TACE 2: A randomized placebo-controlled, double-blinded, phase III trial evaluating sorafenib in combination with transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC).

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Running head: The TACE 2 trial

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ABSTRACT

Purpose

TACE is the standard-of-care for patients with intermediate stage 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.

Patients and methods

Patients were randomised 1:1 to continuous sorafenib (400mg BD) or placebo combined with TACE using drug-eluting beads (DEB-TACE) performed 2-5 weeks post-randomisation. Further DEB-TACE was performed according to radiological response and patient tolerance. Inclusion criteria included unresectable, liver-confined HCC, patent main portal vein, ECOG PS ≤ 1 and Child-Pugh A. The primary outcome was PFS and secondary outcomes included overall survival (OS), toxicity and QOL.

Results

The trial was terminated after a planned interim futility analysis and data from 313 randomised patients is presented. Median age was 67, 62.7% were PS 0 and alcohol was the most common cause of liver disease. The median daily dose and duration of therapy was 660mg versus 800mg, and 120 versus 162 days 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. Similarly, there was no evidence of difference in overall survival; HR

0.91 (95% CI 0.67-1.24, p = 0.57) with median survival 631 (95% CI 473, 879) and 598 (95% CI 500, 697) days.

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

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 chemoembolization (TACE) is recommended according to international guidelines [2]. The evidence for TACE comes from two 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 embolization (TAE) are equivalent to those of TACE [7,8]. The introduction of drug-eluting beads has provided a more standardised approach for TACE (DEB-TACE) allowing a 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 [9].

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 [10,11]. 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 [12] 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 treatment

This was a phase III multicentre, randomised, double-blind, placebo-controlled study in which patients were randomised 1:1 to receive continuous sorafenib 400mg BD or matched placebo starting within 24 hours of randomisation. DEB-TACE was performed 2-5 weeks post-randomisation using drug-eluting beads (DC Bead™, (Biocompatibles UK Ltd (BTG PLC)) loaded with doxorubicin 150mg according to the manufacturer's instructions. 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. On progression, patients were unblinded and entered the post-study treatment period. 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. The protocol was approved by the central ethical review board (IRAS Ref 09/H1102/114) and all patients provided written informed consent. The trial was registered on the European Clinical Trials Database (EudraCT Number: 2008-005073-36), the ISRCTN registry (ISRCTN93375053) and ClinTrials.gov (NCT01324076).

Patients

Inclusion criteria included: histological or non-invasive diagnosis according to AASLD criteria[13], at least one uni-dimensional lesion measurable according to RECIST criteria v1.1, not a candidate for surgical resection or liver transplant, performance status ≤ 1, Child Pugh A, hemoglobin ≥ 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-embolization, systemic or radiation therapy for HCC, any contraindication to hepatic embolization, 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 six months or prolonged QT/QTc >450ms

Outcome measures

The primary endpoint was progression free survival (PFS) defined as the interval between randomisation and progression according to RECIST version 1.1[14] or death due to any cause. 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; number of TACE procedures performed within 12 months of randomisation, toxicity graded 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; best response rate according to RECIST 1.1; and quality of life using the

EORTC QOL questionnaire (QLQ-C30) version 3, EORTC QLQ-HCC18 and the EuroQoL (EQ-5D) questionnaire requested at baseline, pre-TACE, week 10 and 6-weekly thereafter until progression.

Sample size

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 α=0.05, and with 85% power. The design incorporated a formal interim analysis for futility following the method of Freidlin et al[15], and performed after 43% (147) of PFS events. Randomisation was stratified by randomising centre and serum alpha-fetoprotein levels (AFP) (<400, ≥400 ng/ml)).

Statistical Analysis

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 cycle of TACE and 6 weeks of sorafenib. Safety was assessed in those patients who received one or more dose of study drug. The primary analysis of PFS and secondary outcome measures OS and TTP were analysed through multilevel 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 assumption was tested where applicable. Patients not experiencing an event were censored at the date last known to be event-free.

Quality of life, measured using EORTC-QLQ-C30 and -HCC18 questionnaires, was analysed through repeated measures modelling. 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 [16] will be reported in a follow-on QOL article. Safety data were reported descriptively. Deaths deemed related to treatment must have occurred within 30 days of last treatment. All analyses were performed using Stata version 14.

RESULTS

Patients

Between Nov 2010 and Dec 2015, a total of 313 patients were randomised from 20 centres in the United Kingdom; 157 to sorafenib and 156 to placebo (Figure 1). Overall, the median age was 67 years and 88.5% percent were male, 62.5% had a performance status of 0, and 80.2% had cirrhosis. Child Pugh score was 5 in 70.9% and the most common known single aetiology for liver disease was alcohol. The patient characteristics were well balanced (Table 1). The median of the mean daily dose of sorafenib was 660mg compared with 800mg for placebo and the median duration of treatment was 120 days versus 162 respectively (Table 2). At least one DEB-TACE was delivered to 89.4% patients; 89.2% in the sorafenib-treated group and 92.9% in the placebo-treated group confirming that sorafenib associated toxicity did not reduce delivery of first DEB-TACE. Within the first 12 months from randomisation, 253 and 310 DEB-TACE procedures were performed within the

sorafenib-treated and placebo patients respectively. Fifty-six 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. Regarding the primary endpoint, an analysis was performed on the final data which included additional data accrued during trial closure period, by which point 246 PFS events had been observed. 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 (95% CI 221-281) vs 235 (95% CI 209-322) respectively, (Table 2 and 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 (95% CI 240-410) vs 320 (95% CI 234-400), nor for OS with HR 0.91 (95% CI 0.67-1.24, p=0.57) with a median survival 631 (95% CI 437-879) and 598 (95% CI 500-697) (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 (p=0.98); TTP HR 0.87 (p=0.35); OS HR 0.99 (p=0.95). Furthermore, analyses in the PP population also revealed no evidence of a difference for all survival measures. The HAP score was also confirmed as a robust method of prognostic stratification resulting in a median overall survival (days) of 946 (95% CI 641, 1316), 631 (95% CI 510, 816), 463 (95% CI 259, 573) and 169 (95% CI 86, 420) 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, defined as complete response (CR) or partial response (PR), for the sorafenib and placebo-treated group was 35.7% and 31.4%, and the disease control rate (DCR) [(CR, PR and stable disease (SD)] was 74.5% and 77.6% (Table 3). Response was also assessed using modified RECIST (mRECIST) which resulted in a response rate of 53.5% compared with 51.9%, and DCR of 74.5% and 76.9%. Comparing RECIST v1.1 and mRECIST demonstrated a very similar overall rate of progression; 10.2% versus 8.9%, but differences were observed in the other response criteria; CR 2.9% versus 25.9%, PR 30.7% versus 26.8%, and SD 42.5% versus 23.0%.

Quality of life

Overall, 1764 QOL forms were returned by 289 patients, with 89.2% and 94.2% of patients allocated to sorafenib and 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 ($p=0.045$ and $p=0.050$) for patients in the sorafenib-treated group (online Figure 1). Of the symptom scales, diarrhoea and appetite loss were found to be 13% and 10% higher in the sorafenib treated group ($p=0.009$ and $p<0.001$ respectively). The difference in appetite appeared to reduce over time. According to HCC-18, nutritional problems were up to 7% worse in the sorafenib-treated group

(p=0.001). No significant differences were observed in other patient reported outcomes.

Safety

Safety was assessed in the 311 patients that received at least one dose of study drug. The addition of sorafenib did not appear to increase toxicity associated with DEB-TACE as evidenced by similar rates of liver failure, liver infection, 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 hypertension 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 days and 249 days after randomisation. Four deaths were attributed to study drug, one of which 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 days after randomisation, the second died of infection 134 days after randomisation and the third died of hepatorenal failure 250 days after randomisation.

DISCUSSION

The combination of sorafenib and TACE has been evaluated in a number of single arm phase I and II trials in which both sequential and concurrent administration has been shown to be feasible and safe [17-20]. 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[21]. 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 III 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 by an initial phase I trial which evaluating 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[17]. 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 II trial confirmed the safety of this approach in combination with DEB-TACE and also reported a DCR of 95%[18]. Most recently, a global placebo controlled randomised phase II trial (SPACE) has been reported for which TTP was the primary endpoint[22]. Patients were randomly allocated to sorafenib 400mg BD 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 III trial to explore the concurrent administration of sorafenib and DEB-TACE. Since crossover on progression was permitted, PFS was selected as the primary endpoint but OS was a secondary endpoint. 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. The trial recruited exclusively in the UK and opened before SPACE providing sufficient median follow-up to report mature survival data. Despite these important differences, TACE2 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. Moreover, despite the more flexible protocol, 48% patients in the sorafenib arm received less than two DEB-TACE treatments compared with 34% in the placebo arm. Yet, despite the optimal design and delivery of the TACE 2 trial, comparison of the two arms resulted in no evidence of a significant or meaningful difference between the PFS, OS, 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 and mRECIST as radiological response criteria and confirm our previously published retrospective finding, that progression is equivalent regardless of which criteria are applied[23]. Hence, for the assessment of both TTP and PFS, either RECIST or mRECIST can be used. The major difference between the two criteria is in the definition of CR which was 2.9% by RECIST compared with 25.9% by mRECIST. We have also prospectively evaluated the HAP score which was designed to provide prognostic information for patients undergoing TACE[24]. In the TACE 2 data-set, 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 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 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 trials.

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)
ECOG		
0	98 (62%)	97 (62%)
1	58 (37%)	58 (37%)
Unknown	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%)
Unknown	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%)
Unknown	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		
Child-Pugh Group		
5	108 (69%)	114 (73%)
6	41 (26%)	34 (22%)
>6	4 (3%)	2 (1%)
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	253	310
Duration of sorafenib/placebo treatment		
	120.0 days (95% CI 76.0, 154.0)	162.0 days (95% CI 152.0, 231.0)
Patient duration-weighted mean sorafenib/placebo dose (mg)		
	660.0 mg (389.2, 800.0)	800.0 mg (758.2, 800.0)
Progression Free Survival		
Median (95% CI)	238.0 (221.0, 281.0)	235.0 (209.0, 322.0)
HR (95% CI)	0.99 (0.77, 1.27)	
Two-sided p value	0.94	
Overall Survival		
Median (95% CI)	631.0 (473.0, 879.0)	598.0 (500.0, 697.0)
HR (95% CI)	0.91 (0.67, 1.24)	
Two-sided p value	0.57	
Time to Progression		
Median (95% CI)	326.0 (240.0, 410.0)	320.0 (234.0, 400.0)
HR (95% CI)	0.88 (0.67, 1.17)	
Two-sided p value	0.38	

Table 3: Disease response assessed using RECIST 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**	**mRECIST**	**RECIST**	**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 and Treatment emergent deaths* in safety population
*defined as those deaths occurring within 30 days of last treatment.

	TACE + Sorafenib(N=156)		TACE + Placebo(N=155)	
	All-grade (%)	**Grade 3/4 (%)**	**All-grade (%)**	**Grade 3/4 (%)**
Fatigue	40.5	8.7/0.3	38.9	6.4/0.3
Abdominal Pain	29.9	6.4/0	28.3	3.9/0
Diarrhoea	28.0	4.8/0.3	15.4	1.0/0
Nausea	23.2	0.6/0	21.2	0.3/0
Hand Foot	20.9	3.9/0	4.2	0/0
Rash	19.3	1.0/0	10.3	0/0
Anorexia	17.0	1.0/0	16.7	0.6/0
Stomatisis	13.2	1.6/0	5.8	0.3/0
Bleed	9.6	2.3/0.6	5.1	0.3/0.3
Constipation	7.4	0/0	14.5	0/0
Vomiting	7.4	0.6/0	5.5	0/0.3
Alopecia	7.1	0/0.3	4.5	0/0
Pain	7.1	0/0	5.8	0/0
Dry Skin	6.8	0/0	5.1	0.3/0
Weight Loss	6.1	0/0	4.2	0/0
Hypertension	5.8	3.5/0	2.3	1.0/0
Pruritus	3.5	0/0	7.4	0.6/0
Liver Failure	1.9	1.6/0.3	1.6	1.6/0
Liver Infection	0.3	0/0.3	0.6	0.6/0

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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 for known prognostic factors. * Not pre-planned

Online Figure 1: 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).

Figure 1

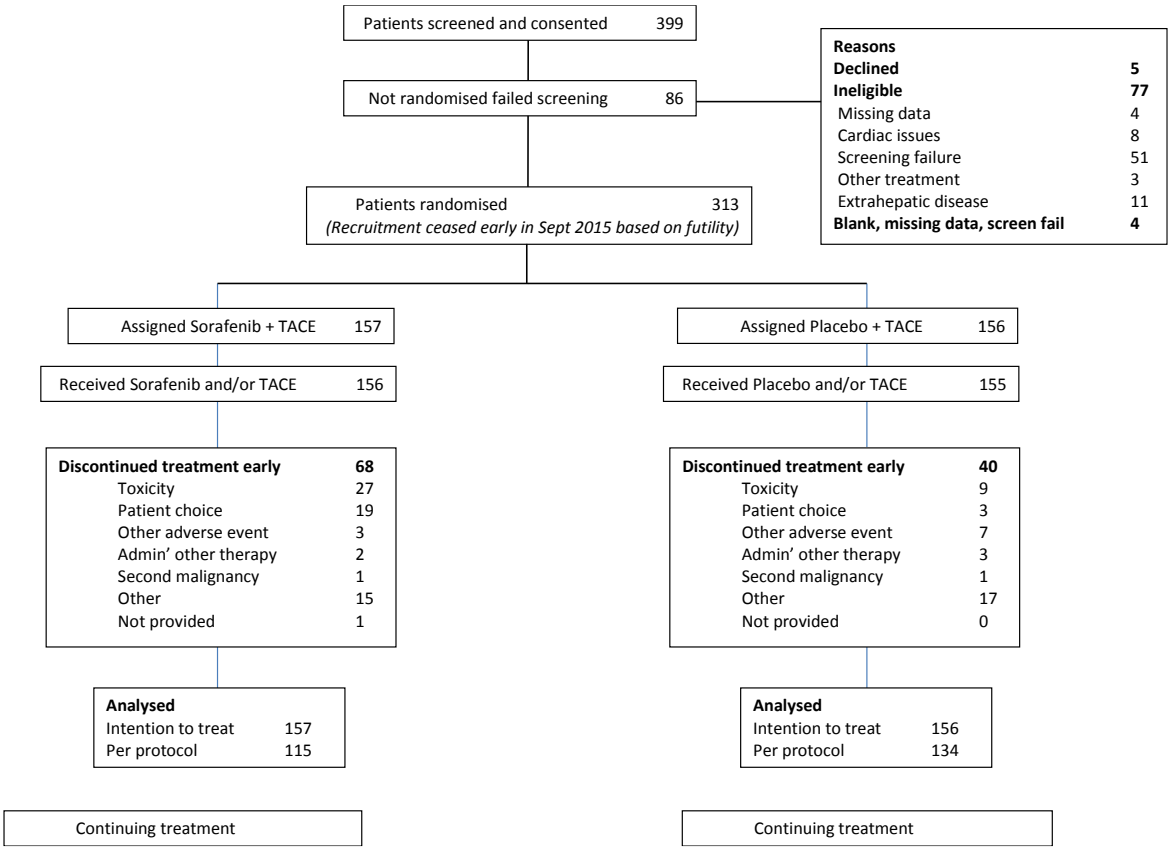
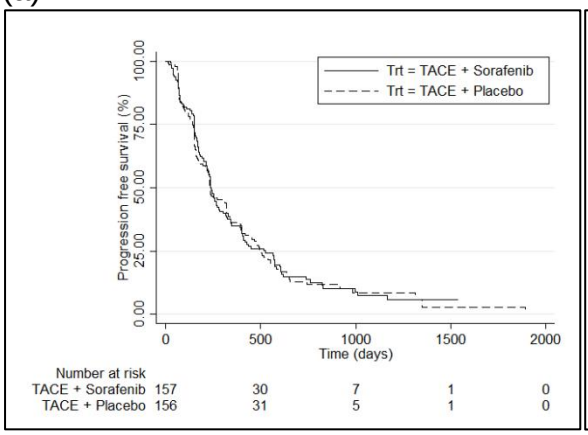
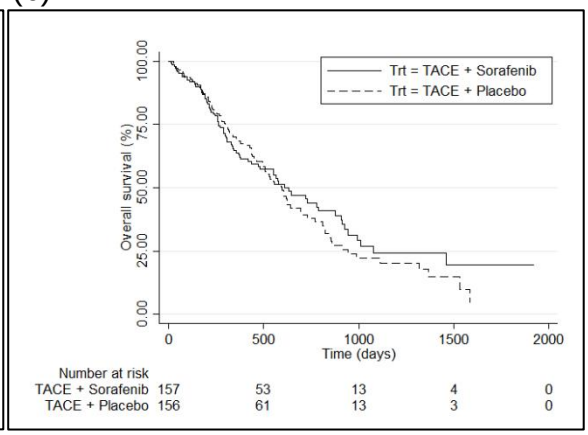

Patients screened and consented 399
Not randomised failed screening 86
Reasons
Declined 5
Ineligible 77
Missing data 4
Cardiac issues 8
Screening failure 51
Other treatment 3
Extrahepatic disease 11
Blank, missing data, screen fail 4
Patients randomised 313
(Recruitment ceased early in Sept 2015 based on futility)
Assigned Sorafenib + TACE 157
Assigned Placebo + TACE 156
Received Sorafenib and/or TACE 156
Received Placebo and/or TACE 155
Discontinued treatment early 68
Toxicity 27
Patient choice 19
Other adverse event 3
Admin' other therapy 2
Second malignancy 1
Other 15
Not provided 1
Discontinued treatment early 40
Toxicity 9
Patient choice 3
Other adverse event 7
Admin' other therapy 3
Second malignancy 1
Other 17
Not provided 0
Analysed
Intention to treat 157
Per protocol 115
Analysed
Intention to treat 156
Per protocol 134
Continuing treatment
Continuing treatment

Figure 2

(a)



(b)



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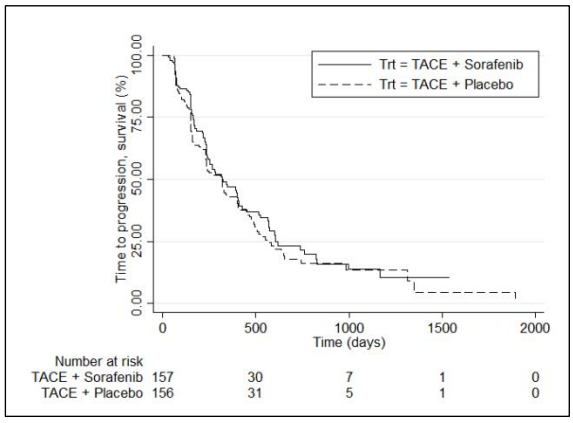

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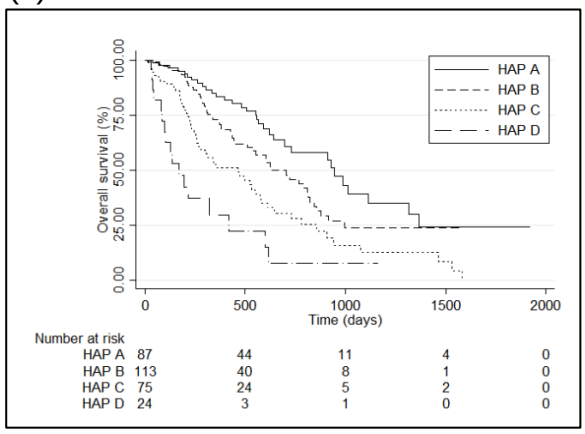
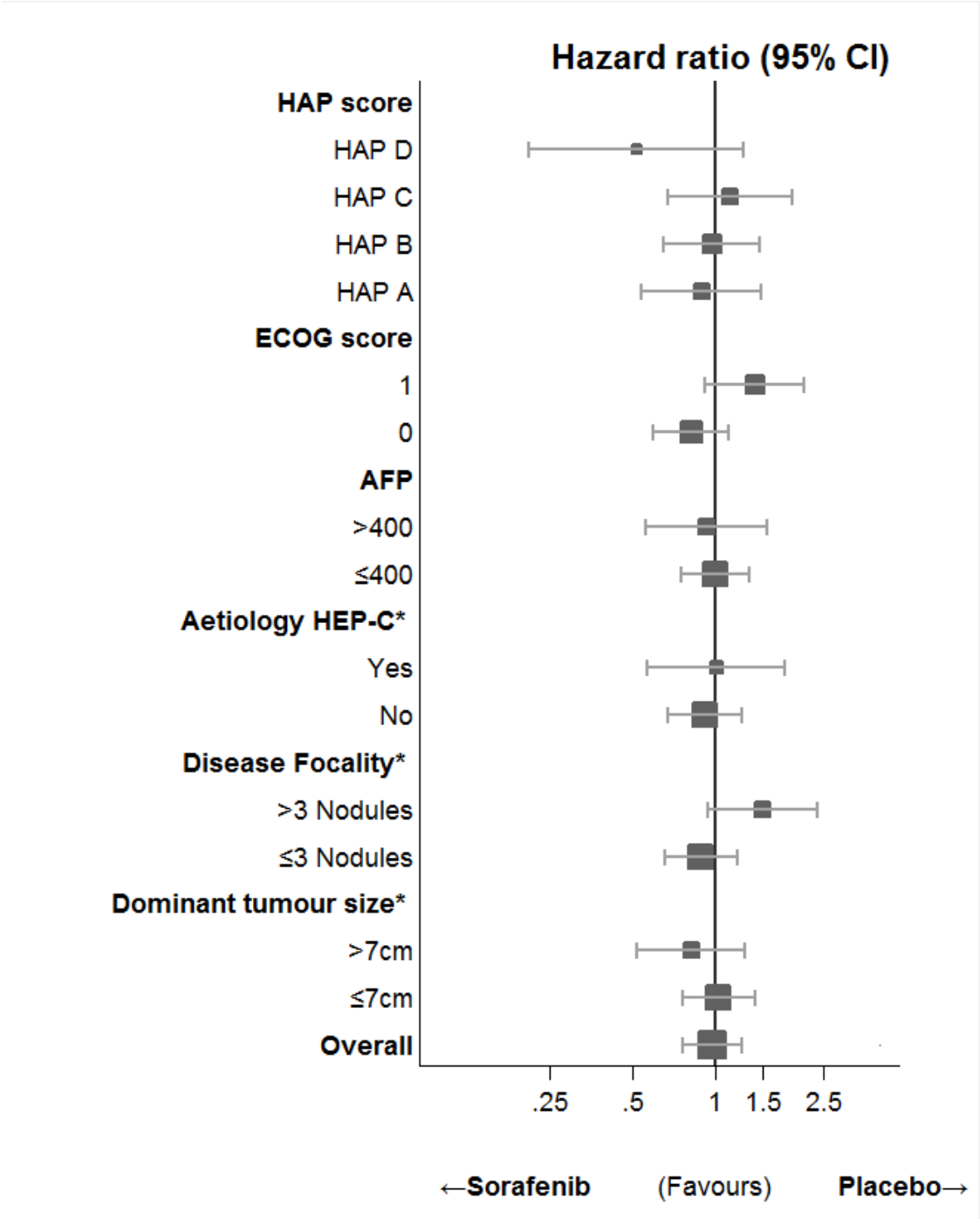
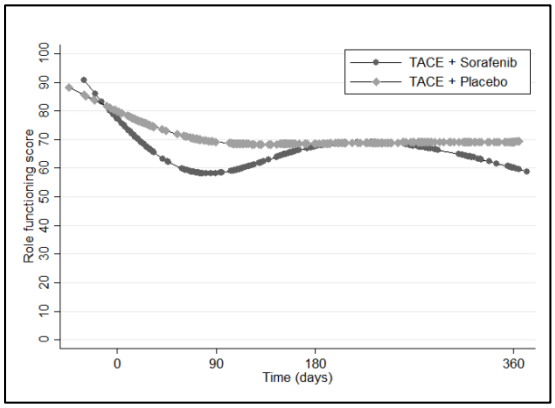


Figure 3


Hazard ratio (95% CI)
HAP score
HAP D
HAP C
HAP B
HAP A
ECOG score
1
0
AFP
>400
≤400
Aetiology HEP-C*
Yes
No
Disease Focality*
>3 Nodules
≤3 Nodules
Dominant tumour size*
>7cm
≤7cm
Overall
.25
.5
1
1.5
2.5
←Sorafenib
(Favours)
Placebo→

Online Figure 1

(a)



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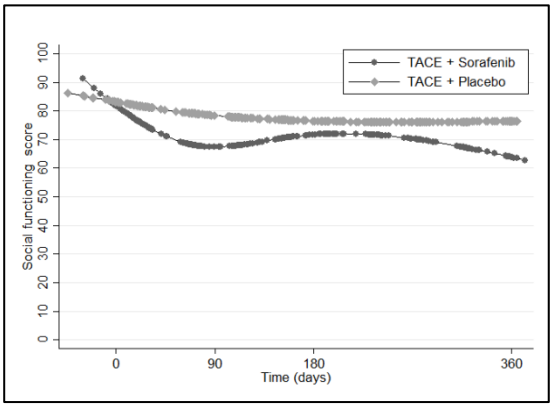

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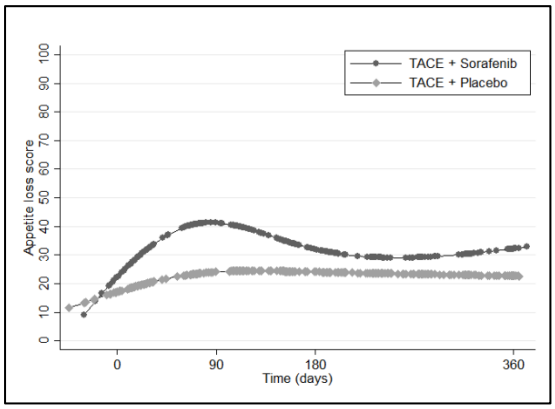

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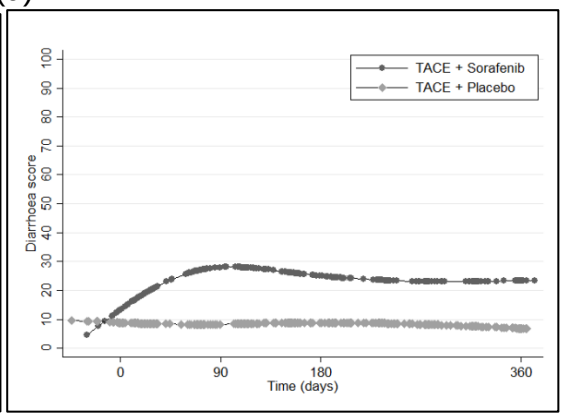

(e)