Research Article

JOURNAL OF HEPATOLOGY

Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial

Riccardo Lencioni[1,2,*,†,‡], Josep M. Llovet[3,4,5,†], Guohong Han[6], Won Young Tak[7], Jiamei Yang[8], Alfredo Guglielmi[9], Seung Woon Paik[10], Maria Reig[3], Do Young Kim[11], Gar-Yang Chau[12], Angelo Luca[13], Luis Ruiz del Arbol[14], Marie-Aude Leberre[15], Woody Niu[16], Kate Nicholson[17], Gerold Meinhardt[18], Jordi Bruix[3,†]

[1]*University of Miami Miller School of Medicine, Miami, FL, USA;* [2]*Pisa University School of Medicine, Pisa, Italy;* [3]*Barcelona Clínic Liver Cancer (BCLC) Group, Liver Unit, Institut d'Investigacions Biomèdiques, August Pi i Sunyer (IDIBAPS), Hospital Clínic Barcelona, CIBERehd, Barcelona, Spain;* [4]*Mount Sinai Liver Cancer Program, Mount Sinai School of Medicine, New York, NY, USA;* [5]*Institució Catalana de Recerca i Estudis Avançats, Catalonia, Spain;* [6]*Xijing Hospital, Fourth Military Medical University, Xi'an, China;* [7]*Kyungpook National University Hospital, Daegu, South Korea;* [8]*Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China;* [9]*University of Verona Medical School, Verona, Italy;* [10]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea;* [11]*Yonsei University College of Medicine, Seoul, South Korea;* [12]*Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan;* [13]*Mediterranean Institute for Transplantation and Advanced Specialized Therapies, University of Pittsburgh Medical Center Italy, Palermo, Italy;* [14]*Hospital Ramón y Cajal, University of Alcalá, Madrid, Spain;* [15]*Bayer HealthCare Pharmaceuticals, Loos, France;* [16]*Bayer HealthCare Co, Ltd, Beijing, China;* [17]*Bayer Plc, Newbury, UK;* [18]*Bayer HealthCare Pharmaceuticals, Montville, NJ, USA*

Background & Aims: Transarterial chemoembolization with doxorubicin-eluting beads (DC Bead®; DEB-TACE) is effective in patients with Barcelona clinic liver cancer stage B hepatocellular carcinoma (HCC). The multikinase inhibitor sorafenib enhances overall survival (OS) and time-to-tumor progression (TTP) in patients with advanced HCC. This exploratory phase II trial tested the efficacy and safety of DEB-TACE plus sorafenib in patients with intermediate stage HCC.

Methods: Patients with intermediate stage multinodular HCC without macrovascular invasion (MVI) or extrahepatic spread (EHS) were randomized 1:1 to DEB-TACE (150 mg doxorubicin) plus sorafenib 400 mg twice daily or placebo. The primary endpoint was TTP by blinded central review. Secondary endpoints included time to MVI/EHS, OS, overall response rate (ORR) using modified response evaluation criteria in solid tumors, disease control rate (DCR), time to unTACEable progression (TTUP), and safety.

Results: Of 307 patients randomized, 154 received sorafenib and 153 received placebo. Median TTP for subjects receiving sorafenib plus DEB-TACE or placebo plus DEB-TACE was similar (169 *vs.* 166 days, respectively; hazard ratio (HR) 0.797, $p = 0.072$). Median time to MVI/EHS (HR 0.621, $p = 0.076$) and OS (HR 0.898, $p = 0.29$) had not been reached. The ORRs for patients in the sorafenib and placebo groups with post-baseline scans were 55.9% and 41.3%, respectively, and the DCRs were 89.2% and 76.1%, respectively. TTUP was lower with sorafenib than with placebo (HR 1.586; 95% confidence intervals, 1.200–2.096; median 95 *vs.* 224 days). No unexpected adverse events related to sorafenib were observed.

Conclusion: Sorafenib plus DEB-TACE was technically feasible, but the combination did not improve TTP in a clinically meaningful manner compared with DEB-TACE alone.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver; the sixth most common cancer, and the third most common cause of cancer-related deaths worldwide [1,2]. Resection, liver transplantation, and local ablation are considered potentially curative in carefully selected patients, with 5-year survival rates of 40–70%, compared with 20% in untreated patients [3–5].

Transarterial chemoembolization (TACE) is the standard of care for patients with intermediate stage (Barcelona clinic liver cancer (BCLC) stage B) HCC. These patients are defined as being asymptomatic, with non-invasive, multinodular, unresectable tumors and adequate preservation of liver function [3–7]. TACE can deliver higher concentrations of drug to tumors than systemic chemotherapy, while decreasing systemic exposure [8–10]. TACE has also been reported to achieve objective

Keywords: Sorafenib; TACE; HCC.
Received 19 March 2015; received in revised form 21 December 2015; accepted 11 January 2016; available online 22 January 2016

* Corresponding authors. Address: University of Miami Miller School of Medicine Director, Interventional Oncology Research, Sylvester Comprehensive Cancer Center, 1475 NW 12th Ave, Miami, FL 33136, USA. Tel.: +1 (305) 243 1343.
E-mail address: rlencioni@med.miami.edu (R. Lencioni).
† These authors were co-principal investigators of this trial and contributed equally.
‡ Author's affiliation changed after completion of trial.

responses in 16%–61% of HCC patients, to significantly delay tumor progression and vascular invasion and to improve survival [5,11].

Despite the survival benefits of TACE in patients with unresectable HCC [7], the optimal technique is less clear [12]. TACE procedures can vary substantially, with regards to both the chemotherapeutic agent and embolization method, making these procedures quite heterogeneous [13]. Moreover, no consensus has been reached concerning the number of TACE administrations or the time between administrations. TACE with embolic doxorubicin-eluting beads (DC Bead®; Biocompatibles UK Ltd) was developed to simplify the procedure, reduce peak concentrations and total systemic exposure to doxorubicin, and ensure high concentrations in the tumor and adequate arterial occlusion [14–18]. These beads show sustained, continuous release of doxorubicin for 14 days (9), with a significantly lower systemic plasma concentration of doxorubicin compared with intra-arterial injection [9,19]. A randomized phase II trial found that TACE with doxorubicin-eluting beads (DEB-TACE) reduced the rates of systemic adverse events (AE) and liver toxicity compared with conventional TACE with Lipiodol® (Guerbet Group, Villepinte, France) and doxorubicin [10]. Median overall survival (OS) in a highly selected population (95% Child-Pugh A) was approximately 4 years [20]. Moreover, in a recent trial in 173 patients, 59% Child-Pugh class A, DEB-TACE resulted in a median survival of 43.8 months and a 5-year OS rate of 22.5% [21].

Sorafenib is a multikinase inhibitor [22–24] shown in two large, double-blind, randomized, placebo-controlled phase III clinical trials to significantly improve OS and time-to-tumor progression (TTP) in patients with advanced HCC [25,26]. Similar improvements in OS and TTP were observed in the subgroup of patients with intermediate stage HCC (BCLC B) [27]. Sorafenib is currently approved as the only systemic therapy for HCC.

Sorafenib has been reported to provide no significant benefit in TTP or OS in selected HCC patients when administered after initial response to TACE [28]. Because TACE has been shown to lead to a spike in the intratumoral concentration of vascular endothelial growth factor (VEGF), blockade of VEGF receptors prior to TACE may prevent the effects of a surge in pro-angiogenic factors [29–31]. Moreover, because both TACE and sorafenib have been shown to enhance patient survival without obvious overlapping toxicities [11,25,26,32], their combination may improve clinical outcomes. Single-arm studies combining sorafenib with various forms of chemoembolization have suggested that this combination is safe and effective [33–41]. This signal-generating phase II trial was designed to compare TTP in patients with intermediate stage HCC treated with sorafenib or placebo plus DEB-TACE.

Patients and methods

Patient characteristics

This phase II randomized, double-blind, placebo-controlled study enrolled 307 patients with intermediate stage HCC at 85 centers in 13 countries (Fig. 1). Patients were included if they had unresectable, multinodular, asymptomatic HCC (BCLC stage B) [5], with measurable lesions on CT or MRI; no macrovascular invasion (MVI) or extrahepatic spread (EHS); Child-Pugh class A and compensated liver function; an Eastern Cooperative Oncology Group (ECOG) performance status of 0; no ascites; age $\geqslant$18 years, with a life expectancy $\geqslant$12 weeks; and adequate bone marrow function (hemoglobin >9.0 g/dl; absolute neutrophil count (ANC) >1500/mm^3; platelet count $\geqslant 60 \times 10^9$/L), liver function (bilirubin <3 mg/dl; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <5 times the upper limit of normal (ULN); alkaline phosphatase <4 times ULN; prothrombin time-international normalized ratio (PT-INR) <2.3 or PT <6 seconds above control), and kidney function (serum creatinine <1.5 times ULN; amylase and lipase <3 times ULN).

Patients were excluded if they had diffuse HCC; vascular invasion (including segmental portal obstruction); extrahepatic tumor spread; advanced liver disease, as shown by Child-Pugh class B or C liver function, gastrointestinal bleeding, encephalopathy, or ascites; or contraindications for embolization, including known hepatofugal blood flow or portosystemic shunt. Patients were also excluded if the target lesion had previously undergone local treatment, including resection, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), or TACE; if they had received local therapy within 4 weeks of a baseline scan; had

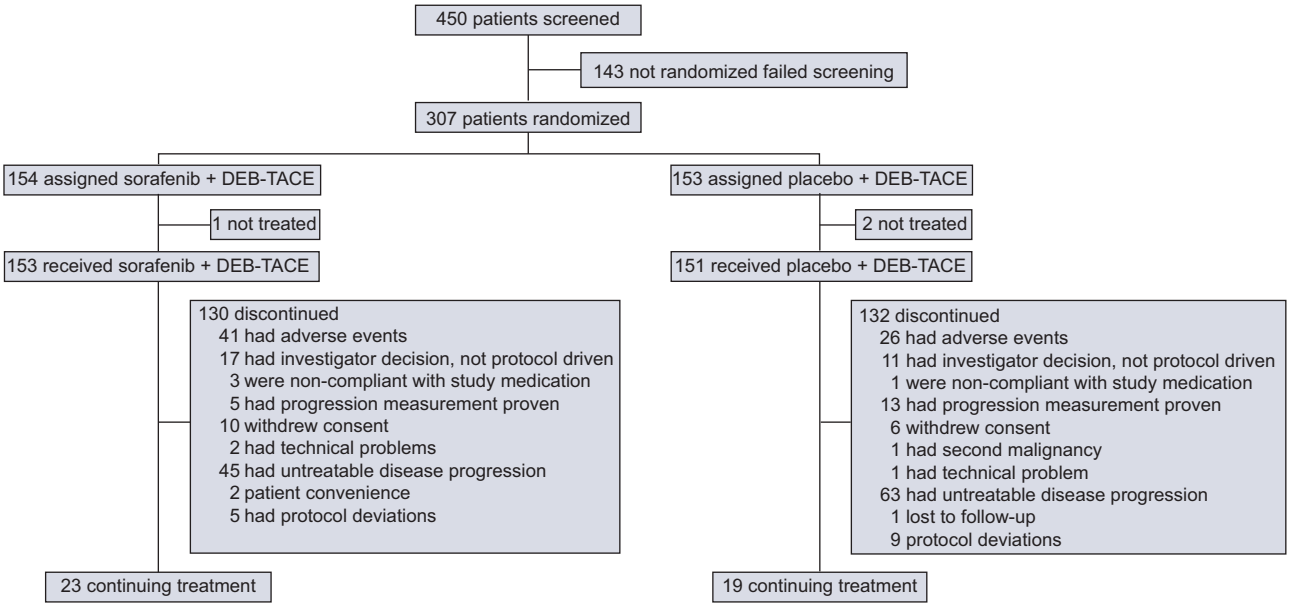

Fig. 1. Trial profile.

prior transarterial embolization or TACE; were previously treated with a kinase inhibitor; or had received anthracyclines or radiotherapy for HCC. The study protocol was approved by the Institutional Review Board of each participating center and all patients provided written informed consent.

Study protocol

Patients were randomized 1:1 to DEB-TACE (300–500 μm beads; 150 mg doxorubicin) plus sorafenib (400 mg twice daily, continuously) or matching placebo. Patients were stratified by geographic region (Americas, Europe, Asia Pacific) and by serum alpha-fetoprotein (AFP) concentration (<400 ng/L and ⩾400 ng/L; Table 1). Treatment was divided into 4-week cycles from the starting date of study drug. Sorafenib or placebo was initiated on day 1 and the first DEB-TACE session was performed 3–7 days later. Bilobar HCCs were treated in a single session. Subsequent TACE treatments were performed on day 1 (± 4 days) of cycles 3, 7, and 13 and every 6 cycles thereafter.

AEs were investigator-assessed and graded according to national cancer institute-common terminology criteria for adverse events (NCI-CTCAE) version 3.0. Treatment interruptions and up to two dose reductions (to 400 mg once daily and to 400 mg every other day) were permitted for drug-related AEs; patients who required further dose reductions were withdrawn from the study. Also, at the discretion of the investigator, re-escalations to 400 mg twice daily were permitted after resolution of the AE.

Table 1. Baseline demographic and clinical characteristics of the intent-to-treat (efficacy) population.

	Sorafenib, n (%) (n = 154)	Placebo, n (%) (n = 153)
Median age at enrollment	64.5 yr	63.0 yr
Sex		
Male	135 (87.7)	126 (82.4)
Female	19 (12.3)	27 (17.6)
Etiology		
Hepatitis B	55 (35.7)	50 (32.7)
Hepatitis C	39 (25.3)	41 (26.8)
Alcohol use	27 (17.5)	30 (19.6)
Non-alcoholic steatohepatitis	6 (3.9%)	7 (4.6%)
Hepatitis B and alcohol use	3 (1.9%)	1 (0.7%)
Hepatitis C and alcohol use	3 (1.9%)	3 (2.0%)
Hepatitis B and C	2 (1.3%)	0
Hemachromatosis	2 (1.3%)	0
Fatty liver disease	1 (0.6%)	0
Adenoma: Malignant transformation	0	1 (0.7%)
Autoimmune hepatitis	0	1 (0.7%)
Biliary cirrhosis primary	0	2 (1.3%)
Unknown	16 (10.4%)	17 (11.1%)
HCC proven by biopsy	60 (39.0)	67 (43.8)
Liver cirrhosis present	139 (90.3)	131 (85.6)
Geographic region		
Europe	78 (50.6)	79 (51.6)
Asia	59 (38.3)	57 (37.3)
North America	17 (11.0)	17 (11.1)
AFP		
<400 ng/ml	113 (73.4)	112 (73.2)
≥400 ng/ml	41 (26.8)	41 (26.8)
Child-Pugh score		
Missing	0	1 (0.7)
5	98 (63.6)	105 (68.6)
6	55 (35.7)	47 (30.7)
7	1 (0.6)	0 (0)

Abbreviations: AFP, alpha-fetoprotein.

Outcome measures

The primary efficacy objective was TTP by blinded central review, measured from the time of randomization until radiologic disease progression, according to modified response evaluation criteria in solid tumors (mRECIST), which takes into account reduction in viable tumor using contrast-enhanced radiologic imaging rather than strict tumor size [42]. Secondary efficacy objectives included time to MVI/EHS, defined as the time from randomization to evidence of MVI/EHS on CT/MRI scans; OS, measured from the time of randomization until death from any cause; overall response rate (ORR); disease control rate (DCR); and a novel endpoint of time to unTACEable progression (TTUP). TTUP was defined based on one or more of these criteria: a) failure of the treated nodule to achieve an objective response [43] after at least two DEB-TACE sessions; b) the appearance of protocol-specific contraindications to TACE, including MVI, EHS, sustained ascites, or Child-Pugh class B liver function; c) an ECOG performance status >2; or d) platelet count $\leqslant 60 \times 10^9$/L. ORR was defined as the percentage of patients achieving either complete response (CR) or partial response (PR) [44], and DCR as the percentage of patients achieving CR, PR, or stable disease (SD).

Safety outcomes included AEs, as determined by NCI-CTCAE version 3.0, with treatment-emergent, drug-related, and procedure-related AEs and safety laboratory parameters summarized by treatment group and common terminology criteria grade.

Patients were assessed at screening and randomization, on day 1 of every 4-week cycle (with CT and/or MRI performed every 8 weeks), and at the end of the study (7–14 days after stopping the study drug).

Statistical methods

The sample size was based on the primary efficacy endpoint, TTP. Considering the signal-generating nature of this trial, a one-sided alpha of 0.15 was chosen. With a randomization ratio of 1:1 between sorafenib and placebo, it was estimated that 151 events would be required to have 85% power to detect a 40% increase in TTP, or a hazard ratio (HR) of 0.71 for sorafenib over placebo (with 151 events, a 35% increase in TTP can be detected with 80% power). Assuming an exponential distribution in the occurrence of events over time, a median TTP of 12 months in the placebo group, and a dropout rate of 5%, we estimated that 300 patients (150 per group) would be required.

Efficacy was assessed in the intention-to-treat (ITT) population, defined as all randomized patients. The safety population consisted of all patients who received at least one dose of study drug. TTP, time to MVI/EHS, OS, and TTUP in the two groups were compared using stratified log-rank tests, with a one-sided alpha of 0.15. Survival outcomes were determined by the Kaplan-Meier method and compared by log-rank tests. HRs and 95% confidence intervals (CIs) were calculated for the sorafenib plus DEB-TACE relative to the placebo plus DEB-TACE group.

Results

A total of 307 patients were randomized, 154 to sorafenib and 153 to matching placebo (Fig. 1); Table 1 shows their baseline demographic and clinical characteristics. Mean age at enrollment was 62.6 years; 85% of the patients were male; 87.9% had liver cirrhosis; 51.1% were from Europe, 37.8% from Asia, and 11.1% from North America; and 73.3% and 26.7% had baseline AFP concentrations <400 ng/ml and ⩾400 ng/ml, respectively. Approximately two-thirds of patients had a Child-Pugh score of 5 and one-third had a score of 6; none had ascites. The two treatment arms were well balanced at baseline.

The safety population consisted of the 304 patients who received at least 1 dose of study drug. Table 2 shows all-grade treatment-emergent AEs related to sorafenib or placebo (i.e., non-TACE) with frequency >15% in either group, corresponding grade 3/4 AEs, and all-grade 5 AEs. No unexpected AEs related to sorafenib were observed. The most commonly reported AEs with all-grade differences >10% across arms (sorafenib *vs.* placebo) included diarrhea (52.9% *vs.* 17.2%), hand-foot skin reaction (HFSR) (46.4% *vs.* 6.6%), anorexia (30.7% *vs.* 20.5%), hypertension (30.1% *vs.* 16.6%), hepatobiliary (23.5% *vs.* 11.3%), rash (21.6% *vs.*

7.3%), and weight loss (20.3% *vs.* 1.6%). Treatment-emergent grade 5 AEs were balanced across arms (n = 14). Four deaths in the sorafenib arm (two due to hepatobiliary/liver dysfunction and one each to constitutional (unspecified) and syndrome-other (unspecified)) and one in the placebo arm (due to perforation of the duodenum) were attributed as possibly being related to study medication. Additional expected AEs were ascribed to the DEB-TACE procedure or to doxorubicin (data not shown).

The primary endpoint of the study was TTP by blinded central independent review. The HR for TTP for sorafenib plus DEB-TACE *vs.* placebo plus DEB-TACE was 0.797 (95% CI, 0.588–1.080, one-sided $p = 0.072$; Fig. 2A). Median TTPs were numerically similar, 169 days (95% CI, 166–219 days) for sorafenib plus DEB-TACE and 166 days (95% CI, 113–168 days) for placebo plus DEB-TACE.

Analysis of secondary endpoints showed that the HR for time to MVI/EHS for sorafenib plus DEB-TACE *vs.* placebo plus DEB-TACE was 0.621 (95% CI, 0.321–1.200, $p = 0.076$; Fig. 2B); with the median not reached in either group. Similarly, the HR for

Table 2. All-grade treatment-emergent AEs with frequency >15% in either group, corresponding grade 3/4 AEs, and all-grade 5 AEs, in the safety population.

	Sorafenib, % (n = 153)		Placebo, % (n = 151)	
	All-grade	Grade 3/4	All-grade	Grade 3/4
Abdominal pain NOS	60.1	7.8/0	61.6	10.6/0.7
Diarrhea	52.9	3.9/0	17.2	0.7/0
HFSR	46.4	9.2/0	6.6	1.3/0
Fatigue	43.1	9.8/1.3	33.1	4.6/0.7
Fever	38.6	0/0	34.4	0/0
Nausea	37.9	0.7/0	39.1	0.7/0
Anorexia	30.7	2.0/0	20.5	0.7/0
Hypertension	30.1	16.3/0	16.6	9.3/0
Alopecia*	28.1	-	7.3	-
Elevated AST	24.8	14.4/9.8	19.2	13.9/4.0
Hepatobiliary/pancreas	23.5	5.2/2.6	11.3	1.3/1.3
Rash/desquamation	21.6	2.6/0	7.3	0/0
Hemorrhage/bleeding	20.9	0.7/2.6	14.6	2.0/2.0
Weight loss	20.3	2.0/0	1.6	0/0
Infection	20.9	7.2/1.3	26.5	9.9/0.7
Constipation	19.0	0/0	17.9	0/0
Vomiting	18.3	0.7/0	26.5	3.3/0
Ascites	17.6	5.2/0.7	13.9	4.0/0
Elevated ALT	17.0	11.8/3/3	16.6	12.6/0.7
Hyperbilirubinemia	16.3	9.8/2.6	8.6	2.6/0.7
	Grade 5		Grade 5	
Treatment-emergent Grade 5 AEs	9.2		9.3	
Related to study medication	2.6**		0.7**	
Related to TACE	3.3		1.3	
Related to DEB	2.0		0	

*Alopecia: 26.8% grade 1 and 1.3% grade 2.
**Grade 5 AEs attributable to study medication included 4 patients in the sorafenib arm, 2 due to hepatobiliary/liver dysfunction and one each to constitutional (unspecified) and syndrome, other (unspecified); and one in the placebo arm, due to GI perforation/duodenum.
Abbreviations: NOS, not otherwise specified; HFSR, hand-foot skin reaction; AST, aspartate aminotransferase, ALT, alanine aminotransferase.

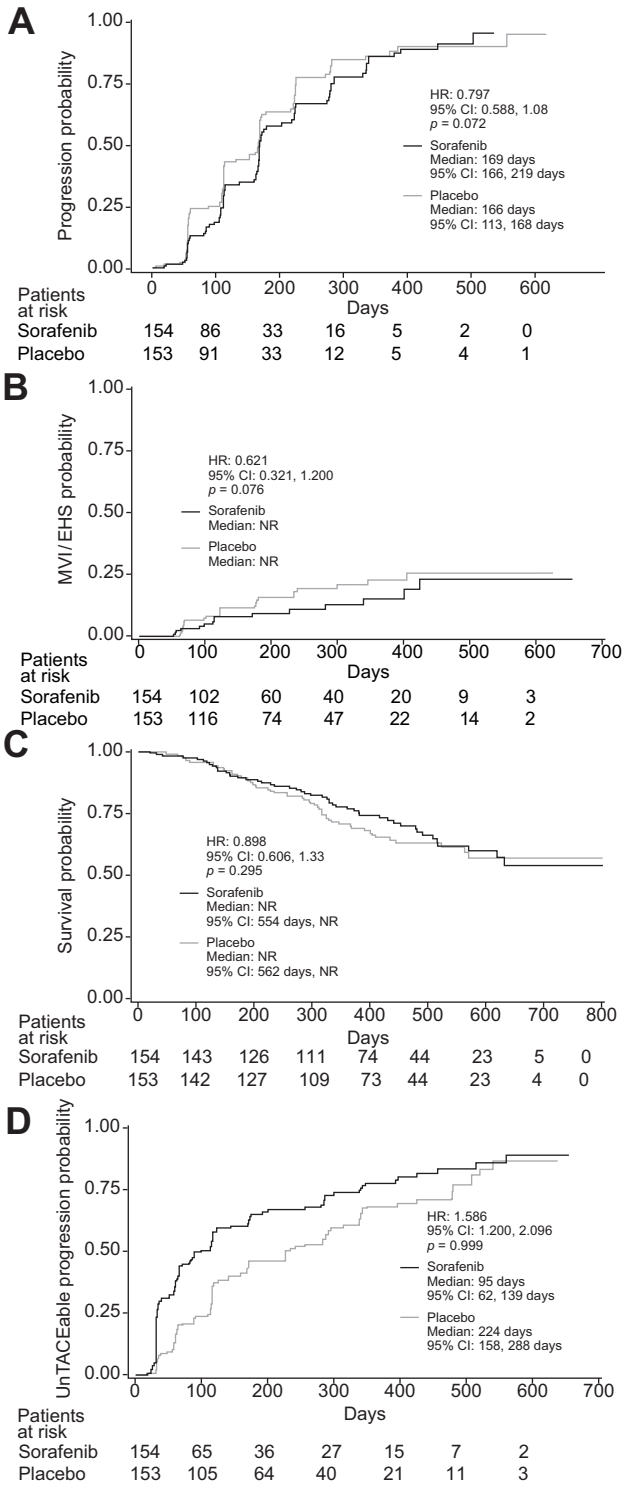

Fig. 2. Efficacy outcomes in patients in the SPACE trial randomized to sorafenib or placebo plus DEB-TACE. A) Time-to-progression (TTP) by blinded central review, B) time to macrovascular invasion/extrahepatic spread (MVI/EHS), C) overall survival (OS), and D) time to unTACEable progression (TTUP) by investigator assessment. NR, not reached.

OS in the sorafenib plus DEB-TACE *vs.* the placebo plus DEB-TACE group was 0.898 (95% CI, 0.606–1.330, $p = 0.295$; Fig. 2C), with the median OS not reached in either group after a median follow-up of 270 days (52 events) and 272 days (49 events), respectively. By investigator assessment, TTUP was shorter in the sorafenib plus DEB-TACE than in the placebo plus DEB-TACE group (HR 1.586, 95% CI, 1.200–2.096, $p = 0.999$; Fig. 2D), with median TTUPs of 95 days (95% CI, 62–113 days) and 224 days (95% CI, 158–288 days), respectively.

A total of 110 patients in the sorafenib arm and 96 in the placebo had protocol defined unTACEable progression. The leading cause in the sorafenib arm was deterioration of Child-Pugh status (68/110 or 61.8% of patients), whereas in the placebo arm it was failure to achieve an objective response (50/96 or 52.1%) followed by deterioration of Child-Pugh status (41/96 or 42.7%). The deterioration of Child-Pugh status following sorafenib was greater in patients from non-Asian than Asian countries (44/62 or 71.0% *vs.* 24/48 or 50.0%), whereas reduction in platelet counts below 60,000/mm^3 was more prominent in Asian than non-Asian countries (20/48 or 41.7% *vs.* 5/62 or 8.1%).

Scan evaluation of the 154 patients in the sorafenib plus DEB-TACE group and in the 153 in the placebo plus DEB-TACE group by blinded central independent review showed that only 111 (72.1%) and 100 (65.4%), respectively, had confirmed baseline target lesions after randomization. Ninety-three (60.4%) and 92 (59.5%) patients, respectively, had post-baseline scans following completion of cycle 2 (Table 3). ORRs (complete response + partial response) by mRECIST criteria following central review in the randomized population were 35.7% and 28.1%, respectively. For patients with post-baseline scans, the ORR per central review was higher in the sorafenib plus DEB-TACE than in the placebo plus DEB-TACE group (55.9% *vs.* 41.3%).

Mean and median doses were lower and duration of study drug treatment was shorter in the sorafenib plus DEB-TACE than in the placebo plus DEB-TACE group. Patients in the combination group tended to receive fewer TACE sessions, with 36% and 19%, respectively, receiving only the first TACE (Table 4). The median daily dose of sorafenib delivered was approximately 70% of planned dose, with dose reductions and interruptions being more frequent in the sorafenib plus DEB-TACE group. AEs were the principal reason for dose modification.

Table 4. Study drug and DEB-TACE administration – safety population.

	Sorafenib (n = 153)	Placebo (n = 151)
Daily dose per cycle, mg		
Mean	557	733
Median	566	791
Duration of treatment, weeks		
Mean	28.6	33.3
Median	21.0	27.3
Dose reduction, %	60.8	20.5
Due to AEs	87.1	61.3
Dose interruption, %	86.3	69.5
Due to AEs	84.1	41.9
Percentages of patients receiving 1, 2, 3, or ≥4 DEB-TACE sessions		
1	35.9	19.2
2	35.3	37.7
3	13.1	19.2
≥4	13.7	21.9
Patients receiving 150 mg doxorubicin, n		
Cycle 1	107/153	105/151
Cycle 3	40/91	56/116

Per protocol, further analysis showed noteworthy differences between patients from Asian and non-Asian countries (Table 5). TACE administration in the Asian group was balanced between the sorafenib and placebo arms, whereas a higher percentage of non-Asian patients in the sorafenib than in the placebo arm received only the first TACE (42.4% *vs.* 17.8%). In non-Asian patients, both the mean and median durations of sorafenib treatment were lower than for placebo. Sorafenib plus DEB-TACE had greater benefit in patients from Asian countries, with an improvement in TTP and a similar trend for an improvement in OS compared with non-Asian patients.

Discussion

The SPACE trial was the first global randomized, placebo-controlled trial combining TACE with a systemic anti-cancer

Table 3. Summary of best response by mRECIST criteria in the randomized population and in patients with target lesions and post-baseline scans receiving sorafenib or placebo plus DEB-TACE.

Response	Best response rate					
	Central review		Investigator review		Patients with target lesions and post-baseline scans (central review)	
	Sorafenib n (%) (n = 154)	Placebo n (%) (n = 153)	Sorafenib n (%) (n = 154)	Placebo n (%) (n = 153)	Sorafenib n (%) (n = 93)	Placebo n (%) (n = 92)
ORR (CR + PR)	55 (35.7)	43 (28.1)	66 (42.9)	53 (34.6)	52 (55.9)	38 (41.3)
CR	20 (13.0)	17 (11.1)	21 (13.6)	20 (13.1)	18 (19.4)	13 (14.1)
PR	35 (22.7)	26 (17.0)	45 (29.2)	33 (21.6)	34 (36.6)	25 (27.2)
DCR (CR + PR + SD)	107 (69.5)	99 (64.7)	124 (80.5)	110 (71.9)	83 (89.2)	70 (76.1)
SD	52 (33.8)	56 (36.7)	58 (37.7)	57 (37.3)	31 (33.3)	32 (34.8)
PD	20 (13.0)	36 (22.5)	16 (10.4)	30 (19.6)	10 (10.8)	22 (23.9)
N/A	27 (17.5)*	18 (11.8)*	22 (14.3)*	13 (8.5)*	**	**

*N/A – Patients without assessable post-baseline scans.
**19 sorafenib and 10 placebo patients with target lesions did not have post-baseline scans and were excluded from the analysis.
Abbreviations: CR, complete response; PR, partial response; ORR, overall response rate; SD, stable disease; PD, progressive disease; DCR, disease control rate, ORR + SD.

Table 5. Asian* and non-Asian subgroups: study drug and DEB-TACE administration and efficacy outcomes.

Safety population	Asian (n = 104)		Non-Asian (n = 200)		Total (N = 304)	
	Sorafenib (n = 54)	Placebo (n = 50)	Sorafenib (n = 99)	Placebo (n = 101)	Sorafenib (n = 153)	Placebo (n = 151)
Duration of sorafenib/placebo treatment, weeks						
Mean	33.6	32.7	26.0	33.7	28.6	33.3
Median	30.0	25.8	17.4	27.9	21.0	27.3
Percentages of patients receiving 1, 2, or ≥3 DEB-TACE sessions						
1	24.1	22.0	42.4	17.8	35.9	19.2
2	35.2	32.0	35.4	40.6	35.3	37.7
≥3	38.9	44.0	20.2	39.6	26.8	41.1
ITT population	Asian (n = 116)		Non-Asian (n = 191)		Total (N = 307)	
	Sorafenib (n = 59)	Placebo (n = 57)	Sorafenib (n = 95)	Placebo (n = 96)	Sorafenib (n = 154)	Placebo (n = 153)
TTP						
Median, wk	24.0	16.1	25.0	24.0	24.1	23.7
HR	0.720		0.865		0.797	
95% CI	0.457, 1.135		0.576, 1.300		0.588, 1.080	
One-sided *p* value	0.078		0.243		0.072	
OS						
Median, wk	n.d.	n.d.	86.1	n.d.	N/D	n.d.
HR	0.677		1.062		0.898	
95% CI	0.355, 1.292		0.646, 1.745		0.606, 1.330	
One-sided *p* value	0.117		0.594		0.295	

n.d., not determined (upper bound could not be estimated due to censored data).
*Patients from China, Korea, Taiwan, Singapore, and Australia.

agent. This trial attempted to standardize TACE by using a bead-based TACE procedure (DEB-TACE) and by prescribing the TACE schedule as backbone to the combination in patients with intermediate stage (BCLC B) HCC. Sorafenib plus DEB-TACE improved TTP according to the predefined statistical threshold for this exploratory study (HR 0.79, one-sided $p = 0.072$), although there was no difference in median TTPs in the sorafenib plus DEB-TACE (169 days) and placebo plus DEB-TACE (166 days) groups. Consistent with earlier single-arm studies, the dosing schedule of sorafenib plus DEB-TACE shown here was technically feasible, with manageable toxicities. Most AEs related to study drug (sorafenib or placebo) were grades 1 and 2, were higher in the sorafenib plus DEB-TACE arm, and were the principal reason for dose reductions and interruptions.

Patients in the sorafenib plus DEB-TACE arm tended to show improvements in secondary endpoints, including time to MVI/EHS and OS, although TTUP was poorer. Per protocol assessment of response in the ITT population may have been lower than expected because 45 patients (27 sorafenib and 18 placebo) did not have an assessable post-baseline scan due to early discontinuation, and because target lesions from 93 patients (42 sorafenib and 51 placebo) were not confirmed by central radiological assessment (per mRECIST criteria, unless all non-target lesions completely resolved, patients without measureable lesions only qualify for SD as best response). Restricting the analysis to patients with target lesions and at least one post-baseline scan (93 sorafenib and 92 placebo), the ORR (complete response + partial response) was higher in the sorafenib than in the placebo plus DEB-TACE group (55.9% *vs.* 41.3%).

At the time of conception of this study, limited information was available about the concomitant use of sorafenib plus TACE, resulting in the application to the protocol of conservative TACE continuation criteria. More than one-third of patients in the sorafenib group received only one round of TACE, with the major reasons for TACE discontinuations in the sorafenib arm being worsening of liver function and decrease of platelet count to <60,000/mm^3. In retrospect, such strict criteria did not take into account transient changes in liver function or platelet count and indeed at least 30% deemed ineligible for additional TACE per protocol did receive further TACE outside the study. A retrospective study reported that a significant number of patients failing to respond to initial TACE responded after a second TACE treatment [45]. Moreover, survival of patients who responded to a second TACE procedure was significantly greater than for patients who did not respond to the first or second TACE treatments, suggesting that patients receive at least two TACE procedures before being classified as nonresponders. Thus the conservative TACE continuation rules in the SPACE trial may have contributed to the low response rate and shorter TTUP.

Several single-arm phase I and II trials have explored the combination of sorafenib plus conventional TACE [32,37,46,47] or DEB-TACE [32], demonstrating that these combinations were feasible in patients with intermediate stage HCC. In this trial, there was a greater improvement in TTP and OS HRs in patients from Asian than from non-Asian countries. Because the number of TACE treatments in the Asian subset were balanced across arms, the improved TTP and OS were likely to have been related to the sorafenib treatment. In contrast, non-Asian patients in the sorafenib arm discontinued TACE treatments earlier and had a shorter duration of sorafenib treatment, both of which may have contributed to the lack of difference in TTP and OS compared with the placebo group. In this regard, an earlier phase III study in Japanese and Korean patients tested whether administration of sorafenib following response to TACE improved TTP in patients with unresectable HCC [28]. While the study was negative, an exploratory subgroup analysis in the Korean subgroup suggested that longer sorafenib treatment duration was associated with improved TTP, in contrast to Japanese patients where no difference in TTP was seen and treatment duration was substantially shorter. Those results parallel the results seen here, with longer

sorafenib treatment duration in Asian than in non-Asian patients (median 30 weeks *vs.* 17 weeks, respectively) being associated with improved TTP and OS, suggesting that duration of sorafenib treatment (albeit in combination with TACE) may be critical for improved outcomes. Similarly, the timing of administration of a multikinase inhibitor in patients being treated with TACE may be critical. A recent phase III trial with the inhibitor brivanib as adjuvant therapy after TACE, also conducted primarily in Asian patients, failed to improve OS in patients with HCC [48].

The overall results of this exploratory trial suggest that the combination of sorafenib plus DEB-TACE was feasible, with manageable toxicities, in patients with intermediate stage HCC and good liver function. The combination did not provide meaningful clinical benefit compared with DEB-TACE alone. The regional differences highlight that the amount of combined treatment received may have been a critical determinant of the clinical outcomes. Likewise, discordance between investigator and central radiologic review and the criteria for additional TACE also may have impacted outcomes. Finally, whether DEB-TACE is the optimal backbone for combination with sorafenib is still unresolved. These experiences may help in the design of studies aiming to clarify the role of sorafenib plus TACE for patients with intermediate stage HCC.

Financial support

Bayer HealthCare, Onyx Pharmaceuticals and Biocompatibles UK, Ltd; NCT 00855218; http://www.clinicaltrials.gov.

Conflict of interest

Riccardo Lencioni has received honoraria from Bayer HealthCare and Biocompatibles UK Ltd, and research funding from Bayer HealthCare; Josep M. Llovet has received consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Bristol-Myers-Squibb, Biocompatibles, Imclone-Lilly, and Novartis; and research funding from Bayer HealthCare Pharmaceuticals, Boehringer-Ingelheim, and Bristol-Myers-Squibb; Guohong Han, Won Young Tak, Jiamei Yang, Alfredo Guglielmi, Seung Woon Paik, Do Young Kim, Gar-Yang Chau, Angelo Luca, and Luis Ruiz del Arbol have no relevant relationships to disclose; Maria Reig has received consulting fees and honoraria from Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals; Marie-Aude Leberre, Woody Niu, Kate Nicholson, and Gerold Meinhardt are employees of Bayer HealthCare Pharmaceuticals; Jordi Bruix has received honoraria and research funding from Bayer HealthCare Pharmaceuticals and consulting fees from Bayer HealthCare Pharmaceuticals, Onyx Pharmaceuticals, Biocompatibles, Bristol-Myers Squibb, Glaxo, Kowa, Novartis, and ArQule.

Authors' contributions

Drs. Riccardo Lencioni, Jordi Bruix, Josep M. Llovet, and Gerold Meinhardt were involved with the SPACE study concept and design; acquisition of data; analysis and interpretation of primary and subset data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; and study supervision. Drs. Guohong Han, Won Young Tak, Jiamei Yang, Alfredo Guglielmi, Seung Woon Paik, Maria Reig, Do Young Kim, Gar-Yang Chau, Angelo Luca, and Luis Ruiz del Arbol, were involved with analysis and interpretation of primary and subset data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and statistical analysis. Drs. Marie-Aude Leberre and Woody Niu were involved with the SPACE study concept and design; acquisition of primary and subset data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision; and administrative and technical support. Kate Nicholson was involved with analysis and interpretation of primary and subset data; drafting of the manuscript; critical revision of the manuscript for important intellectual content and study supervision. The corresponding authors had full access to all of the data and take full responsibility for the veracity of the data and the statistical analyses.

Acknowledgments

The authors would like to thank BelMed Professional Resources, Inc. (New Rochelle, NY, USA) for editorial support.

The following principal investigators (listed alphabetically by country) enrolled patients in the SPACE trial: Australia: P. Gow, S. Strasser, D. Crawford, G. Jeffrey, S. Roberts, W. Sievert; Austria: M. Peck-Radosavljevic, W. Vogel; Belgium: I. Borbath, J. Delwaide, J. Van Laethem, C. Verslype; Canada: M. Sherman, K. Burak, K. Peltekian; China: J. Wang, P. Wu, R. Yang, J. Yang, J. Wang, G. Han; France: P. Merle, M. Ducreux, J. Bronowicki, J. Grange, P. Mathurin, O. Rosmorduc, J. Seitz, D. Samuel, T. Decaens; Germany: H. Blum, H. Wege, T. Ganten, P. Galle, G. Gerken, F. Kolligs, J. Trojan, D. Strobel, F. Lammert, R. Wiest, H. Schmidt, S. Pluntke; Italy: R. Lencioni, M. Colombo, L. Bolondi, F. Farinati, A. Attili, A, Guglielmi, A. Luca, V. Mazzaferro, S. Petronelli, F. Brunello; South Korea: D. Kim, J. Yoon, S. Paik, W. Tak; Singapore: S. Choo; Spain: J. Bustamante, R. Planas, L. Castells, P. Barrera, E. Quintero, J. Pascual, M. Varela, M. Vergara, J. Irurzun, L. del Arbol, C. González, J. Fernández, J. Bruix, M, Reig; Taiwan: S. Wu, P. Chen, G. Chau; United States: J. Llovet, L. Feun, A. Befeler, J. Schwartz, N. Pyrsopoulos, M. Sellers, M. Bloomston, R. Cabrera, D. Heuman, T. Malpass, C. Frenette.

Role of the funding source

Bayer, Onyx, and Biocompatibles UK, Ltd., sponsored the study, oversaw treatment, and performed all statistical analyses. Data were managed in parallel by the sponsors and the principal investigators. This manuscript was written by the study investigators, who had full access to all study data and final responsibility for its interpretation, and made the decision to submit for publication.

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.

[2] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–2128.

[3] Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–1022.

[4] European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.
[5] Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012;379: 1245–1255.
[6] Verslype C, Rosmorduc O, Rougier PESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:vii41–vii48.
[7] Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma. Chemoembolization improves survival. Hepatology 2003;37:429–442.
[8] Raoul JL, Sangro B, Forner A, Mazzaferro V, Piscaglia F, Bolondi L, et al. Evolving strategies for the management of intermediate-stage hepatocellular carcinoma: available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treat Rev 2011;37:212–220.
[9] Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007;46:474–481.
[10] Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. PRECISION V Investigators. 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: 41–52.
[11] Llovet JM, Real MI, Montaña X, Planas R, Coll S, Aponte J, et al. Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734–1739.
[12] Bruix J, Sala M, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology 2004;127:S179–S188.
[13] Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafeNib) non-interventional study. Int J Clin Pract 2012;66:675–683.
[14] Hong K, Khwaja A, Liapi E, Torbenson MS, Georgiades CS, Geschwind JF. New intra-arterial drug delivery system for the treatment of liver cancer: preclinical assessment in a rabbit model of liver cancer. Clin Cancer Res 2006;12:2563–2567.
[15] Lewis AL, Gonzalez MV, Lloyd AW, Hall B, Tang Y, Willis SL, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol 2006;17:335–342.
[16] Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006;17: 1335–1343.
[17] Malagari K, Chatzimichael K, Alexopoulou E, Kelekis A, Hall B, Dourakis S, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31:269–280.
[18] Malagari K, Pomoni M, Spyridopoulos TN, Moschouris H, Kelekis A, Dourakis S, et al. Safety profile of sequential transarterial chemoembolization with DC Bead™: results of 237 hepatocellular carcinoma (HCC) patients. Cardiovasc Intervent Radiol 2011;34:774–785.
[19] Poon RTP, Tso WK, Pang RW, Ng KK, Woo R, Tai KS, et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007;5:1100–1108.
[20] Burrel M, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads: implications for clinical practice and trial design. J Hepatol 2012;56:1330–1335.
[21] Malagari K, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefanioutou A, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012;35:1119–1128.
[22] Wilhelm SM, Carter C, Tang L, Wilkie D, McNabola A, Rong H, et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099–7109.
[23] Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008;7:3129–3140.
[24] Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D, et al. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006;66:11851–11858.
[25] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378–390.
[26] Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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;10:25–34.
[27] Bruix J, Raoul JL, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821–829.
[28] Kudo M, Imanaka K, Chida N, Nakachi K, Tak WY, Takayama T, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011;47:2117–2127.
[29] Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164–1171.
[30] Wang B, Xu H, Gao ZQ, Ning HF, Sun YQ, Cao GW. Increased expression of vascular endothelial growth factor in hepatocellular carcinoma after transcatheter arterial chemoembolization. Acta Radiol 2008;49:523–529.
[31] Xiao EH, Guo D, Bian DJ. Effect of preoperative transcatheter arterial chemoembolization on angiogenesis of hepatocellular carcinoma cells. World J Gastroenterol 2009;15:4582–4586.
[32] 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;29:3960–3967.
[33] Cabrera R, Pannu DS, Caridi J, Firpi RJ, Soldevila-Pico C, Morelli G, et al. The combination of sorafenib with transarterial chemoembolisation for hepatocellular carcinoma. Aliment Pharmacol Ther 2011;34:205–213.
[34] Sieghart W, Pinter M, Reisegger M, Müller C, Ba-Ssalamah A, Lammer J, et al. Conventional transarterial chemoembolisation in combination with sorafenib for patients with hepatocellular carcinoma: a pilot study. Eur Radiol 2012;22:1214–1223.
[35] Park JW, Koh YH, Kim HB, Kim HY, An S, Choi JI, et al. Phase II study of concurrent transarterial chemoembolization and sorafenib in patients with unresectable hepatocellular carcinoma. J Hepatol 2012;56: 1336–1342.
[36] Qu XD, Chen CS, Wang JH, Yan ZP, Chen JM, Gong GQ, et al. The efficacy of TACE combined sorafenib in advanced stages hepatocellular carcinoma. BMC Cancer 2012;12:263.
[37] Chung YH, Han G, Yoon JH, Yang J, Wang J, Shao GL, 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;132:2448–2458.
[38] Han G, Yang J, Shao G, Teng G, Wang M, Yang J, et al. Sorafenib in combination with transarterial chemoembolization in Chinese patients with hepatocellular carcinoma: a subgroup interim analysis of the START trial. Future Oncol 2013;9:403–410.
[39] Zhao Y, Wang WJ, Guan S, Li HL, Xu RC, Wu JB, et al. Sorafenib combined with transarterial chemoembolization for the treatment of advanced hepatocellular carcinoma: a large-scale multicenter study of 222 patients. Ann Oncol 2013;24:1786–1792.
[40] Cui HZ, Dai GH, Shi Y, Chen L. Sorafenib combined with TACE in advanced primary hepatocellular carcinoma. Hepatogastroenterology 2013;60: 305–310.
[41] Chao Y, Chung YH, Han G, Yoon YH, Yang J, Wang J, et al. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. Int J Cancer 2015;136:1458–1467.
[42] Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010;30:52–60.
[43] Bruix J, Reig M, Rimola J, Forner A, Burrel M, Vilana R, et al. Clinical decision making and research in hepatocellular carcinoma: pivotal role of imaging techniques. Hepatology 2011;54:2238–2244.
[44] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–216.
[45] Georgiades C, Geschwind JF, Harrison N, Hines-Peralta A, Liapi E, Hong K, et al. Lack of response after initial chemoembolization for hepatocellular carcinoma: does it predict failure of subsequent treatment? Radiology 2012;265:115–123.

[46] Dufour JF, Hoppe H, Heim MH, Helbling B, Maurhofer O, Szucs-Farkas Z, et al. Continuous administration of sorafenib in combination with transarterial chemoembolization in patients with hepatocellular carcinoma: results of a phase I study. Oncologist 2010;15:1198–1204.
[47] Erhardt A, Kolligs F, Dollinger M, Schott E, Wege H, Bitzer M, et al. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. J Clin Oncol 2014;74:947–954.
[48] Kudo M, Han G, Finn RS, Poon RT, Blanc JF, Yan L, et al. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: a randomized phase III trial. Hepatology 2014;60:1697–1707.