Sorafenib in combination with transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma (TACE 2): a randomised placebo-controlled, double-blind, phase 3 trial

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Summary

Background Transarterial chemoembolisation (TACE) is the standard of care for patients with intermediate stage hepatocellular carcinoma, while the multikinase inhibitor sorafenib improves survival in patients with advanced disease. We aimed to determine whether TACE with sorafenib improves progression-free survival versus TACE with placebo.

Methods We did a multicentre, randomised, placebo-controlled, phase 3 trial (TACE 2) in 20 hospitals in the UK for patients with unresectable, liver-confined hepatocellular carcinoma. Patients were eligible if they were at least aged 18 years, had Eastern Cooperative Oncology Group performance status of 1 or less, and had Child-Pugh A liver disease. Patients were randomised 1:1 by computerised minimisation algorithm to continuous oral sorafenib (400 mg twice-daily) or matching placebo combined with TACE using drug-eluting beads (DEB-TACE), which was given via the hepatic artery 2–5 weeks after randomisation and according to radiological response and patient tolerance thereafter. Patients were stratified according to randomising centre and serum α-fetoprotein concentration (<400 ng/mL and ≥400 ng/mL). Only the trial coordinator was unmasked to treatment allocation before patient progression during the study. The primary endpoint was progression-free survival defined as the interval between randomisation and progression according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) or death due to any cause, and was analysed by intention-to-treat. Safety was 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 Between Nov 4, 2010, and Dec 7, 2015, the trial enrolled 399 patients and was terminated after a planned interim futility analysis. 86 patients failed screening and 313 remaining patients were randomly assigned: 157 to sorafenib and 156 to placebo. The median daily dose was 660 mg (IQR 389·2–800·0) sorafenib versus 800 mg (758·2–800·0) placebo, and median duration of therapy was 120·0 days (IQR 43·0–266·0) for sorafenib versus 162·0 days (70·0–323·5) for placebo. There was no evidence of difference in progression-free survival between the sorafenib group and the placebo group (hazard ratio [HR] 0·99 [95% CI 0·77–1·27], p=0·94); median progression-free survival was 238·0 days (95% CI 221·0–281·0) in the sorafenib group and 235·0 days (209·0–322·0) in the placebo group. The most common grade 3–4 adverse events were fatigue (29 [18%] of 157 patients in the sorafenib group vs 21 [13%] of 156 patients in the placebo group), abdominal pain (20 [13%] vs 12 [8%]), diarrhoea (16 [10%] vs four [3%]), gastrointestinal disorders (18 [11%] vs 12 [8%]), and hand–foot skin reaction (12 [8%] and none). At least one serious adverse event was reported in 65 (41%) of 157 patients in the sorafenib group and 50 (32%) of 156 in the placebo group, and 181 serious adverse events were reported in total, 95 (52%) in the sorafenib group and 86 (48%) in the placebo group. Three deaths occurred in each group that were attributed to DEB-TACE. Four deaths were attributed to study drug; three in the sorafenib group and one in the placebo group.

Interpretation The addition of sorafenib to DEB-TACE does not improve progression-free survival in European patients with hepatocellular carcinoma. Alternative systemic therapies need to be assessed in combination with TACE to improve patient outcomes.

Funding Bayer PLC and BTG PLC.

Introduction

Hepatocellular carcinoma is the sixth most common cancer and the second most common cause of death from cancer worldwide.[1] Less than 30% of patients are eligible for potentially curative therapies such as transplantation, resection, or ablation. For selected patients not suitable for such interventions but who have liver-confined disease, preserved liver function, and good performance status, transarterial chemoembolisation (TACE) is recommended according to international guidelines.[2]

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Research in context

Evidence before the study

We searched PubMed for articles published between Jan 1, 2000, and the start of the TACE 2 trial on Nov 1, 2010, using the search terms, "hepatocellular carcinoma" and "sorafenib". This search yielded two randomised placebo-controlled trials assessing 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 with good performance status and Child-Pugh A liver disease. Additionally, we identified one phase 1 trial that showed the feasibility of combining sorafenib with transarterial chemoembolisation (TACE) in 14 patients with hepatocellular carcinoma, but we identified no randomised trials including the combination of sorafenib and TACE. We therefore initiated the first randomised phase 3 trial of TACE combined with continuous sorafenib with the aim to determine the effect of addition of sorafenib on progression-free survival in patients treated with TACE. We did a subsequent search of PubMed for articles published between Nov 1, 2010, and April 12, 2017, using the search terms "sorafenib", "hepatocellular carcinoma", "TACE", and "randomised". This search identified three prospective trials. One trial was a phase 3 trial comparing sorafenib with placebo in Japanese and Korean patients who had achieved at least 25% tumour necrosis after TACE, which showed no improvement in time to progression for

individuals receiving sorafenib. By contrast, a small randomised trial of 80 patients infected with hepatitis C showed a significant improvement in time to progression for patients treated with TACE after sorafenib treatment compared with placebo. The only randomised trial to assess concurrent sorafenib and TACE was the SPACE trial: a global randomised phase 2 trial, which showed no improvement in time to progression for sorafenib and TACE versus TACE alone. Follow-up in the SPACE trial was too short to provide a meaningful comparison of overall survival.

Added value of this study

To our knowledge, 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 of all available evidence

Together with the existing evidence, we believe that this trial provides definitive evidence that the combination of sorafenib and TACE, while feasible, is not effective, and alternative strategies to improve outcomes for intermediate stage hepatocellular carcinoma should be explored.

The evidence for TACE comes from two small randomised controlled trials and a meta-analysis showing a significant survival benefit for TACE-treated patients compared with those receiving best supportive care.[3–5] In clinical practice, the application of TACE varies widely with regard to embolic particle, chemotherapeutic used, frequency, and schedule of administration.[6] Patient selection also varies in terms of tumour extent, vascular invasion, presence of extrahepatic disease, and performance status. Emerging evidence also calls into question the role of chemotherapy, suggesting that outcomes from bland embolisation (TAE) are equivalent to those of TACE;[7,8] a Cochrane review[9] also questioned the survival benefit attributable to TACE. The introduction of drug-eluting beads (DEB-TACE) has provided a method of embolising tumours with a more controlled local release of chemotherapy. Although this approach has not been shown to be superior to conventional TACE in terms of survival, less chemotherapy-associated toxicity occurs 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 the results of two large placebo-controlled, randomised trials showing a median survival benefit of 2–3 months.[13,14] Sorafenib is a multikinase inhibitor targeting, among others, VEGFR, RAF, and PDGFR thereby exerting both anti-angiogenic and direct antitumour effects. 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 patients who receive TACE. TACE causes acute hypoxia leading to upregulation of VEGF, which might contribute to revascularisation. As such, the rationale is clear to combine TACE with sorafenib, to inhibit both revascularisation and tumour proliferation. We therefore did a randomised, placebo-controlled trial with the aim to assess the role of sorafenib combined with standard DEB-TACE.

Methods

Study design and participants

We did a phase 3 multicentre, randomised, double-blind, placebo-controlled study in 20 hospitals in the UK (appendix). Inclusion criteria included: histological or non-invasive diagnosis according to the American Association for the Study of Liver Diseases (AASLD) criteria,[16] aged 18 years or older, at least one unidimensional lesion measurable according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1),[17] not being a candidate for surgical resection or liver transplant, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less, Child-Pugh A liver disease, haemoglobin of 9 g/L or higher, neutrophil count of at least $1·5 \times 10^9$ cells per L, platelet count of at least 60×10^9 platelets per L, bilirubin of no more than 50 µmol/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of 5 times upper limit of normal

or less, alkaline phosphatase (ALP) of less than 4 times upper limit of normal, creatinine of 1·5 times upper limit of normal or less, international normalised ratio (INR) of 1·5 times upper limit of normal or less, and left ventricular ejection fraction of at least 45%. Exclusion criteria included: extrahepatic metastasis, previous embolisation, systemic therapy or radiotherapy for hepatocellular carcinoma, any contraindication to hepatic embolisation, previous investigational therapy, major surgery or history of bleeding within 4 weeks of trial entry, hepatic encephalopathy, occlusion of the hepatic artery or main portal vein, myocardial infarction within 6 months or prolonged QT/QTc of more than 450 ms. 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 Cancer Research UK Clinical Trial Unit (CRCTU; Birmingham, UK) was responsible for managing the randomisation, drug allocation, and drug discontinuation processes using an online trial management portal. Randomisation was done by randomisation officers based at CRCTU. Sharp Clinical Services (Crickhowell, UK) managed drug labelling and drug dispensing. Patients were randomly assigned, on a 1:1 basis and in a masked fashion, to the sorafenib group or placebo group based on a minimisation randomisation algorithm. Randomisation was stratified by randomising centre and serum α-fetoprotein (AFP) concentration (<400 ng/mL and ≥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 masking 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 suspected unexpected serious adverse reaction. The trial coordinator only did the unmasking after the clinical coordinator had confirmed expectedness for the serious adverse reaction. The result was kept confidential. On disease progression, patients were unmasked to allow for further clinical decision making and for the provision of open-label sorafenib. This process was managed through the online trial management portal by the trial coordinator at CRCTU. The trial statistician had access to the unmasked information in accordance with CRCTU standard operating procedures. At the end of

the study, an unmasked patient randomisation report was run from the system by the statistician and provided to the trial coordinator to match the patient by trial number and date of birth.

Procedures

Oral sorafenib at a dose of 400 mg twice-daily or matching placebo was commenced within 24 h of randomisation and continued until disease progression according to RECIST v1.1. Two dose reductions, level –1 (400 mg once-daily) and level –2 (400 mg alternated days), were defined in the protocol, 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 given 2–5 weeks post-randomisation using drug-eluting

For the **online protocol** see http://www.birmingham.ac.uk/ Documents/college-mds/trials/ crctu/tace2/TACE-2-Protocol-v8-0-28-Jun-2016-Clean-CI-signed.pdf
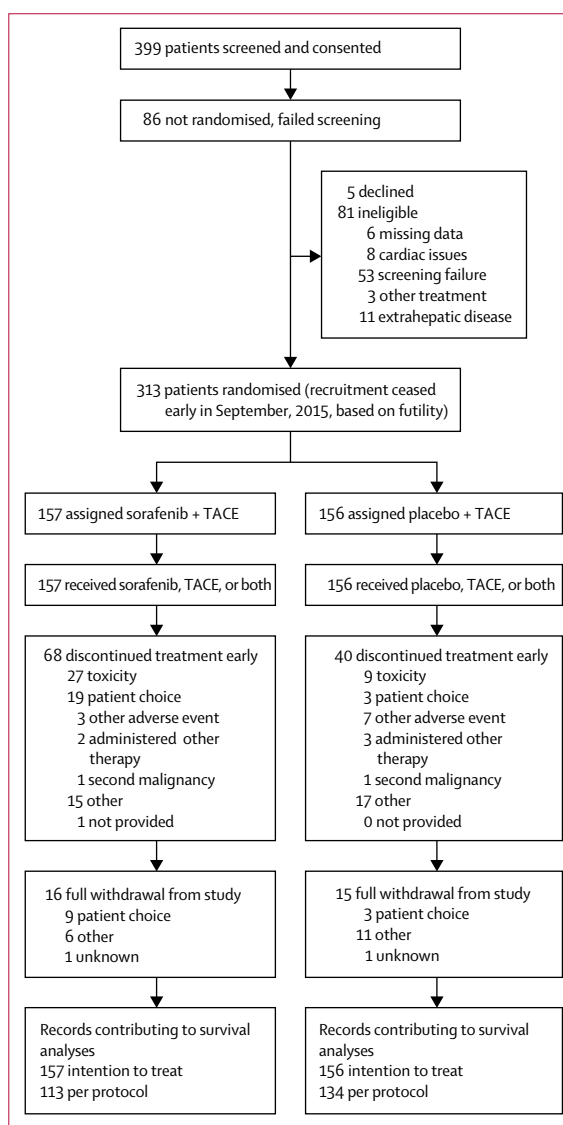

Figure 1: Trial profile

	TACE with sorafenib (n=157)	TACE with placebo (n=156)
Sex		
Male	139 (89%)	138 (88%)
Female	18 (11%)	18 (12%)
Age (years)	65 (57–71)	68 (63–74)
AFP (KU/L)	23 (5–241)	25 (5–280)
Creatinine (μmol/L)	75 (64–89)	75 (65–92)
Bilirubin (μmol/L)	14 (9–21)	13 (10–20)
ECOG PS		
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%)
Cause of cirrhosis		
Alcohol	44 (34%)	40 (33%)
Hepatitis C	15 (12%)	9 (7%)
Hepatitis C and alcohol	10 (8%)	12 (10%)
Hepatitis B	7 (5%)	7 (6%)
Hepatitis B, hepatitis C	3 (2%)	3 (2%)
Hepatitis B, hepatitis C, and alcohol	3 (2%)	2 (2%)
Hepatitis B and 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	3 (2%)
Dominant tumour diameter (cm)	6 (4–8)	5 (4–8)
Previous 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%)
Not known	6 (4%)	8 (5%)

Data are n (%) for categories, and median (IQR) for continuous data. TACE=transarterial chemoembolisation. AFP=α-fetoprotein. ECOG PS=Eastern Cooperative Oncology Group performance status. HAP=hepatoma arterial-embolisation prognostic.

Table 1: **Baseline characteristics**

beads (DC Bead; BTG PLC, London, UK) loaded with doxorubicin 150 mg according to the manufacturer's instructions. Administration 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 (100–300 μm) followed by the larger DC Beads (300–500 μm) to achieve the angiographic endpoint defined as sluggish flow in the main feeding vessels with stasis in the intralesional and perilesional branches. The maximum delivery dose was two vials of DC Beads loaded with 75 mg doxorubicin per vial. All baseline screening tests were required within 28 days of randomisation. Baseline imaging and follow-up imaging was done by CT of the chest and dual phase abdominal CT or contrast enhanced abdominal MRI. The first follow-up imaging was done at week 10 post-randomisation and further DEB-TACE was given as required according to the presence of persistent tumour enhancement. Further follow-up imaging was done at week 22 and every 3 months thereafter. Laboratory evaluation, including haematology, coagulation, biochemistry, and AFP tests, was done during screening and on day 1, 72 h before DEB-TACE, 8 days post-DEB-TACE, week 10, and every 6 weeks thereafter. Left ventricular ejection fraction was estimated by echocardiography or multigated acquisition scan during screening, and electrocardiograms were performed during screening, within 72 h of DEB-TACE, day 7 post-TACE, week 10, and every 6 weeks thereafter. Toxicity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) 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) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ-C30) version 3, EORTC QLQ-HCC18, and the EuroQoL (EQ-5D) questionnaire, which were requested at baseline, pre-TACE, week 10, and every 6 weeks thereafter until progression. On progression, patients were unmasked and entered the post-study treatment period. To avoid delays in unmasking and initiating appropriate treatment on progression, an amendment was implemented during the trial to allow unmasking on local review rather than central review. Patients in the placebo group were offered sorafenib at the discretion of the treating clinician and patients in the sorafenib group could continue if there was deemed to be patient benefit. No standard therapy was recommended for patients progressing on sorafenib who discontinued sorafenib.

Outcomes

The primary endpoint was progression-free survival defined as the interval between randomisation and progression according to RECIST v1.1[17] or death due to any cause. Patients who did not progress or die 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 measured from date of randomisation to death; time to progression, measured from date of randomisation to date of progression; response and disease control according to RECIST v1.1 guidelines; QOL, scored according to the EORTC manuals; and number of TACE procedures given within 12 months of randomisation. Toxicity was assessed in all patients according to NCI CTCAE v4.0 from the start of study treatment until 30 days after last administration of study treatment or until the end of the study. All serious adverse events were assessed with reference to the summary of product characteristics (SmPC) for sorafenib and clinically assessed in a masked fashion. Unmasking only occurred at the point of requirement for suspected unexpected serious adverse event (SUSAR) reporting. Response according to mRECIST[18] was collected prospectively and an exploratory comparison with RECIST v1.1 was planned on completion of the study.

Statistical analysis

The null hypothesis was that the survival distributions were equal, and the alternative, that the survival distributions differed. We calculated that 412 patients were required to detect an improvement in median progression-free survival from 8·9 months to 12·4 months, equating to a hazard ratio (HR) for DEB-TACE and sorafenib of 0·72, with a two-sided α of 0·05, and with 85% power. The design incorporated a formal interim analysis for futility following the method of Freidlin and colleagues,[19] after 147 (43%) of progression-free survival events, at which a HR of 1 or more 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 done in the intention-to-treat population, which included all randomised patients. Further analyses assessed efficacy in the per-protocol population, defined as all patients receiving at least one DEB-TACE and 6 weeks of sorafenib or placebo, and excluding ineligible patients. Safety was assessed in the intention-to-treat population. We analysed the primary outcome of progression-free survival and secondary outcome measures, overall survival and time to progression, through multilevel flexible parametric survival models with adjustment for stratification factors, with randomising centre entered as a random component. We estimated HR with 95% CI, and the placebo group was the reference group in all cases. We did sensitivity analyses with adjustment for prognostic factors identified in univariable analyses. We tested the proportional hazards assumption when applicable. Efficacy was also assessed in prognostic subgroups, including stratification factors, with tests of heterogeneity.

	TACE with sorafenib (n=157)	TACE with placebo (n=156)
Number of TACE procedures		
0	11 (7%)	7 (5%)
1	65 (41%)	44 (28%)
2	40 (26%)	55 (35%)
3	21 (13%)	22 (14%)
4	10 (6%)	14 (9%)
>5	4 (3%)	10 (6%)
Not known	6 (4%)	4 (3%)
TACE procedures in first 12 months	268	326
Duration of treatment (days)	120·0 (43·0–266·0)	162·0 (70·0–323·5)
Patient duration-weighted median dose (mg)	660·0 (389·2–800·0)	800·0 (758·2–800·0)

Data are n (%) for categories, and median (IQR) for continuous data. DEB-TACE=drug-eluting beads transarterial chemoembolisation. DEB=drug-eluting beads. TACE=transarterial chemoembolisation.

Table 2: Study drug and DEB-TACE administration and efficacy outcomes

QOL was explored graphically by fitting smoothed trends to the observed data, and analysed QOL data 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. We assumed patients had the worst possible symptomatic score, or lowest level of functioning at death. We assessed model fit for survival and QOL measures through Akaike-information criterion and Bayesian-information criterion. Modelling of the EQ5D utility score with overall survival on the basis of the integrated quality survival product methods of Billingham and colleagues[20] will be reported in a subsequent publication. We report safety data descriptively, with adverse events summarised as worst-grade experienced at the patient level for each CTC category, and with frequency of serious adverse events reported by treatment group and their relative expectedness to sorafenib. Deaths deemed associated with treatment must have occurred within 30 days of last treatment. Data were analysed with Stata version 14. The trial was registered on the European Clinical Trials Database (EudraCT Number: 2008-005073-36), the ISRCTN registry (ISRCTN93375053), and ClinicalTrials.gov (NCT01324076).

Role of the 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
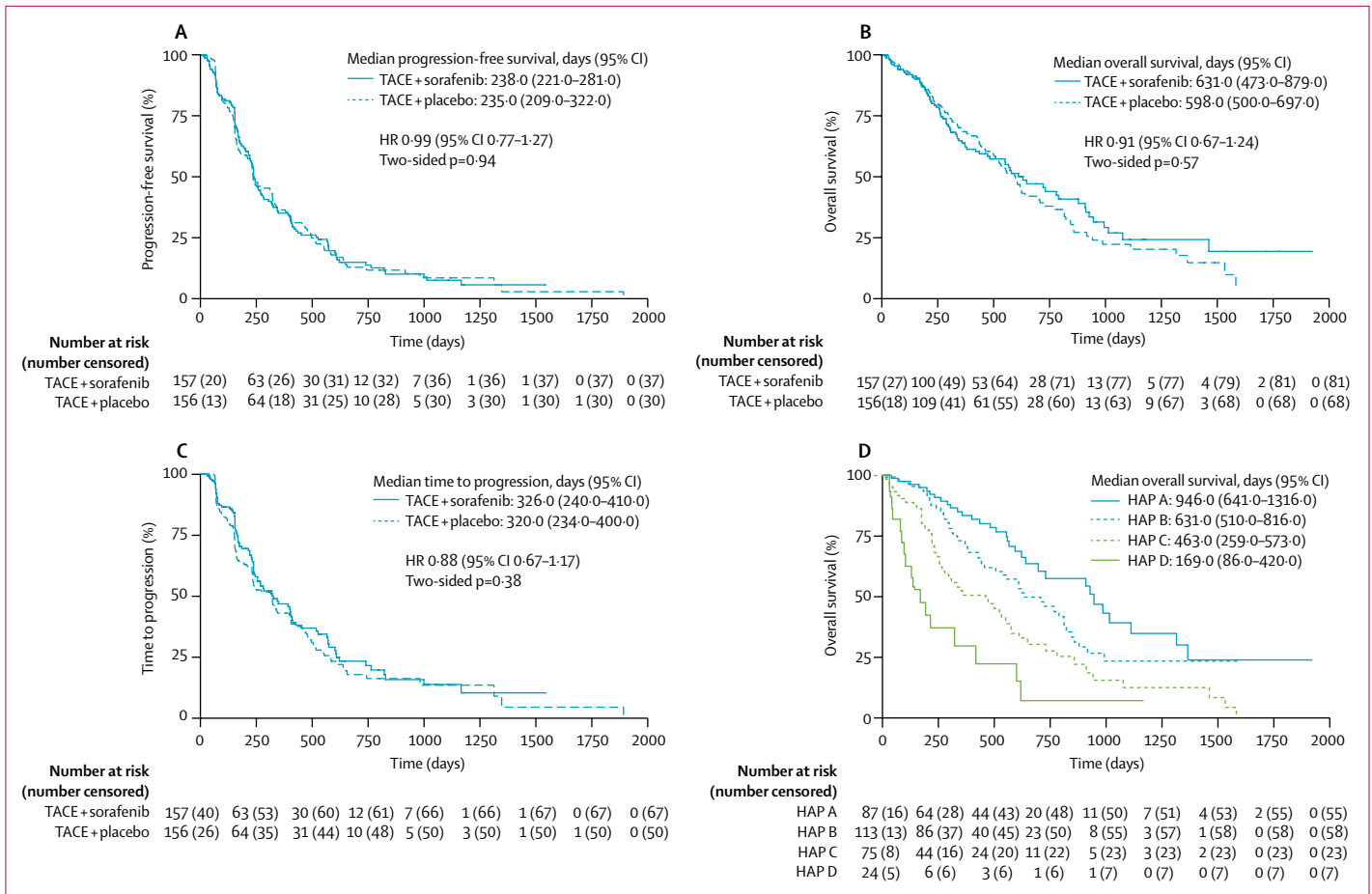
Figure 2: Kaplan-Meier plots for survival outcomes
(A) Progression free survival; (B) overall survival; (C) time to progression; and (D) overall survival by HAP score. HAP=hepatoma arterial-embolisation prognostic. HR=hazard ratio.

(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, and 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. Data collection and analysis was done by the CRCTU. TM, RF, and 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

Between Nov 4, 2010, and Dec 7, 2015, 313 patients were randomised; 157 to sorafenib and 156 to placebo (figure 1). Patient characteristics were similar between groups (table 1). Of the 313 patients randomly assigned to treatment, their median age was 67 years (IQR 60–73), 277 (89%) percent were men, 195 (62%) had an ECOG performance score of 0, and 251 (80%) had cirrhosis (table 1). All patients were Child-Pugh A at screening; at randomisation, Child-Pugh score was 5 in 220 (70%) of

331 patients and was 6 in 73 patients (23%); eight (3%) of 313 patients had become Child-Pugh B (table 1). The most common known single cause for liver disease was alcohol (table 1). The median daily dose of sorafenib was 660 mg (IQR 389·2–800·0) compared with 800 mg (758·2–800·0) for placebo and the median duration of treatment was 120·0 days (IQR 43·0–266·0) versus 162·0 days (70·0–323·5; table 2).

274 DEB-TACE procedures were given within the sorafenib group and 340 procedures were given within the placebo group; 268 (98%) of 274 procedures, and 326 (96%) of 340 procedures were done within the first 12 months from randomisation. The most commonly used bead size was 100–300 μm, which was used in 205 (75%) of 274 embolisation procedures in the sorafenib group and 240 (71%) of 340 procedures in the placebo groups. 100% of the loaded beads (two vials) were administered in 144 (53%) of the 274 embolisation procedures in the sorafenib group and 203 (60%) of the 340 procedures in the placebo group. The angiographic endpoint was reached in 232 (85%) procedures in the sorafenib group and 275 (81%) in the placebo group.

At least one DEB-TACE was delivered to 285 (91%) of all patients; 140 (89%) of 157 in the sorafenib group and 145 (93%) of 156 in the placebo group. 56 (36%) patients in the placebo group received post-progression sorafenib.

The formal interim futility analysis of progression-free analysis was done in July, 2015, and indicated an HR of 1·03 (95% CI 0·75–1·42, p=0·85), which led to early trial closure. We then analysed 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 (95% CI 572–784), and 246 progression-free survival events and 164 overall survival events had been observed. There was no evidence of a difference in progression-free survival, the primary outcome, between the sorafenib group and the placebo group. Median progression-free survival was 238·0 days (95% CI 221·0–281·0) in the sorafenib group versus 235·0 days (209·0–322·0) in the placebo group (HR 0·99 [95% CI 0·77–1·27], p=0·94; figure 2). 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 overall survival between groups: median overall survival was 631·0 days (95% CI 437·0–879·0) in the sorafenib group versus 598·0 days (500·0–697·0) in the placebo group (HR 0·91 [95% CI 0·67–1·24], p=0·57; figure 2). There was also no evidence of a difference time to progression also between the sorafenib group and the placebo group, with an HR of 0·88 (95% CI 0·67–1·17, p=0·38; figure 2); median time to progression was 326·0 days (95% CI 240·0–410·0) in the sorafenib group versus 320·0 (234·0–400·0) in the placebo group. Sensitivity analyses involving adjustment for prognostic factors identified through univariable analyses confirmed no evidence of a difference for all survival measures: the HR for progression-free survival was 1·01 (95% CI 0·78–1·30; p=0·94); the HR for overall survival was 0·99 (95% CI 0·73–1·35; p=0·96); and the HR for time to progression was 0·87 (95% CI 0·66–1·16; p=0·35). Furthermore, analyses in the per-protocol population, which comprised 113 patients in the sorafenib group and 134 in the placebo group, also revealed no evidence of a difference for all survival measures (data not shown). The proportional hazards assumption was upheld throughout. The hepatoma arterial-embolisation prognostic (HAP) score was also confirmed as a robust method of prognostic stratification resulting in a median overall survival of 946·0 days (95% CI 641·0–1316·0) for HAP A, 631·0 days (510·0–816·0) for HAP B, 463·0 days (259·0–573·0) for HAP C, and 169·0 days (86·0–420·0) for HAP D (figure 2); but in the subgroup analysis, there was no indication of a treatment effect in any HAP category (figure 3). Subgroup analyses according to AFP, tumour size, ECOG performance status, hepatitis C aetiology, and focality did not suggest a survival benefit, indicating that sorafenib did not confer benefit for progression-free
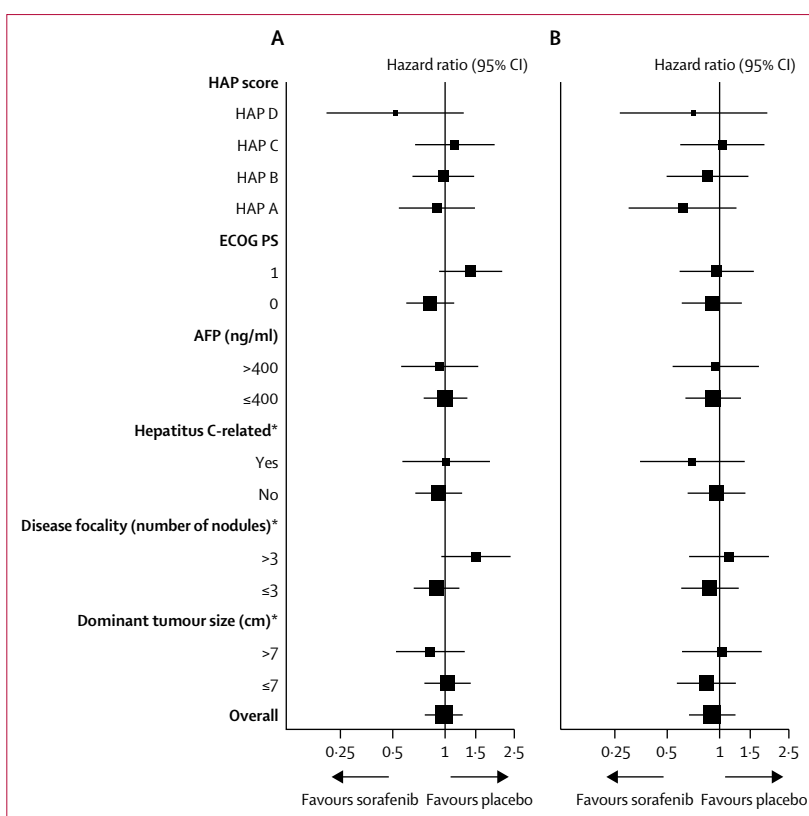

Figure 3: Subgroup analyses of (A) progression-free survival and (B) overall survival for known prognostic factors
HAP=hepatoma arterial-embolisation prognostic. ECOG PS=Eastern Cooperative Oncology Group performance status. AFP=α-fetoprotein levels. *Not pre-planned.
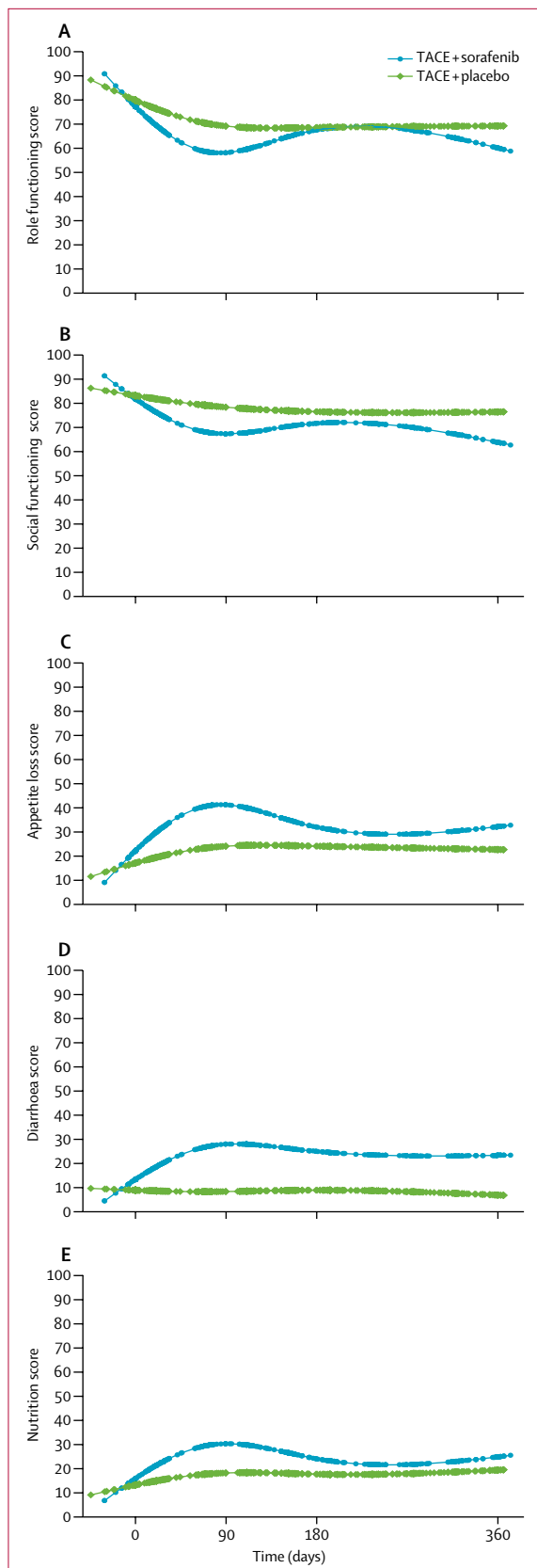
	TACE with sorafenib (n=157)		TACE with placebo (n=156)	
	RECIST v1.1	mRECIST	RECIST v1.1	mRECIST
Complete response	4 (3%)	45 (29%)	5 (3%)	36 (23%)
Partial response	52 (33%)	39 (25%)	44 (28%)	45 (29%)
Stable disease	61 (39%)	33 (21%)	72 (46%)	39 (25%)
Disease progression	15 (10%)	13 (8%)	17 (11%)	15 (10%)
Overall response*	56 (36%)	84 (54%)	49 (31%)	81 (52%)
Disease control†	117 (75%)	117 (75%)	121 (78%)	120 (77%)
Not evaluated or available	25 (16%)	27 (17%)	18 (12%)	21 (14%)

Data are n (%) for categories, and median (IQR) for continuous data. RECIST=Response Evaluation Criteria In Solid Tumors. mRECIST=modified RECIST. TACE=transarterial chemoembolisation. *Complete or partial response. †Complete response, partial response, or stable disease.

Table 3: Disease response assessed locally using RECIST v1.1 and modified RECIST criteria

survival or overall survival, even in the high-risk group—defined by a higher HAP score, high AFP or greater tumour burden (figure 3).

According to RECIST v1.1, 56 (36%) of 157 patients in the sorafenib group and 49 (31%) of 156 in the placebo group had an overall response (ie, complete response or partial response; table 3); 117 (75%) patients in the sorafenib group and 121 (78%) in the placebo group achieved disease control (ie, complete response, partial

Figure 4: Restricted cubic splines fit to quality-of-life scales
Quality of life was measured through EORTC QLQ-C30 and QLQ-HCC18.
All 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 or healthy level of functioning, but a high score for a symptom scale represents a high level of symptomatology or problems. Functioning scales were (A) role, and (B) social. Symptom scales were (C) appetite loss, (D) diarrhoea, and (E) nutrition.

response, or stable disease; table 3). Response was also assessed locally using modified RECIST (mRECIST), as shown in table 3.

1764 QOL questionnaire forms were returned by 289 (92%) of 313 patients, with 140 (89%) of 157 patients in the sorafenib group, and 149 (96%) of 156 in the placebo group returning at least one form. According to multilevel regression of QLQ-C30 scores over 360 days, both the mean social and role functioning scales were found to be up to 6% lower (p=0·045 and p=0·050) for patients in the sorafenib group (figure 4). Of the symptom scales, mean diarrhoea score was up to 13% higher on average in the sorafenib group (p=0·0095) and mean appetite loss score was up to 10% higher (p=0·0018). According to HCC18, mean nutritional problem scores were up to 7% worse in the sorafenib group (p=0·0084; data not shown). No evidence of non-zero interactions was observed. No significant differences were observed in other QOL scales.

The addition of sorafenib did not seem to increase toxicity associated with DEB-TACE, as evidenced by similar incidence of abdominal pain and nausea (table 4). The major differences between the two groups were consistent with well-known toxicities associated with sorafenib, namely stomatitis, diarrhoea, hand–foot skin reaction, rash, and bleeding, which were all more common in the sorafenib group. The most common grade 3–4 adverse events were fatigue (29 [18%] of 157 patients in the sorafenib group vs 21 [13%] of 156 patients in the placebo group), abdominal pain (20 [13%] vs 12 [8%]), diarrhoea (16 [10%] vs four [3%]), gastrointestinal disorders (18 [11%] vs 12 [8%]) and hand–foot skin reaction (12 [8%] and none). At least one serious adverse event was reported in 65 (41%) of 157 patients in the sorafenib group and 50 (32%) of 156 patients in the placebo group. 181 serious adverse events were reported in total: 95 (52%) in the sorafenib group and 86 (48%) in the placebo group. 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 group 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 masked review, was in the placebo group and was caused by massive variceal haemorrhage. Of the three treatment-related deaths in the sorafenib group, one was after acute liver failure 14·0 days after randomisation, the second due to infection 134·0 days after randomisation, and the third due to hepatorenal failure 250·0 days after randomisation.

Discussion

The combination of sorafenib and TACE has been assessed 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.[21–24] Sequential therapy was found to be ineffective in a large randomised controlled trial[25] done 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. There was no significant difference in time to progression but the daily dose of sorafenib administered was very low (median 387 mg). Additionally, the anti-angiogenic agent brivanib has also been assessed as an adjuvant therapy after TACE a large phase 3 trial,[26] which was terminated early after randomisation of 502 patients when intention-to-treat analysis showed no improvement in overall survival. However, there is a strong rationale for concurrent rather than sequential therapy in view of 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 shown in an initial phase 1 trial[21] that assessed escalating doses of sorafenib combined with doxorubicin-based conventional TACE, and confirmed that sorafenib could be safely given at full dose continuously from 7 days before TACE. In support of the rationale for the combination, the plasma concentration of VEGF was found to be reduced after combined therapy by contrast with increases previously reported in response to TACE alone. A subsequent phase 2 trial[22] confirmed the safety of this approach in combination with DEB-TACE and also reported disease control in 95% of patients. A global placebo-controlled randomised phase 2 trial (SPACE)[27] has been reported for which time to progression was the primary endpoint. Patients were randomly allocated to sorafenib 400 mg twice-daily or matched placebo starting 2–7 days before the first TACE performed using DEB-TACE. Additional DEB-TACE was given according to fixed schedule at cycle 3, 7, and 13, and every six cycles thereafter, where each cycle was 4 weeks long. The primary endpoint was determined by central radiological review according to mRECIST criteria. The SPACE trial did not show a clinically meaningful improvement in time to progression with the addition of sorafenib, but the study had significant methodological flaws that were acknowledged by the authors and that could 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, the treatments delivered in different geographical locations differed significantly, which might have contributed to different outcomes. Finally, although overall survival was a predefined secondary endpoint, the trial was reported before median overall survival had been reached.

	TACE with sorafenib (n=157)				TACE with placebo (n=156)			
	Grade 1/2	Grade 3	Grade 4	Grade 5	Grade 1/2	Grade 3	Grade 4	Grade 5
Fatigue	98 (62%)	28 (18%)	1 (1%)	0	101 (65%)	20 (13%)	1 (1%)	0
Abdominal pain	73 (47%)	20 (13%)	0	0	77 (49%)	12 (8%)	0	0
Diarrhoea	71 (45%)	15 (10%)	1 (1%)	0	45 (29%)	4 (3%)	0	0
Nausea	70 (45%)	2 (1%)	0	0	66 (42%)	1 (1%)	0	0
Rash	57 (36%)	3 (2%)	0	0	32 (21%)	0	0	0
Hand foot skin reaction	53 (34%)	12 (8%)	0	0	13 (8%)	0	0	0
Stomatisis	36 (23%)	5 (3%)	0	0	17 (11%)	1 (1%)	0	0
Bleed	21 (13%)	7 (5%)	2 (1%)	0	14 (9%)	1 (1%)	1 (1%)	0
Anorexia	50 (32%)	3 (2%)	0	0	50 (32%)	2 (1%)	0	0
Constipation	23 (15%)	0	0	0	46 (30%)	0	0	0
Gastrointestinal disorders	7 (5%)	16 (10%)	2 (1%)	0	6 (4%)	10 (6%)	2 (1%)	1 (1%)
Pain	22 (14%)	0	0	0	18 (12%)	0	0	0
Vomiting	21 (13%)	2 (1%)	0	0	16 (10%)	0	1 (1%)	0
Dry skin	21 (13%)	0	0	0	15 (10%)	1 (1%)	0	0
Alopecia	21 (13%)	0	1 (1%)	0	14 (9%)	0	0	0
Pruritus	11 (7%)	0	0	0	21 (14%)	2 (1%)	0	0
Weight loss	19 (12%)	0	0	0	13 (8%)	0	0	0
General disorders and administration site conditions	7 (5%)	8 (5%)	0	1 (1%)	8 (5%)	3 (2%)	0	2 (1%)

CTC=Common Terminology Criteria. TACE=transarterial chemoembolisation.

Table 4: CTC adverse event categories (occurring in 10% or more of patients)

To our knowledge, TACE 2 is the first randomised, placebo-controlled, phase 3 trial to explore the concurrent administration of sorafenib and DEB-TACE. We aimed to compare combination treatment with sorafenib and DEB-TACE versus treatment with DEB-TACE alone (controlled with placebo). Because sorafenib was standard of care for patients progressing after TACE, and to ensure patients were not disadvantaged by participation, all patients were unmasked on progression and allowed to crossover to sorafenib if they were in the placebo group. No post-progression therapy was recommended for those on sorafenib because no effective second-line therapies were available during the recruitment period. We reasoned that the high rate of crossover to sorafenib might obscure any benefit of the combination if overall survival was chosen as the primary endpoint. Furthermore, the choice of time to progression as an endpoint might obscure toxicity leading to death in the combination arm. Hence, we felt that progression-free survival was the most appropriate primary endpoint, but both overall survival and time to progression were included as secondary endpoints. By contrast with 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, although the SPACE trial was a global study, TACE 2 was done exclusively in the UK and recruited over a longer time 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, administration of sorafenib did not seem to compromise the subsequent delivery or efficacy of TACE because the number 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, nearly half of the patients in the sorafenib group received less than two DEB-TACE treatments compared with just over a third in the placebo group, and fewer TACE procedures occurred in the first 12 months in the sorafenib group than in the placebo group. Possible explanations for fewer TACE procedures being given in the sorafenib group 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 groups were equivalent favour the efficacy 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 the scales that were found to differ, graphical analyses suggest that increased diarrhoea continued throughout the analysed period, while 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. Because gastrointestinal and dietary complications are recognised side-effects of sorafenib and TACE, these findings are plausible, especially in the period when both TACE and sorafenib are received. Equally, role and social functioning could deteriorate on receipt of combined therapy. Other than for diarrhoea, the difference in these scales for average QOL was reduced beyond 180 days. However, at approximately 270 days there was a suggestion of renewed detriment. We note that this coincides approximately with the median duration of progression-free survival.

Despite the design and delivery of the TACE 2 trial, comparison of the two groups did not provide evidence of a significant or meaningful difference between groups in progression-free survival, overall survival, or time to progression. Similarly, although not formally compared, disease control and best response did not seem to differ between treatments. We believe that these results, taken together with those from the SPACE trial, provide definitive evidence that combined therapy does not improve outcome compared with DEB-TACE alone.

In light of this, an unmet need remains to improve outcomes for intermediate stage hepatocellular carcinoma and alternative systemic therapies combined with TACE need to be explored. 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 have confirmed our previously published retrospective finding, that progression is equivalent regardless of which criteria are applied.[28] Hence, for the assessment of both time to progression and progression-free survival, we believe either RECIST v1.1 or mRECIST can be used. Although the proportion of patients who had an overall response or achieved disease control was similar by each method, there were discrepancies between RECIST v1.1 and mRECIST, the most significant of which was the major difference between the two criteria in the definition of complete response (which occurred in 3% of patients by RECIST v1.1 compared with 26% 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.[29] 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. The risk of death was significantly higher for individuals with a HAP score of D (HR 5·8, 95% CI 3·2–10·6, p<0·0001) compared with HAP A and median survival was only 169·0 days for this group. We therefore propose that the HAP score could 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 with DEB-TACE alone, and also provides valuable lessons to inform future trial development.

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