inclusion criteria included: histological or non-invasive diagnosis according to the American Association for the Study of Liver Diseases (AASLD) criteria[16], age ≥18 years at least one uni-dimensional lesion measurable according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1)[17], not a candidate for surgical resection or liver transplant, ECOG performance status ≤ 1, Child Pugh A liver disease, haemoglobin ≥ 9g/L, neutrophil count ≥1.5x10^9/L, platelet count ≥ 60x10^9/L, bilirubin ≤50 μmol/L, AST or ALT ≤5 x ULN, ALP <4 x ULN, creatinine ≤1.5 x ULN, INR ≤1.5, and left ventricular ejection fraction of ≥45%. Exclusion criteria included: extrahepatic metastasis, prior-embolisation, systemic or radiation therapy for HCC, any contraindication to hepatic embolisation , investigational therapy, major surgery or history of bleeding within four weeks of trial

entry, hepatic encephalopathy, occlusion of the hepatic artery or main portal vein, myocardial infarction within six months or prolonged QT/QTc >450ms. The protocol was approved by the central ethical review board (IRAS Ref 09/H1102/114) and all patients provided written informed consent.

Randomisation and Masking

The CRCTU was responsible for managing the randomisation, drug allocation, drug discontinuation processes using an online trial management portal. Randomisation was performed by randomisation officers based at CRCTU. Sharp Clinical Services (Crickhowell, UK) were contracted to manage drug labelling and drug dispensing. Patients were randomly assigned, on a 1:1 basis and in a blinded fashion, to the sorafenib or placebo arm based on a minimisation randomisation algorithm. Randomisation was stratified by (i) randomising centre and (ii) serum alpha-fetoprotein levels (<400, ≥400 ng/ml). At randomisation, staff at the CRCTU verified patient details and eligibility criteria before informing the site of trial number and treatment allocation. Allocation concealment was achieved by the use of tablets identical in appearance and in numbered bottles. Bottles contained 70 days' supply of sorafenib or matching placebo. The CRCTU randomisation system allocated patients to each treatment group and directly informed the pharmacy at each site of the numbered bottle to distribute to which patients. To maintain the blinding throughout the trial, all subsequent issue of study medication was managed by CRCTU through the allocation and provision of bottle numbers at each follow up visit. Only the Trial Coordinator was unmasked to treatment allocation before patient progression during the study. Patients were unmasked only in the event of a possible suspected unexpected serious adverse reaction. The Trial Coordinator conducted the unmasking only after the Clinical Coordinator had confirmed expectedness for

the serious adverse reaction. The result was kept confidential. On progression, patients were unblinded to allow for further clinical decision making, and for the provision of open-label sorafenib. This was managed through the online trial management portal by the Trial Coordinator at CRCTU. The Trial Statistician gained access to the unblinded information in accordance with CRCTU Standard Operating procedures. At the end of the study, an unblinded patient randomisation report was run from the system by the statistician and provided to the Trial Coordinator to match the patient by two pieces of information; trial number and date of birth.

Methods and Procedures

Oral sorafenib at a dose of 400mg twice-daily or matching placebo was commenced within 24 hours of randomisation and continued until disease progression according to RECIST v1.1. There were two protocol defined dose reductions, level -1 (400mg once-daily) and Level -2 (400mg alternated days), and drug was discontinued in the event of disease progression, protocol defined unacceptable toxicity, a dose interruption of more than 30 days, patient choice or the recommendation of the investigator. DEB-TACE was performed 2-5 weeks post-randomisation using drug-eluting beads (DC Bead™ (BTG PLC)) loaded with doxorubicin 150mg according to the manufactures instructions which were detailed and in the trial protocol . Administrations was via the hepatic artery accessed via the femoral artery, and a superselective approach was recommended. The protocol advised first injecting the smaller DC Bead (100-300µm) followed by the larger DC Beads (300-500µm) to achieve the angiographic endpoint defined as sluggish flow in the main feeding vessels with stasis in the intra and peri-lesional branches. The maximum dose to be delivered was two vials of DC Beads loaded with 75mg doxorubicin per vial. All baseline screening tests were required within 28 days of randomisation. Baseline

imaging and follow-up imaging was performed by computerised tomography (CT) of the chest and dual phase abdominal CT or contrast enhanced abdominal magnetic resonance imaging (MRI). The first follow-up imaging was performed at week 10 post-randomisation and further DEB-TACE performed as required according to the presence of persistent tumour enhancement. Further follow-up imaging was performed at week 22 and at three-monthly thereafter. Laboratory evaluation including haematology, coagulation, biochemistry and alpha fetoprotein was performed during screening and on day 1, 72 hours before DEB-TACE and 8 days post-DEB-TACE, week 10, 16, 22 and every 6 weeks thereafter. Left ventricular ejection fraction was estimated by echocardiography or multigated acquisition (MUGA) scan during screening, and electrocardiograms performed during screening, within 72 hours of DEB-TACE, day 7 post TACE, week 10, 16, 22 and every 6 weeks thereafter. Toxicity was graded according to the NCI CTCAE v4 and was recorded from the start of study treatment up to 30 days after last administration of study treatment or until end of study. Quality of Life (QOL) using the EORTC QOL questionnaire (QLQ-C30) version 3, EORTC QLQ-HCC18 and the EuroQoL (EQ-5D) questionnaire were requested at baseline, pre-TACE, week 10 and 6-weekly thereafter until progression. On progression, patients were unblinded and entered the post-study treatment period. To avoid delays in unbinding and instituting appropriate treatment on progression, an amendment was implemented during the trial to allow unbinding on local review rather than central review. Patients on the placebo arm were offered sorafenib at the discretion of the treating clinician and patients on the sorafenib arm could continue if there was deemed to be patient benefit. No standard therapy was recommended for patients progressing on sorafenib who discontinued sorafenib

Outcome measures

The primary endpoint was progression free survival (PFS) defined as the interval between randomisation and progression according to RECIST v1.1[17] or death due to any cause. Patients not experiencing progression or death were censored at the date last known to be event-free. The primary endpoint was determined by local review and additional central review was provided by IXICO PLC (London UK). Secondary endpoints included: overall survival (OS) measured from date of randomisation to death; time to progression (TTP) measured from date of randomisation to date of progression; response and disease control rate according to RECIST v1.1 guidelines; QOL scored according to the EORTC QLQ-C30 manual and guidelines and number of TACE procedures performed within 12 months of randomisation. Toxicity was assessed in all patients according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4) from start of study treatment up to 30 days after last administration of study treatment or until end of study. All (serious) adverse events were assessed with reference to the Summary of Product Characteristics (SmPC) for sorafenib and clinically evaluated in a blinded fashion. Unblinding only occurred at the point of requirement for SUSAR reporting.

Statistical Analysis

The null hypothesis was that the survival distributions were equal, and the alternative, that the survival distributions differed. In total, 412 patients were required to detect an improvement in median PFS from 8.9 to 12.4 months, equating to a HR for DEB-TACE and sorafenib of 0.72, with a 2-sided significance of $\alpha=0.05$, and with

85% power. The protocol incorporated a formal interim analysis for futility following the method of Freidlin et al[18], performed after 147 (43%) of PFS events, at which a HR ≥ 1 would be indicative of futility. Overall error rates were not adjusted for the interim analyses. Sample size was estimated using PS software (version 3.0.2). Primary efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomised patients. Further analyses assessed efficacy in the per-protocol (PP) population, defined as all patients having at least one DEB-TACE and 6 weeks of sorafenib or placebo, and excluding ineligible patients. Safety was assessed all patients. The primary analysis of PFS and secondary outcome measures OS and TTP were analysed through multilevel flexible parametric survival models with adjustment for stratification factors, with randomising centre entered as a random component. Hazard ratios with 95% CI were estimated, and in all cases are reported with the placebo arm as the reference group. Sensitivity analyses were performed with adjustment for prognostic factors identified in univariable analyses. The proportional hazards (PH) assumption was tested where applicable. Efficacy was also assessed in prognostic subgroups, including stratification factors, with tests of heterogeneity. QOL, measured using EORTC-QLQ-C30 and -HCC18 questionnaires, was explored graphically by fitting smoothed trends to the observed data, and was analysed through mixed-effects linear regression models with the random component specified at the patient level. Exploratory interactions between treatment group and time from randomisation allowed trends to differ by treatment group. Patients were assumed to have worst possible symptomatic score, or lowest level of functioning at death. Model fit for survival and QOL measures was assessed through Akaike-(AIC) and Bayesian-information criterion (BIC). Modelling of the EQ5D utility score with overall survival based on the integrated quality survival

product (IQSP) methods of Billingham et al [19] will be reported in a follow-on QOL article. Safety data were reported descriptively, with adverse events summarised as worst-grade experienced at the patient level for each CTC category, and with frequency of serious adverse events (SAEs) reported by treatment group and their relative expectedness to sorafenib. Deaths deemed related to treatment must have occurred within 30 days of last treatment. All analyses were performed using Stata version 14. The trial was registered on the European Clinical Trials Database (EudraCT Number: 2008-005073-36), the ISRCTN registry (ISRCTN93375053) and ClinTrials.gov (NCT01324076).

Role of Funding Source

The funders of the study (Bayer PLC and BTG PLC) had no role in the study design, data collection, analysis, interpretation or writing of the report. Bayer PLC provided sorafenib and matching placebo and BTG provided DC Beads. The study was endorsed by Cancer Research UK and adopted into the NIHR trial portfolio. The study was sponsored by UCL and the chief investigator (TM) is employed by UCL. The study was designed by TM and members of the trial management group including DHP, PJJ, JNP, AW, NH, DS, RF, CS. The trial was monitored by an independent data monitoring committee (IDMC) who had full access to the data and reported to the Trial Steering Committee (TSC). Both the IDMC and TSC approved termination of recruitment on achieving the primary endpoint. Data collection and analysis was performed by the Cancer Research UK Clinical Trials Unit, University of Birmingham. TM, RF, CS had access to the raw data and the corresponding author (TM) had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Patients

Between 04 Nov 2010 and 07 Dec 2015, a total of 313 patients were randomised from 20 centres in the United Kingdom (Appendix 1); 157 to sorafenib and 156 to placebo (Figure 1). The median (IQR) age was 67 (60, 73) years. Of the 313 patients randomised, 277 (88.5%) percent were male, 195 (62.3%) had an ECOG PS of 0, and 251 (80.2%) had cirrhosis. All patients were Child Pugh A at screening, and at randomisation, Child Pugh score was 5 in 220 (70.3%), 6 in 73 (23.3%) and 8 (2.6%) of 313 patients had become Child Pugh B. The most common known single aetiology for liver disease was alcohol. The patient characteristics were well balanced (Table 1). The median (IQR) daily dose of sorafenib was 660mg (389.2, 800.0) compared with 800mg (758.2, 800.0) for placebo and the median (IQR) duration (days) of treatment was 120.0 days (43.0, 266.0) versus 162.0 days (70.0, 323.5) (Table 2).

Overall, 274 and 340 DEB-TACE procedures were performed within the sorafenib-treated and placebo patients respectively; 268 (97.8%) of 274, and 326 (95.3%) of 340 within the first 12 months from randomisation. The most commonly used bead size used was 100-300µm which was used in 205 (74.8%) of 274 embolization procedures and 240 (70.6%) of 340 for the sorafenib and placebo groups respectively. Of the 274 and 340 embolization procedures, 100% of the loaded beads (two vials) were administered in 144 (52.6%) and 203 (59.7%), and the end-point was reached in 232 (84.7%) and 275 (80.9%) respectively. At least one DEB-TACE was delivered to 285 (91.1%) of all patients; 140 (89.2%) of 157 in the

sorafenib-treated group and 145 (92.9%) of 156 in the placebo-treated group. Fifty-six (35.9%) patients on the placebo arm received post-progression sorafenib.

Efficacy

The formal interim futility analysis of PFS was performed in July 2015 and resulted in a treatment HR 1.03 (95%CI 0.75-1.42, p=0.85) which led to early trial closure. An analysis was performed on the final data which included additional data accrued during trial closure period, by which point 31 patients had fully withdrawn from the study, the median follow-up was 620.0 days, and 246 PFS and 164 OS events had been observed. Regarding the primary endpoint, based on HR 0.99 (95%CI 0.77-1.27, p=0.94), there was no evidence of a difference in PFS between the sorafenib-treated group and the placebo-treated group; median PFS (days) was 238.0 (95% CI 221.0-281.0) vs 235.0 (95% CI 209.0-322.0) respectively (Figure 2A). A high proportion of scans (22%) were not reported by central review making robust interpretation of outcomes by central review unreliable.

Similarly, there was no evidence of a difference in TTP; HR 0.88 (95% CI 0.67, 1.17, p = 0.38) with a median (days) of 326.0 (95% CI 240.0-410.0) vs 320.0 (95% CI 234.0-400.0), nor for OS with HR 0.91 (95% CI 0.67-1.24, p=0.57) with a median survival 631.0 (95% CI 437.0-879.0) and 598.0 (95% CI 500.0-697.0) (Figure 2B and C). Sensitivity analyses involving adjustment for prognostic factors identified through univariable analyses confirmed no evidence of a difference for all survival measures: PFS HR 1.00 (95% CI 0.78, 1.28; p=0.99); OS HR 0.99 (95% CI 0.73, 1.35; p=0.95); TTP HR 0.87 (95% CI 0.66, 1.16; p=0.35). Furthermore, analyses in the PP population, which comprised 113 sorafenib-treated and 134 placebo patients respectively, also revealed no evidence of a difference for all survival measures. The

PH assumption was upheld throughout. The HAP score was also confirmed as a robust method of prognostic stratification resulting in a median overall survival (days) of 946.0 (95% CI 641.0, 1316), 631.0 (95% CI 510.0, 816.0), 463.0 (95% CI 259.0, 573.0) and 169.0 (95% CI 86.0, 420.0) for HAP A, B, C and D respectively (Figure 2D), but in the subgroup analysis, there was no indication of a treatment effect in any HAP category (Figure 3). Sub-group analyses according to AFP, tumour size, ECOG PS, Hep-C and focality did not suggest a survival benefit for either treatment arm suggesting that sorafenib did not confer benefit, even in the high-risk group (Figure 3).

According to RECIST v1.1, the overall response rate (ORR), defined as complete response (CR) or partial response (PR), for the sorafenib and placebo-treated group was 56 (35.7%) of 157 and 49 (31.4%) of 156 patients, and the disease control rate (DCR) [(CR, PR and stable disease (SD)] was 117 (74.5%) and 121 (77.6%) (Table 3). Response was also assessed locally using modified RECIST (mRECIST) which resulted in an ORR in 84 (53.5%) of 157 compared with 81 (51.9%) of 156 patients, and DCR of 117 (74.5%) and 120 (76.9%). Comparing RECIST v1.1 and mRECIST in the 157 sorafenib and 156 placebo-treated patients demonstrated a very similar rate of progression; 32 (10.2%) versus 28 (8.9%), but differences were observed in the other response criteria; CR 9 (2.9%) versus 81 (25.9%), PR 96 (30.7%) versus 84 (26.8%), and SD 133 (42.5%) versus 72 (23.0%).

Quality of life

Overall, 1764 QOL forms were returned by 289 (92.3%) of 313 patients, with 140 (89.2%) of 157 patients allocated to sorafenib, and 149 (94.2%) of 156 to the placebo-treated group returning at least one QOL form. According to QLQ-30, both

the social and role functioning scales were found to be 6% lower on average (p=0.045 and p=0.050) for patients in the sorafenib-treated group (Figure 4). Of the symptom scales, diarrhoea and appetite loss were found to be 13% and 10% higher on average in the sorafenib treated group (p=0.0095 and p=0.0018 respectively). According to HCC-18, nutritional problems were on average 7% worse in the sorafenib-treated group (p=0.0084). No evidence of non-zero interactions was observed. No significant differences were observed in other QOL scales.

Safety

Safety was assessed in all patients. The addition of sorafenib did not appear to increase toxicity associated with DEB-TACE as evidenced by similar rates of abdominal pain and nausea (Table 4). The major differences between the two arms were consistent with well-known toxicities associated with sorafenib, namely stomatitis, diarrhoea, hand foot skin reaction (HFSR), rash and bleeding which were all more common in the sorafenib treated patients. Deaths were classified as treatment related if the death was reported as possibly, probably or definitely related, by the local primary investigator. There were three deaths in each arm that were attributed to DEB-TACE occurring between 36.0 days and 249.0 days after randomisation. Four deaths were attributed to study drug, one of which, based on blinded review, was in the placebo-treated arm and was caused by massive variceal haemorrhage. Of the three treatment-related deaths in the sorafenib-treated arm, one died following acute liver failure 14.0 days after randomisation, the second died of infection 134.0 days after randomisation and the third died of hepatorenal failure 250.0 days after randomisation.

DISCUSSION

The combination of sorafenib and TACE has been evaluated in a number of single arm phase 1 and 2 trials in which both sequential and concurrent administration has been shown to be feasible and safe [20-23]. Sequential therapy was found to be ineffective in a large randomised controlled trial conducted in Japan and South Korea in which patients with at least 25% necrosis after TACE were randomised to sorafenib or placebo 1-3 months post-TACE[24]. There was no significant difference in TTP but the daily dose of sorafenib administered was very low; median 387mg. In addition, the anti-angiogenic agent brivanib has also been evaluated as an adjuvant therapy after TACE in a large phase 3 trial which was terminated early after randomisation of 502 patients when intention to treat analysis showed no improvement in OS. However, there is a strong rationale for concurrent rather than sequential therapy given the potential of sorafenib to suppress the angiogenic effect of VEGF released by the acute hypoxia induced by TACE. The feasibility of this approach was first demonstrated in an initial phase 1 trial which evaluated escalating doses of sorafenib combined with doxorubicin-based conventional TACE cTACE, and confirmed that sorafenib could be safely given at full dose continuously from seven days pre-TACE[20]. In support of the rationale for the combination, the levels of plasma VEGF were found to decrease after combined therapy in contrast to increases previously reported in response to TACE alone. A subsequent phase 2 trial confirmed the safety of this approach in combination with DEB-TACE and also reported a DCR of 95%[21]. Most recently, a global placebo controlled randomised phase 2 trial (SPACE) has been reported for which TTP was the primary endpoint[25]. Patients were randomly allocated to sorafenib 400mg twice-daily or matched placebo commencing 2-7 days before the first TACE performed using DEB-TACE. Further DEB-TACE was given according to fixed schedule at cycle 3, 7 and 13 of a 4 week

cycle. The primary endpoint was determined by central radiological review according to mRECIST criteria. The SPACE trial did not demonstrate a clinically meaningful improvement in TTP with the addition of sorafenib but there were significant methodological flaws which were acknowledged by the authors and that may have compromised the outcome. First, almost 30% patients were not evaluable for the primary endpoint since a primary target lesion could not be defined by the central reviewers. Second, the strict criteria for retreatment resulted in a high rate of non-compliance with 30% receiving further TACE in breach of the protocol. Third, there were significant differences between the treatments delivered in different geographical locations which might have contributed to different outcomes, and finally, although OS was a pre-defined secondary endpoint the trial was reported before median OS had been reached.

TACE 2 is the first randomised placebo controlled phase 3 trial to explore the concurrent administration of sorafenib and DEB-TACE. The aim was to establish if combination treatment with sorafenib and DEB-TACE was more effective than treatment with DEB-TACE alone (controlled with placebo). Since sorafenib was standard of care for patients progressing after TACE, and in order to ensure patients were not disadvantaged by participation, all patients were unblinded on progression and allowed to crossover to sorafenib if they were on the placebo arm. There was no post-progression therapy recommended for those on sorafenib since, during the recruitment period, there were no effective second line therapies available. We reasoned that the high rate of crossover to sorafenib may obscure any benefit of the combination if OS was chosen as the primary endpoint. Furthermore, the choice of TTP as an endpoint might obscure toxicity leading to death in the combination arm. Hence, we felt that PFS was the most appropriate primary endpoint but both OS and

TTP were included as secondary endpoints. In contrast to the SPACE trial, the endpoint for TACE 2 was determined by local review. Study drug was commenced 2-5 weeks before DEB-TACE allowing a suitable period to establish a tolerable dose and subsequent DEB-TACE was according to clinical demand rather than a fixed schedule. Finally, whilst the SPACE trial was a global study, TACE 2 was conducted exclusively in the UK and recruited over a longer period thereby providing sufficient follow-up to report mature survival data. Despite these important differences, TACE 2 and SPACE were similar in the treatment delivered; the median dose of sorafenib was approximately 25% lower than that of placebo and was given for a shorter period in both studies. In TACE 2, the administration of sorafenib did not appear to compromise the subsequent delivery or efficacy of TACE since the numbers of patients who received at least one DEB-TACE was equivalent between arms, as was the volume of DC Beads administered and the proportion of patients achieving the angiographic endpoint. However, 48% patients in the sorafenib arm received less than two DEB-TACE treatments compared with 34% in the placebo arm and there were fewer TACE procedures in the first 12 months in sorafenib arm compared with the placebo arm. Possible explanations for fewer TACE procedures being performed in the sorafenib arm include toxicity from sorafenib precluding TACE, or that the efficacy of sorafenib obviated the need for TACE. The fact that the clinical outcomes of the two arms were equivalent favour the later explanation although an effect of additional toxicity cannot be excluded. Indeed, the analyses of QOL revealed some detriment to functioning, and increased symptoms for patients receiving sorafenib. In each of scales that were found to differ, graphical analyses suggest that increased diarrhoea continued throughout the analysed period, whilst for appetite loss and nutritional symptoms, and the role and social functioning scales, the differences were

most pronounced in the period up to 180 days post-randomisation. Since gastrointestinal and dietary complications are recognised side effects of sorafenib and TACE, these findings are plausible, especially in the period where both TACE and sorafenib are received. Equally, it is plausible that role and social functioning could deteriorate on receipt of combined therapy. Other than for diarrhoea, there was less difference in average QOL for these scales beyond 180 days. However, at approximately 270.0 days there was a suggestion of renewed detriment. We note that this coincides approximately with the median PFS time.

Despite the optimal design and delivery of the TACE 2 trial, comparison of the two arms did not provide evidence of a significant or meaningful difference between groups in PFS, OS and TTP. Similarly, although not formally compared, DCR and best response did not appear to differ between treatments. These results, taken together with the SPACE trial provide definitive evidence that combined therapy does not improve outcome compared with DEB-TACE alone. In light of this, there remains an unmet need to improve outcomes for intermediate stage HCC by exploring alternative systemic therapies combined with TACE. To this end, TACE 2 has provided useful data to inform the design of future TACE-based trials. First, we have prospectively evaluated both RECIST v1.1 and mRECIST as radiological response criteria and confirm our previously published retrospective finding, that progression is equivalent regardless of which criteria are applied[26]. Hence, for the assessment of both TTP and PFS, either RECIST v1.1 or mRECIST can be used. The major difference between the two criteria is in the definition of CR which was 2.9% by RECIST v1.1 compared with 25.9% by mRECIST.

Within the context of a prospective trial, we have also validated the HAP score which was designed to provide prognostic information for patients undergoing TACE[27]. The

data points for the HAP score were collected prospectively as part of the TACE 2 data-set and, as in our original study, the HAP score was able to define four distinct prognostic groups with respect to overall survival. Those with a HAP score of D had a 6 fold increased risk of death (HR 5.8, 95% CI 3.21, 10.6, p<0.001) compared to HAP A and their median survival was only 169.0 days. We therefore propose that the HAP score should be used as a stratification factor for TACE trials in future.

In summary, the TACE 2 trial contributes compelling evidence that the concurrent administration of sorafenib with DEB-TACE does not improve outcomes compared to DEB-TACE alone, and also provides valuable lessons to inform future trial development.

Contributors

Concept and design; TM, RF, DS, PJJ, DHP. Obtaining funding; TM, DS, CS, PJJ, DHP. Analysis and interpretation of data; TM, RF, JNP, PJJ, DHP, Data acquisition; TM, YTM, PJR, MWJ, RS, LW, AW, NH, TRJE, PC, RH, DC, JNP, PJJ, DHP. Drafting of manuscript; TM, RF, PJJ, DHP. Manuscript review; All

Declaration of Interests

TM held the grant from Bayer PLC and BTG PLC, and reports personal fees from BMS, Eisai, Ipsen and Merck and Bayer. YTM reports personal fees from Bayer and Baxalta. PR reports grant support from Sanofi and personal fees from Bayer, Sirtex, Celgene, Roche, Sanofi and Amgen. LW received support from Bayer to attend conference. NH reports personal fees from BTG, Boston Scientific and Terumo. TRJE reports support for trials and fees to the Institution from Bayer, BMS, Clovis, Karus Therapeutics, Baxalta, Celgene, Eisai, GSK, Otsuka, Roche, TC Biopharm, Immunova, Basilea, e-Therapeutics, Immunocore, Vertex, Verastem, Daiichi and

Merck. PC reports personal fees from Bayer. RH reports personal fees from BTG and Bayer. DC reports grant funding from Amgen, Astra Zeneca, Bayer, Celgene, Medimmune, Merck Serono, Merrimack and Sanofi. DHP reports grant personal fees from Beyer.The other authors declared no conflict of interest.

Acknowledgements

This study was sponsored by UCL, London, UK, endorsed by Cancer Research UK and adopted into the NIHR portfolio. Trial management was performed by Cancer Research UK Clinical Trials Unit University of Birmingham with invaluable support from Anne-Marie Hodgkins, Donna Smith, Sonia Fox and Jenny Barnwell who acted as trial coordinators during the course of the study. TM is part funded by the NIHR University College London Hospitals Biomedical Research Centre. MWJ is supported by NIHR Biomedical Research Unit in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and University of Nottingham. We thank the Members of the Independent Data Monitoring Committee which included Christopher Russell, Peter Clark, and Roger Ahern, and Members of the Trial Steering Committee which included Nick Reed, Nick Reed, Fergus Macbeth, Richard Stephens, Andrew Clamp. Finally, we are profoundly grateful to the patients who participated in this trial and the relatives for their support

Table 1: Baseline characteristics. Measures are N (%) for categories, and median (IQR) for continuous data.

	TACE + Sorafenib (n=157)	**TACE + Placebo (n=156)**
Male	139 (89%)	138 (88%)
Age (years)	65 (57, 71)	68 (63, 74)
AFP (KU/L)	23 (5, 241)	25 (5, 280)
Creatinine (µ mol/L)	75 (64, 89)	75 (65, 92)
Bilirubin (µ mol/L)	14 (9, 21)	13 (10, 20)
ECOG		
0	98 (62%)	97 (62%)
1	58 (37%)	58 (37%)
Not known	1 (1%)	1 (1%)
Disease focality		
1	59 (38%)	40 (26%)
2	33 (21%)	41 (26%)
3	16 (10%)	17 (11%)
> 3	42 (27%)	49 (31%)
Not known	7 (4%)	9 (6%)
Unilobar	94 (60%)	76 (49%)
Patient has Cirrhosis	129 (82%)	122 (78%)
Etiology of cirrhosis		
Alcohol	44 (34%)	40 (33%)
Hep C	15 (12%)	9 (7%)
Hep C, Alcohol	10 (8%)	12 (10%)
Hep B	7 (5%)	7 (6%)
Hep B, Hep C	3 (2%)	3 (2%)
Hep B, Hep C, Alcohol	3 (2%)	2 (2%)
Hep B, Alcohol	2 (2%)	2 (2%)
Other	45 (35%)	47 (39%)
Diagnosis Method		
Histology	35 (22%)	47 (30%)
Radiology	122 (78%)	106 (68%)
Not known	0 (0%)	3 (2%)
Dominant tumour (cm)	6 (4, 8)	5 (4, 8)
Prior Liver Resection or Ablative Therapy	11 (7%)	20 (13%)
Child-Pugh Score		
5	106 (68%)	114 (73%)
6	39 (25%)	34 (22%)
7	4 (3%)	2 (1%)
8	1 (1%)	1 (1%)
Not known	7 (4%)	5 (3%)
HAP score		
HAP A	44 (28%)	43 (28%)
HAP B	52 (33%)	61 (39%)

HAP C	41 (26%)	34 (22%)
HAP D	14 (9%)	10 (6%)

Table 2: Study drug and DEB-TACE administration and efficacy outcomes. Measures are N (%) for categories, and median (IQR) for continuous data.

	TACE + Sorafenib (157)	**TACE + Placebo (156)**
No. TACE procedures		
0	11 (7.0)	7 (4.5)
1	65 (41.4)	44 (28.2)
2	40 (25.5)	55 (35.3)
3	21 (13.4)	22 (14.1)
4	10 (6.4)	14 (9.0)
>5	4 (2.5)	10 (6.4)
Not known	6 (3.8)	4 (2.6)
TACE procedures in first 12 months	268	326
Duration of sorafenib/placebo treatment		
	120.0 days (43.0, 266.0)	162.0 days (70.0, 323.5)
Patient duration-weighted median sorafenib/placebo dose (mg)		
	660.0 mg (389.2, 800.0)	800.0 mg (758.2, 800.0)

Table 3: Disease response assessed locally using RECIST v1.1 and Modified RECIST criteria.SD=stable disease; PR=partial response; CR=complete response; PD=progressive disease

	TACE + Sorafenib n (%) (n=157)		**TACE + Placebo n (%)** (n=156)	
Response	**RECIST v1.1**	**mRECIST**	**RECIST v 1.1**	**mRECIST**
Complete Response (CR)	4 (2.5)	45 (28.7)	5 (3.2)	36 (23.1)
Partial Response (PR)	52 (33.1)	39 (24.8)	44 (28.2)	45 (28.8)
Stable Disease (SD)	61 (38.9)	33 (21.0)	72 (46.2)	39 (25.0)
Disease Progression (PD)	15 (9.6)	13 (8.3)	17 (10.9)	15 (9.6)
ORR (CR + PR)	56 (35.7)	84 (53.5)	49 (31.4)	81 (51.9)
DCR (CR + PR + SD)	117 (74.5)	117 (74.5)	121 (77.6)	120 (76.9)
Not evaluated/available	25 (15.9)	27 (17.2)	18 (11.5)	21 (13.5)

Table 4: CTC Adverse events categories (occurring in 10% or more of patients)

	TACE + Sorafenib (N=157)				**TACE + Placebo (N=156)**			
	Grade				**Grade**			
	1/2 (%)	**3 (%)**	**4 (%)**	**5 (%)**	**1/2 (%)**	**3 (%)**	**4 (%)**	**5 (%)**
Fatigue	62.4	17.8	0.6	0	64.7	12.8	0.6	0
Abdominal Pain	46.5	12.7	0	0	49.4	7.7	0	0
Diarrhoea	45.2	9.6	0.6	0	28.8	2.6	0	0
Nausea	44.6	1.3	0	0	42.3	0.6	0	0
Rash	36.3	1.9	0	0	20.5	0	0	0
Hand Foot	33.8	7.6	0	0	8.3	0	0	0
Stomatisis	22.9	3.2	0	0	10.9	0.6	0	0
Bleed	13.4	4.5	1.3	0	9.0	0.6	0.6	0
Anorexia	31.8	1.9	0	0	32.1	1.3	0	0
Constipation	14.6	0	0	0	29.5	0	0	0
Gastrointestinal disorders	4.5	10.2	1.3	0	3.8	6.4	1.3	0.6
Pain	14.0	0	0	0	11.5	0	0	0
Vomiting	13.4	1.3	0	0	10.3	0	0.6	0
Dry Skin	13.4	0	0	0	9.6	0.6	0	0
Alopecia	13.4	0	0.6	0	9.0	0	0	0
Pruritus	7.0	0	0	0	13.5	1.3	0	0
Weight Loss	12.1	0	0	0	8.3	0	0	0
General disorders and administration site conditions	4.5	5.1	0	0.6	5.1	1.9	0	1.3

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**(5): E359-86.

2. European Association For The Study Of The L, European Organisation For R, Treatment Of C. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**(4): 908-43.

3. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**(9319): 1734-9.

4. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; **37**(2): 429-42.

5. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology* 2002; **35**(5): 1164-71.

6. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007; **30**(1): 6-25.

7. Meyer T, Kirkwood A, Roughton M, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. *Br J Cancer* 2013; **108**(6): 1252-9.

8. Brown KT, Do RK, Gonen M, et al. Randomized Trial of Hepatic Artery Embolization for Hepatocellular Carcinoma Using Doxorubicin-Eluting Microspheres Compared With Embolization With Microspheres Alone. *J Clin Oncol* 2016; **34**(17): 2046-53.

9. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev* 2011; (3): CD004787.

10. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; **33**(1): 41-52.

11. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer* 2014; **111**(2): 255-64.

12. Vogl TJ, Lammer J, Lencioni R, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR Am J Roentgenol* 2011; **197**(4): W562-70.

13. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**(4): 378-90.

14. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**(1): 25-34.

15. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**(13): 1344-54.

16. Bruix J, Sherman M, Practice Guidelines Committee AAftSoLD. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**(5): 1208-36.

17. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**(2): 228-47.

18. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials* 2010; **7**(3): 197-208.

19. Billingham LJ, Abrams KR. Simultaneous analysis of quality of life and survival data. *Stat Methods Med Res* 2002; **11**(1): 25-48.

20. Dufour JF, Hoppe H, Heim MH, et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. *Oncologist* 2010; **15**(11): 1198-204.

21. Pawlik TM, Reyes DK, Cosgrove D, Kamel IR, Bhagat N, Geschwind JF. Phase II trial of sorafenib combined with concurrent transarterial chemoembolization with drug-eluting beads for hepatocellular carcinoma. *J Clin Oncol* 2011; **29**(30): 3960-7.

22. Chung YH, Han G, Yoon JH, et al. Interim analysis of START: Study in Asia of the combination of TACE (transcatheter arterial chemoembolization) with sorafenib in patients with hepatocellular carcinoma trial. *Int J Cancer* 2013; **132**(10): 2448-58.

23. Erhardt A, Kolligs F, Dollinger M, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. *Cancer Chemother Pharmacol* 2014; **74**(5): 947-54.

24. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. *Eur J Cancer* 2011; **47**(14): 2117-27.

25. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016; **64**(5): 1090-8.

26. Gillmore R, Stuart S, Kirkwood A, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. *J Hepatol* 2011; **55**(6): 1309-16.

27. Kadalayil L, Benini R, Pallan L, et al. A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. *Ann Oncol* 2013; **24**(10): 2565-70.

FIGURE LEGENDS

Figure 1: Consort Diagram

Figure 2: Kaplan Meier plots for survival outcome measures: (a) progression free survival; (b) overall survival; (c) time to progression; (d) overall survival by HAP Score

Figure 3: subgroup analyses of progression free survival (a) and overall survival (b) for known prognostic factors. * Not pre-planned

Figure 4: Restricted cubic splines fit to quality of life scales measured through EORTC QLQ -c30 and -HCC18. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning, but a high score for a symptom scale represents a high level of symptomatology/problems. Functioning: Role (a), Social (b). Symptom scales: Appetite loss (c), Diarrhoea (d), Nutrition (e).

Appendix 1

PI	Centre	Patients	(%)
Dr Yuk Ting Ma	The Queen Elizabeth Hospital	60	19.2
Dr Paul Ross	King's College Hospital	59	18.8
Dr Martin James	Queen's Medical Centre, Nottingham	39	12.5
Richard Sturgess	University Hospital Aintree	39	12.5
Prof Tim Meyer	Royal Free Hospital	36	11.5
Dr Lucy Wall	Royal Infirmary of Edinburgh	10	3.2
Prof Jeff Evans	Beatson West of Scotland Cancer Centre	9	2.9
Dr Nigel Hacking	Southampton General Hospital	9	2.9
Dr Peter Collins	Bristol Royal Infirmary	8	2.6
Dr Richard Hubner	Christie Hospital	7	2.2
Dr Jonathan Evans	Royal Liverpool University Hospital	7	2.2
Dr Harpreet Wasan	Hammersmith Hospital	6	1.9
Dr Rebecca Jones	St James's University Hospital	6	1.9
Prof David Cunningham	Royal Marsden Hospital Sutton	5	1.6
Dr Louisa Vine	Derriford Hospital	4	1.3
Dr Paul Kooner	St Bartholomew's Hospital	3	1.0
Mr Iain Tait	Ninewells Hospital	2	0.6
Prof David Cunningham	Royal Marsden Hospital London	2	0.6
Dr Kate Sumpter	Freeman Hospital	1	0.3
Prof Anthony Watkinson	Royal Devon and Exeter Hospital	1	0.3