TREATMENT OF HEPATOCELLULAR CARCINOMA COMBINING SORAFENIB AND TRANSARTERIAL LOCOREGIONAL THERAPY: STATE OF THE SCIENCE

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ABSTRACT

The potential for increased efficacy with combined transarterial chemoembolization and sorafenib is of increased interest to specialists who care for patients with unresectable hepatocellular carcinoma. There is strong scientific rationale for combination therapy: transarterial chemoembolization produces ischemia and stimulates hypoxia-inducible factor–1α, resulting in a local and systemic upregulation of vascular endothelial growth factor (VEGF), which can increase tumor angiogenesis. This upregulation can theoretically be counteracted with the multikinase inhibitor sorafenib, which is thought to act directly on platelet-derived growth factor, Raf kinase, and VEGF receptors. The potential of this approach has not yet been fully realized in clinical trials, and many unanswered questions remain. This review article discusses the state of the science of arterial locoregional therapies and sorafenib.

ABBRVIATIONS

AASLD = American Association for the Study of Liver Diseases, AE = adverse event, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CR = complete response, DCR = disease control rate, DEB = doxorubicin-eluting bead, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HFSR = hand–foot skin reaction, HR = hazard ratio, LRT = locoregional therapy, NCT = National Clinical Trials, OR = odds ratio, ORR = objective response rate, OS = overall survival, PS = performance status, RECIST = Response Evaluation Criteria In Solid Tumors, SPACE = Sorafenib or Placebo in Combination with Transarterial Chemoembolization with Doxorubicin-Eluting Beads for Intermediate-Stage Hepatocellular Carcinoma, TTP = time to progression, VEGF = vascular endothelial growth factor

Transarterial chemoembolization and sorafenib have shown efficacy in intermediate and advanced hepatocellular carcinoma (HCC), but tumor recurrence is common and long-term survival rates are low (1–4). Therefore, a critical unmet clinical need remains for safe and novel therapies that prolong survival in patients with unresectable HCC. Combination treatment with sorafenib and transarterial chemoembolization has a strong scientific rationale. Transarterial chemoembolization induces ischemia, resulting in local and systemic increases in vascular endothelial growth factor (VEGF), whereas sorafenib inhibits the activity of VEGF receptors; thus, combination therapy has the theoretical potential to yield improved efficacy versus current standards of care (5). In this article, we discuss recent evidence evaluating the safety and efficacy of combination therapy with sorafenib and transarterial chemoembolization or other locoregional therapies (LRTs) for patients with HCC, and consider the unresolved issues regarding optimal use of this combination.

SORAFENIB MONOTHERAPY PROLONGS SURVIVAL IN PATIENTS WITH ADVANCED HCC

Several growth signaling pathways have been implicated in the pathogenesis of HCC (6). The molecularly targeted agent sorafenib is an oral inhibitor of multiple kinases involved in HCC proliferation and angiogenesis, including platelet-derived growth factor, Raf kinase, and VEGF receptors (7). Two pivotal phase III trials (SHARP [a phase III study of sorafenib in patients with advanced hepatocellular carcinoma] and Asia-Pacific) (1,2) have demonstrated a survival advantage for patients with advanced HCC per Barcelona Clinic Liver Cancer (BCLC) criteria treated with sorafenib. Based on these trials,
sorafenib has been established as the standard of care for treatment of advanced HCC. The American Association for the Study of Liver Diseases (AASLD) recommends sorafenib for the treatment of advanced (ie, BCLC stage C) HCC, and the National Comprehensive Cancer Network guidelines advise administration of sorafenib as an option for unresectable HCC with extensive liver tumor burden or metastases (8,9).

**TRANSCATHETER LOCAL THERAPIES FOR HCC**

Two randomized controlled trials (10,11) have demonstrated improved survival with transarterial chemoembolization compared with symptomatic treatment for patients with BCLC-intermediate, unresectable HCC. Two meta-analyses (12,13) published shortly after the two aforementioned randomized controlled trials (10,11) confirmed a survival benefit (odds ratios [ORs] for survival at 2 y, 0.42 [95% confidence interval (CI), 0.20–0.88] and 0.54 [95% CI, 0.33–0.89]; P = .015) (12,13). In contrast, a more recent meta-analysis (14) of nine randomized controlled trials (six evaluating transarterial chemoembolization and three evaluating transcatheter arterial embolization) including 645 patients with unresectable HCC failed to demonstrate an effect of transarterial chemoembolization or transcatheter arterial embolization on survival (hazard ratio [HR], 0.81 [95% CI, 0.64–1.02]; P = .07). A subgroup analysis of the six transarterial chemoembolization trials also showed no significant effect on survival (HR, 0.79 [95% CI, 0.58–1.06]) (14). However, results of the latter meta-analysis (14) have been called into question, as three of the nine trials included interventions other than transarterial embolization or transcatheter arterial embolization (radiofrequency ablation, percutaneous ethanol injection, and tamoxifen), potentially confounding effects on survival (15,16).

Guidelines developed by the AASLD recommend transarterial chemoembolization for BCLC stage B disease (8). Other guidelines support transcatheter therapies including arterial chemoinfusion, transarterial chemoembolization with drug-eluting beads (DEBs), and radioembolization (17–20). These therapies are currently being investigated with and without the use of systemic agents.

**RATIONALE FOR COMBINATION THERAPY WITH SORAFENIB AND TRANSARTERIAL CHEMOEMBOLIZATION**

Available treatments for intermediate/advanced HCC are associated with substantial limitations. As histologic grade increases, arterial blood supply decreases significantly (21). Similarly, early HCC and dysplastic nodules (≤ 2 cm) have decreased microvascular density compared with moderate-sized tumors (2–5 cm). Tumors larger than 5 cm also start to outgrow their vascular supply and have relatively decreased arterial microvascularity (22).

Because of this variability in vascular supply, transarterial chemoembolization may not always produce a complete tumor response; in a recent pathologic analysis of 122 HCC nodules (23), only 43% showed full necrosis after conventional or selective/supraselective transarterial chemoembolization. Progression rates in patients treated with triple-drug transarterial chemoembolization have been described (24), with time to progression dependent on baseline Child–Pugh class and BCLC stage. Among patients with intermediate-stage HCC who showed an initial response to transarterial chemoembolization, 65% experienced tumor recurrence within 3 years (3). Predictably, long-term survival rates after transarterial chemoembolization are poor (4). Although sorafenib is the only agent proven to increase survival in patients with advanced disease, the survival advantage is modest and suggests a continued need for the examination of new and novel strategies to prolong survival (1,2). A strong biologic rationale exists for combination therapy with both treatments, which has the potential to yield synergistic benefit.

Transarterial chemoembolization is associated with local and systemic increases in VEGF. Embolization interrupts blood supply to liver tumors, inducing hypoxia and necrosis. However, tumor cells that survive treatment upregulate the oxygen-sensitive transcription factor hypoxia-inducible factor–1α and its downstream target, the angiogenic agent VEGF (25,26). Indeed, HCC tumor samples from patients previously treated with transarterial chemoembolization contain significantly more VEGF-positive cells than tumor samples from patients undergoing liver resection without chemoembolization (P < .01) (27).

In several clinical studies (28–31), significant but transient increases in plasma VEGF levels have been observed after transarterial embolization/transcatheter arterial embolization treatment. In the largest of these studies (30) (N = 147), serum samples collected within 1–2 days after chemoembolization contained significantly greater VEGF concentrations than did samples obtained at baseline. In samples obtained 1 month after chemoembolization, mean VEGF levels had decreased to near baseline levels. In addition, patients with the greatest increases in plasma VEGF after chemoembolization were significantly more likely to exhibit extrahepatic metastases at 1- and 6-month follow-up visits and to have worse progression-free survival (30).

In contrast, sorafenib inhibits the activity of VEGF receptors and other proangiogenic signaling pathways (32). In mouse xenograft models of HCC, sorafenib significantly reduced tumor microvessel density (33). These observations, combined with the relatively short half-life of sorafenib, suggest that sorafenib administered during and after transarterial chemoembolization treatment may counteract hypoxia-induced angiogenesis and potentially yield synergistic efficacy in decreasing tumor burden (34). However, these hypothesis-generating findings remain speculative until sufficient clinical trial data can be accumulated.
CLINICAL EVIDENCE FOR COMBINED SORAFENIB AND LRT IS LIMITED

To date, combination therapy with sorafenib and LRT has been evaluated in 22 clinical studies (35–56). The majority of these studies have sample sizes of fewer than 80 patients, except for the phase II Sorafenib or Placebo in Combination with Transarterial Chemoembolization with Doxorubicin-Eluting Beads for Intermediate-Stage Hepatocellular Carcinoma (SPACE) study (N = 307) and the phase III study of Kudo et al (N = 458) (42,43). The phase III Heidelberg Liver Cancer Study (41) is ongoing, and only safety results of the first 21 enrolled patients have been presented. The registry study by Martin and colleagues (55) includes 150 patients treated with DEB chemoembolization, 30 of whom also received sorafenib. In addition, many of the available studies are published in abstract form only (specified in Table 1) (38,40,41,43,44,55,56), further limiting interpretation and application to clinical practice.

EFFICACY OF TRANSCATHETER LRT WITH SORAFENIB

Efficacy Results from Comparative Studies

Two small comparative trials have reported a significant survival advantage for combination treatment with sorafenib and transarterial chemoembolization. In a retrospective study of 20 patients with recurrence of HCC following liver transplantation (52), median overall survival (OS) was 14 months for transarterial chemoembolization with sorafenib versus 6 months for chemoembolization alone (P = .005). In a large retrospective study of transarterial chemoembolization or chemoinfusion for patients with HCC and extrahepatic metastasis at diagnosis (54), a subgroup was also treated with sorafenib or systemic cytotoxic chemotherapy. In this study (54), the choice of systemic chemotherapy was heterogeneous and consisted of a few cycles of 5-fluorouracil, cisplatin, doxorubicin, gemcitabine, or oxaliplatin at the discretion of the treating physician. For the 10 patients treated with transarterial chemoembolization/chemoinfusion and sorafenib, median OS was significantly prolonged to 20.5 months, compared with a median OS of 10 months among seven patients treated with chemoembolization/chemoinfusion plus systemic chemotherapy (P = .0089) (54). However, because the number of sorafenib-treated patients in these studies was small, findings should be interpreted with caution.

In addition, three small comparative trials (37,48,55) showed a nonsignificant trend for increased survival with combination therapy versus monotherapy. As part of a DEB chemoembolization registry study (55), patients receiving sorafenib with DEB chemoembolization (n = 30) were compared with case-matched patients who received DEB chemoembolization alone (n = 120). Median OS times were 12 months and 10 months, respectively (P = .09) (55). In a retrospective study of 32 patients treated with sorafenib and LRT versus LRT alone (37), median survival times were 18.0 months versus 15.6 months, respectively (P = .46). However, this study assessed multiple forms of LRT (radiofrequency ablation, transarterial embolization/chemoembolization, radioembolization, or resection), and sorafenib could have been started at any time within 90 days of LRT (37). In a group of 50 patients with advanced HCC treated with sorafenib with LRT (n = 13) versus sorafenib alone (n = 37), median OS times were 327 days versus 153 days, respectively (P = .327) (48). LRT types in this study included transarterial chemoembolization, radioembolization, brachytherapy, and local ablative therapies. In addition, these types of studies often allow for crossover to alternative therapies, potentially confounding the results. However, these findings underscore the challenges of conducting trials in HCC, a disease in which patients routinely receive multiple treatments as the disease migrates into different BCLC stages throughout its course.

Randomized Studies

Kudo et al Study. A phase III study (42) of 458 patients (100% with Child–Pugh class A disease, 88% with Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 0) with unresectable HCC failed to indicate an added benefit for sorafenib administered after transarterial chemoembolization versus chemoembolization alone. For sorafenib-treated patients, the median time to progression (TTP; the primary endpoint) was 5.4 months, compared with 3.7 months for placebo-treated patients (HR, 0.87; P = .25). Median OS was 29.7 months in the sorafenib group but was not reached in the placebo group (HR, 1.06; P = .790). Notably, this study was confounded by the administration of sorafenib 5.6–13.3 weeks after the last chemoembolization (42). Because plasma VEGF levels decrease to baseline levels within 4 weeks of chemoembolization treatment, this dosing schedule likely precluded optimal efficacy of the combination (28–31). In addition, sorafenib may have been inconsistently administered in this study: Korean patients (n = 71), who generally received sorafenib for much longer than Japanese patients (n = 387; 31 weeks vs 16 weeks, respectively), experienced better outcomes, perhaps as a result of longer therapy (HR for TTP, 0.38 [95% CI, 0.18–0.81] and 0.94 [95% CI, 0.75–1.19], respectively). However, these differences likely reflect real-life variations in clinical practice patterns among regions and specialties, which can confound trial outcomes. Finally, the trial by Kudo et al (42) was the earliest large study to investigate combination therapy with sorafenib and LRT. Results of the SHARP and Asia-Pacific trials were not available at the time of trial design and execution, which may have contributed to the negative outcome.

Sansonno et al Study. Contrary to results of the phase III study by Kudo et al (42), a recent prospective study by Sansonno et al (47) demonstrated a significant survival
### Table 1. Prospective Clinical Studies of More than 20 Patients Receiving Combination Therapy with Sorafenib and Locoregional Therapy for HCC

<table>
<thead>
<tr>
<th>Study, Year, No. of Pts. Comparative studies</th>
<th>Treatment Schema and Sorafenib Timing</th>
<th>Patient Population</th>
<th>Efficacy</th>
<th>Safety</th>
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<tbody>
<tr>
<td>Hoffman et al, 2011 (41) (HeiLivCa interim analysis), N = 21∗</td>
<td>Sorafenib + chemoembolization vs chemoembolization; timing NR</td>
<td>Child–Pugh A, 71%; B, 29%; ECOG PS, 0, 61%; 1, 39%</td>
<td>30-d mortality after liver transplantation: 28%</td>
<td>“No chemoembolization-associated AEs”; grade 3/4 AEs: Hyperbilirubinemia (24%), GGT elevation (19%), AST/ALT elevation (10%)</td>
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<tr>
<td>Sansonno et al, 2012 (47), N = 80</td>
<td>Sorafenib + chemoembolization vs chemoembolization in patients with HCV; sequential (sorafenib started 30 d after chemoembolization)</td>
<td>Child–Pugh A, 100%; BCLC B, 100%; ECOG PS 0, 81%; 1, 19%</td>
<td>Median TTP: 9.2 mo sorafenib vs 4.9 mo placebo (HR, 2.5 [95% CI, 1.66-7.56]; ( P &lt; .001 )); intrahepatic recurrence within 6 mo of chemoembolization: 22% sorafenib vs 71% placebo (( P = .005 )); local progression of ablated lesion: 45% sorafenib vs 52% placebo (( P = .3 )); metachronous, multicentric, intrahepatic tumor progression: 22% sorafenib vs 48% placebo (( P &lt; .05 ))</td>
<td>Postchemoembolization syndrome: 23% sorafenib vs 25% placebo; drug-related grade 3/4 AEs (sorafenib vs placebo): HFSR (10% vs 0%), rash/desquamation (10% vs 0%), fatigue (8% vs 5%), hematologic event (8% vs 0%), anorexia (3% vs 5%), diarrhea (3% vs 0%), nausea (3% vs 0%)</td>
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<td>Martin et al, 2010 (55), N = 150↑</td>
<td>Sorafenib + DEB chemoembolization (n = 30) vs DEB chemoembolization (n = 120); timing NR</td>
<td>Child–Pugh B, 31% (sorafenib + DEB chemoembolization) and 39% (DEB chemoembolization alone)</td>
<td>Median OS: sorafenib + DEB chemoembolization, 12 mo; DEB chemoembolization, 10 mo (( P = .09 ))</td>
<td>Overall AEs: 30% (sorafenib + DEB chemoembolization) vs 34% (DEB chemoembolization; ( P = .20 )); liver AEs (all grades): 13% (sorafenib + DEB chemoembolization) vs 15% (DEB chemoembolization; ( P = .86 )); hematologic AEs (all grades): 13% (sorafenib + DEB chemoembolization) vs 2% (DEB chemoembolization; ( P = .007 ))</td>
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<tr>
<td>Lencioni et al, 2012 (43) (SPACE), N = 307↑</td>
<td>DEB chemoembolization + sorafenib or placebo; continuous (sorafenib started 3–7 d before chemoembolization)</td>
<td>Child–Pugh A, 100%; ECOG PS 0, 100%</td>
<td>Median TTP: 169 d sorafenib vs 166 d placebo (HR, 0.797 [95% CI, 0.588–1.08]; ( P = .072 )); TVI/TEHS: HR, 0.621 (95% CI, 0.321–1.200; ( P = .076 )); OS: HR, 0.898 (95% CI, 0.606–1.33; ( P = .295 )); median TTUP: 95 d sorafenib vs 224 d placebo (HR, 1.586 [95% CI, 1.200–2.096]; ( P = .999 ))</td>
<td>No unexpected safety findings</td>
</tr>
<tr>
<td>Kudo et al, 2011 (42), N = 458</td>
<td>Sorafenib + chemoembolization vs chemoembolization; sequential (sorafenib started at median 9.3 wk [range, 5.6–13.3] after chemoembolization)</td>
<td>Child–Pugh A, 100%; ECOG PS 0, 88.0%; 1, 12%</td>
<td>Median TTP: 5.4 mo sorafenib vs 3.7 mo placebo (HR, 0.87 [95% CI, 0.70–1.09]; ( P = .252 )); median OS: 29.7 mo sorafenib vs NR placebo (HR, 1.06 [95% CI, 0.69–1.64]; ( P = .79 ))</td>
<td>Dose reductions, 73% sorafenib vs 15% placebo; dose interruptions, 91% sorafenib vs 18% placebo; discontinuation due to AEs, 41% sorafenib vs 6% placebo; grade 3/4</td>
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Noncomparative studies with chemoembolization

**Erhardt et al, 2011** (40)
(SOCRATES), N = 45
Sorafenib + chemoembolization; interrupted (sorafenib started 14 d before chemoembolization with drug holidays 3 d before and 1 d after chemoembolization)
Child–Pugh A, 81%; B, 19%; BCLC B, 84%; C, 16%
Disease response: CR (0%), PR (2%), SD (76%), PD (NR), median TTP (18.9 mo), median OS (20.1 mo)
Grade 3/4 AEs: diarrhea (9%), hepatic encephalopathy (9%), HFSR (7%), elevated ALT (7%), thrombocytopenia (5%), ascites (2%)

**Park et al, 2012** (45)
(COTSUN KOREA), N = 50
Sorafenib + chemoembolization; interrupted (sorafenib started 3 d after first chemoembolization with drug holidays 1 d before and 2 d after each subsequent chemoembolization)
Child–Pugh A, 94%; B, 6%; BCLC B, 82%; C, 18%; ECOG PS 0, 44%; 1, 56%
Disease response: CR (0%), PR (44%), SD (40%), median TTP (7.1 mo), median OS (20.8 mo), 6-mo PFS (52%)
Dose reductions in 70%; grade 3/4 AEs: HFSR (42%), elevated ALT (36%), elevated AST (32%), leukocytopenia (14%), thrombocytopenia (10%), diarrhea (6%), rash/desquamation (6%), anorexia (4%), fatigue (4%), nausea (2%), oral mucositis (2%)

**Lee et al, 2011** (56), N = 59
Sorafenib + chemoembolization; timing NR
BCLC B, 100%; HBV, 88%; Child–Pugh A, 93%
Disease response: CR (22%), PR (47%), SD (7%), PD (24%); genetic polymorphisms of FGF2 and HIF-1α may be related to response
Grade 3/4 drug-related AEs: any grade 3/4 AE (62%), HFSR (16%), elevated ALT (13%), neutropenia (13%)

**Chung et al, 2010** (38)
(START second interim analysis), N = 63 (safety), n = 50 (efficacy)
Sorafenib + chemoembolization; sequential (sorafenib started 4 d after first chemoembolization and held 4 d and 4 d after each)
Child–Pugh A, 94%
Disease response: CR (36%), PR or SD (60%), PD (4%)
Grade 3/4 drug-related AEs: any grade 3/4 AE (62%), HFSR (16%), elevated ALT (13%), neutropenia (13%)

Noncomparative studies with DEB chemoembolization

**Pawlik et al, 2011** (57), N = 35
Sorafenib + DEB chemoembolization; continuous (sorafenib started 1 wk before chemoembolization)
Child–Pugh A, 89%; B, 11%; BCLC B, 34%; C, 64%; ECOG PS 0, 46%; 1, 54%
Disease response: CR (0%), PR (9%), SD (86%), PD (5%); 50% decrease in tumor enhancement; 23% increase in tumor ADC values
25 dose reductions, 40 dose interruptions; discontinuations in 66%; grade 3/4 AEs during cycle 1: fatigue (38%), elevated ALT (30%), elevated AST (24%), HFSR (18%), hypertension (6%), encephalopathy (6%); less toxicity in cycle 2

(Continued)
Table 1. Prospective Clinical Studies of More than 20 Patients Receiving Combination Therapy with Sorafenib and Locoregional Therapy for HCC (continued)

<table>
<thead>
<tr>
<th>Study, Year, No. of Pts.</th>
<th>Treatment Schema and Sorafenib Timing</th>
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<th>Efficacy</th>
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<tbody>
<tr>
<td>Cabrera et al, 2011 (35), N = 47</td>
<td>Sorafenib + DEB chemoembolization (85%) and/or 90Y (15%); continuous (sorafenib started 2–4 wk before chemoembolization)</td>
<td>Child–Pugh A, 72%; B, 28%; BCLC B, 81%; C, 19%; ECOG PS 0, 74%; 1, 26%</td>
<td>Disease response: CR (27%), PR (29%), SD (12%), PD (32%), median OS (18.5 mo)</td>
<td>Dose reductions in 66%; dose interruptions in 40%; discontinuation due to AEs in 43%; postchemoembolization syndrome in 23%; grade 3/4 AEs in &gt; 5%; HFSR (26%), hypertension (19%), fatigue (13%), new ascites (9%), leukopenia (9%), diarrhea (6%), abdominal pain (6%), elevated bilirubin (6%), hypotension (6%)</td>
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Noncomparative studies with 90Y radioembolization

<table>
<thead>
<tr>
<th>Study, Year, No. of Pts.</th>
<th>Treatment Schema and Sorafenib Timing</th>
<th>Patient Population</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
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<tbody>
<tr>
<td>Nudo et al, 2009 (44), N = 21†</td>
<td>Sorafenib + 90Y; continuous (sorafenib started ≥ 7 wk before 90Y)</td>
<td>Child–Pugh A, 71%; B, 24%; ECOG PS 0, 29%; 1, 52%; 2, 19%</td>
<td>All patients showed radiologic response; 19% had complete tumor necrosis; SD in 22% of patients</td>
<td>Grade 3/4 AEs: ascites (10%), liver dysfunction (5%)</td>
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</table>

ADC = apparent diffusion coefficient, AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, COTSUN KOREA = a phase II study of the combination of TACE and sorafenib for patients with unresectable hepatocellular carcinoma in National Cancer Center Korea (COTSUN Korea Trial), CR = complete response, DEB = doxorubicin-eluting bead, ECOG = Eastern Cooperative Oncology Group, GGT = g-glutamyl transferase, HBV = hepatitis B virus, HCV = hepatitis C virus, HeiLivCa = Heidelberg Liver Cancer, HFSR = hand–foot skin reaction, HIF-1α = hypoxia-inducible factor–1α, HR = hazard ratio, NR = not reported, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, PS = performance status, RECIST = Response Evaluation Criteria In Solid Tumors, SD = stable disease, SPACE = Sorafenib or Placebo in Combination with Transarterial Chemoembolization with Doxorubicin-Eluting Beads for Intermediate-Stage Hepatocellular Carcinoma, START = study in Asia of the combination of transcatheter arterial chemoembolization (TACE) with sorafenib in patients with hepatocellular carcinoma trial; TTP = time to progression, TTUP = time to untreatable progression, TVI/TEHS = time to vascular invasion/time to extrahepatic spread.

*Safety data from the first 21 consecutive patients analyzed without unblinding as to study arm.
† Abstract data.
‡ Disease response per RECIST unless otherwise indicated.
§ Disease response per modified RECIST.
* Number of patients not reported.
advantage for 80 patients treated with sorafenib beginning 30 days after transarterial chemoembolization. In this study, median TTP was 9.2 months for sorafenib-treated patients, compared with 4.9 months for placebo-treated patients (HR, 2.5; \( P < .001 \)). In addition, fewer patients in the sorafenib arm than the placebo arm experienced intrahepatic tumor recurrence at 6 months after chemoembolization (22% vs 71%, respectively; \( P = .005 \)) (47). One difference between this study and the study by Kudo et al (42) is the higher percentage of patients with hepatitis C virus (HCV)–related HCC (100% vs 63%, respectively) (42,47). Patients with HCV may exhibit an improved OS with sorafenib therapy compared with patients with HCC of other etiologies. A subset analysis of patients with HCV-related HCC enrolled in the phase III SHARP trial showed superior median OS with sorafenib compared with the study population as a whole (14.0 mo vs 10.7 mo, respectively); however, this study was not powered to demonstrate significance (2,58).

**SPACE Study.** Preliminary results of the SPACE study (43) have been presented (Table 1). This was a global phase II study evaluating DEB transarterial chemoembolization with continuous sorafenib/placebo in BCLC-intermediate, multinodular HCC. Sorafenib (400 mg twice daily) was administered in 4-week cycles, with DEB chemoembolization administered on a fixed schedule. As the SPACE study was a hypothesis-generating trial, the groups were compared by using a stratified one-sided log-rank test with an \( \alpha \) of 0.15 (ie, 85% power), rather than an \( \alpha \) of 0.05 (ie, 95% power). Although median TTP (ie, treatment difference at one point in time) was similar in the two treatment arms, the HR of 0.8 suggested a 20% reduction in progression risk over the entire course of treatment (43). The study also investigated the secondary endpoint of time to vascular invasion/time or extrahepatic spread. This concept has been described in a comprehensive analysis of patterns of progression in 285 patients with HCC and is of clinical relevance because it may result in the need for a change in treatment strategy (59). There were no differences in time to vascular invasion/time to extrahepatic spread between treatment groups (43). Preliminary OS was also the same between the two study arms. Response rates slightly favored sorafenib, with an objective response rate (ORR) of 36% for sorafenib versus 28% for placebo by modified Response Evaluation Criteria in Solid Tumors (RECIST) and disease control rates (DCRs) of 70% for sorafenib and 65% for placebo (43). The study also included time to untreated progression, defined as a failure to achieve response after two or more DEB chemoembolization sessions or emergence of contraindication to chemoembolization (vascular invasion, metastases, ascites, Child–Pugh class B status, progression to ECOG PS \( \geq \) 2, or platelet count < 60,000/\( \mu \)L). Time to untreated progression appeared to be longer in the placebo arm, but the difference was not significant (43). This study demonstrated the challenges and complexities of global studies of transarterial chemoembolization with concurrent sorafenib; ongoing phase III trials by American and European groups (as described later) may help resolve outstanding questions regarding sorafenib and LRTs for HCC. Clarification of several unanswered questions is awaited from the final publication.

**Efficacy Results from Noncomparative Studies**

Efficacy results from noncomparative trials assessing sorafenib with transcatheter LRTs for HCC have varied considerably, likely because of differences in study design and/or endpoints. Four prospective single-arm trials with sample sizes of more than 20 patients have evaluated sorafenib in combination with transarterial chemoembolization (38,40,45,56) (Table 1). In all these trials, sorafenib was initiated shortly before the first chemoembolization session (ie, “continuous sorafenib administration”) or soon after the first session (ie, “sequential sorafenib administration”). For three of the studies (38,40,45), a “drug holiday” was instituted surrounding the time of chemoembolization administration (ie, “interrupted sorafenib administration”). Complete response (CR) rates varied from 0% to 36%, and DCRs (CR plus partial response plus stable disease) ranged from 76% to 96% (38,40,45,56). Two of these studies (40,45) reported median TTP and OS. Although median TTP varied considerably between the two studies (7.1 mo and 18.9 mo), median OS was similar (20.8 mo and 20.1 mo). Because results from one of these studies are available only in abstract form, it is difficult to interpret the basis or relevance of the difference in TTP.

Two single-arm prospective studies (35,57) have explored sorafenib in combination with DEB transarterial chemoembolization. Pawlik et al (57) reported an ORR (CR plus partial response) of 9% and a DCR of 95% per RECIST. Per European Association for the Study of the Liver criteria, which assess tumor viability, 58% of study patients showed an objective response and 100% showed disease control (57,60). In addition, mean tumor enhancement decreased by 50% (\( P < .001 \)) and mean apparent diffusion coefficient of the tumor increased by 23% (\( P < .05 \)) (57). Cabrera et al (35) reported response rates per modified RECIST criteria, which, like European Association for the Study of the Liver criteria, evaluate treatment response based on tumor viability. At 6 months, ORR was 56% and DCR was 68% (35).

Two small, prospective, single-arm studies (36,44) evaluated transarterial radioembolization with yttrium-90 microspheres in combination with sorafenib. In one study (44), sorafenib was given continuously throughout transarterial radioembolization; in the other study (36), sorafenib was initiated as long as 2 weeks after transarterial radioembolization. All 21 patients enrolled in the study by Nudo et al (44) showed a radiologic response, and 19% had complete tumor necrosis. In the study by Chow et al (36)
(N = 34), a relatively high ORR of 36% was achieved despite a study population that included a high proportion (65%) of patients with BCLC stage C disease.

Transcatheter LRT Combined with Sorafenib: Adverse Events

As summarized in Table 1, data from prospective clinical trials in patients with HCC suggest that the incidence of selected adverse events (AEs) may be higher with combination therapy than with transarterial chemoembolization or DEB chemoembolization alone (42,43,55). In the phase III trial of sorafenib with transarterial chemoembolization by Kudo and colleagues (42), all patients in the sorafenib group experienced a drug-related AE, compared with 61% of patients in the placebo group. Among sorafenib-treated patients, 41% permanently discontinued study treatment as the result of an AE, compared with 6% of placebo-treated patients (42). The incidences of grade 3/4 hand–foot skin reaction (HFSR) and hypertension were 35% (vs 0% for placebo) and 15% (vs 1% for placebo), respectively. In contrast, in the sorafenib arm of the pivotal SHARP and Asia-Pacific studies (1,2), 8%–11% of patients developed grade 3/4 HFSR and 2% developed grade 3/4 hypertension. Although results from different studies cannot be directly compared, these data intitmate that sorafenib-related AEs may be more frequent when sorafenib is combined with chemoembolization (1,2,42). However, results of these trials also highlight differences in safety outcomes when systemic agents are administered in a clinical trial environment versus routine clinical practice (61).

Notably, a recent prospective study (50) of 15 patients (60%/33% BCLC stage B/C, 80% Child–Pugh class A, 93% ECOG PS 0) treated with transcatheter chemoembolization and continuous sorafenib was terminated prematurely because of safety concerns. Six patients (40%) underwent 10 hospitalizations for serious AEs during the study. One of these events (dehydration) was considered related to sorafenib, and nine AEs in six patients were deemed to be chemoembolization-related (hepatic decompensation [n = 4], febrile neutropenia [n = 2], acute renal failure [n = 1], cholangitis [n = 1], and severe liver dysfunction with hypoglycemia [n = 1]). Five patients (33%) died during the 6-month study period. In addition, 47% of patients experienced all-grade neutropenia and 20% experienced febrile neutropenia. The authors attributed this frequency of serious AEs to high doses of doxorubicin administered. After doxorubicin doses were decreased by 25%, no further febrile neutropenia events were reported (50).

Compared with the phase III study by Kudo et al (42), incidences of grade 3/4 AEs in the SPACE trial (43) were generally lower overall, and were more balanced between study arms (Table 1). In addition, the frequency of grade 3/4 HFSR in the sorafenib arm of the SPACE trial (9%) was consistent with findings in the pivotal sorafenib trials (8%–11%) (1,2,43). However, the rate of grade 3/4 hypertension remained high in the SPACE trial (16%) compared with the sorafenib pivotal trials (2%) (1,2,43). These results suggest that DEB chemoembolization (used in the SPACE study [43]) may be more tolerable than conventional chemoembolization (used in the study by Kudo et al [42]). Indeed, compared with conventional chemoembolization, DEB chemoembolization is associated with a significantly lower maximal concentration of doxorubicin in the peripheral blood (P = .00002) (21). In addition, a phase II randomized study (61) of 212 patients with unresectable HCC (78% Child–Pugh class A, 70% BCLC stage B, 73% ECOG PS 0) supports a superior safety profile for DEB chemoembolization compared with conventional chemoembolization. The mean maximum increases in alanine aminotransferase and aspartate aminotransferase levels were 50% and 41% less, respectively, for patients in the DEB chemoembolization arm compared with patients in the conventional chemoembolization arm (P < .001). In addition, DEB chemoembolization–treated patients experienced fewer doxorubicin-related AEs than conventional chemoembolization–treated patients (P = .0001) (61). Differences in safety outcomes in the SPACE (43) and Kudo et al (42) studies may also be explained by the variations in chemotherapeutic agent used (doxorubicin for SPACE trial [43] vs epirubicin/cisplatin/doxorubicin/mitomycin alone or in combination for Kudo et al [42]) or dose administered. Although neither study reported mean chemotherapeutic dose administered, it is well known that many patients do not receive the prescribed dose of chemoembolic agent in general practice.

Although further studies are required, clinical studies suggest that sorafenib combined with LRT is feasible and tolerable. AEs are generally manageable with dose reductions (35,38,39). In addition, toxicities associated with combination therapy may decrease after the first cycle of LRT. In a phase II study of DEB chemoembolization with continuous sorafenib (57), 54% of patients experienced a grade 3/4 AE during or after the second treatment cycle, compared with 91% of patients during the first cycle.

UNRESOLVED QUESTIONS AND FUTURE DIRECTIONS

Current AASLD guidelines recommend transarterial chemoembolization for treatment of intermediate-stage HCC (per BCLC criteria) and sorafenib for the treatment of advanced HCC (8). Although most of the clinical trials evaluating sorafenib and LRT have enrolled patients with intermediate-stage HCC, the ideal patient population for combination therapy remains undefined. In particular, the safety and efficacy of combination therapy in patients with Child–Pugh class B or C cirrhosis have not been well studied. Only one small prospective study (35) has directly compared survival by Child–Pugh status. Among 47 patients treated with DEB chemoembolization or radioembolization and concurrent sorafenib, median survival
<table>
<thead>
<tr>
<th>NCT Identifier, Name</th>
<th>Phase/No. of Pts.</th>
<th>Key Inclusion Criteria</th>
<th>Treatment Schema</th>
<th>Sorafenib Timing</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00990860, START*</td>
<td>II/36</td>
<td>Unresectable HCC, solitary tumor &gt; 3 cm in diameter or multifocal disease; size of largest tumor ≤ 10 cm; Child–Pugh A/B (score ≤ 7), BCLC stage B, ECOG PS 0/1, no previous LRT</td>
<td>Sorafenib + chemoembolization</td>
<td>Sequential: sorafenib started 4 d after first chemoembolization and held 4 d before and 4 d after each subsequent chemoembolization</td>
<td>Primary, safety; secondary, TTP, OS, PFS, no. of chemoembolization cycles</td>
</tr>
<tr>
<td>NCT00844883</td>
<td>II/50</td>
<td>Unresectable HCC, ≤ 30% with macrovascular invasion and/or asymptomatic extrahepatic disease, multifocal HCC acceptable, ECOG PS 0/1, Child–Pugh A/B (score ≤ 7)</td>
<td>Sorafenib + DEB chemoembolization</td>
<td>NR</td>
<td>Primary, safety; secondary, size and viability of treated lesions</td>
</tr>
<tr>
<td>NCT01170104</td>
<td>II/63</td>
<td>Unresectable HCC, ECOG PS 0/1, Child–Pugh A/B (score ≤ 7)</td>
<td>Sorafenib + chemoembolization</td>
<td>Continuous: sorafenib administered as continuous dosing from day 1 of each cycle until progression, or ≤ 6 cycles of chemoembolization</td>
<td>Primary, TTP; secondary, safety</td>
</tr>
<tr>
<td>NCT01217034, TACTICS</td>
<td>II/228</td>
<td>Unresectable HCC, maximum tumor diameter ≤ 10 cm, maximum number of nodules ≤ 10, 0/1 prior chemoembolizations, ECOG PS 0/1, Child–Pugh A</td>
<td>Chemoembolization + sorafenib vs chemoembolization</td>
<td>Interrupted: sorafenib interrupted 2 d before chemoembolization and resumed 3 d after chemoembolization</td>
<td>Primary, TTUP; secondary, TTP, OS, ORR, tumor markers, safety</td>
</tr>
<tr>
<td>NCT01126645, SORAMIC</td>
<td>II/665</td>
<td>HCC; extrahepatic spread to bone, lymph nodes, and adrenal glands acceptable, but disease must be liver-dominant; Child–Pugh A/B (score ≤ 7); BCLC stage A–C</td>
<td>RF ablation followed by sorafenib or placebo or SIRT + sorafenib vs sorafenib alone</td>
<td>Sequential and NR (RF arm, sorafenib started after completion of RF ablation; SIRT arm, NR)</td>
<td>Primary, time to recurrence, OS, gadoxetic acid–enhanced MR imaging vs contrast-enhanced multislice CT; secondary, QoL, safety</td>
</tr>
<tr>
<td>NCT01004978</td>
<td>III/400</td>
<td>Unresectable HCC confined to &lt; 50% of liver parenchyma, Child–Pugh A/B (score ≤ 7), no extrahepatic spread</td>
<td>Sorafenib + chemoembolization/DEB chemoembolization vs chemoembolization/DEB chemoembolization</td>
<td>Continuous: chemoembolization performed 2 wk after stable dose of sorafenib or placebo is reached</td>
<td>Primary, PFS; secondary, OS, safety</td>
</tr>
</tbody>
</table>

(Continued)
### Table 2: Ongoing Phase II and III Clinical Trials Evaluating Combined Treatment with LRTs and Sorafenib in Patients with HCC (continued)

<table>
<thead>
<tr>
<th>NCT Identifier</th>
<th>Name of Trial</th>
<th>Phase</th>
<th>No. of Pts.</th>
<th>Treatment Schema</th>
<th>Sorafenib Timing</th>
<th>Key Inclusion Criteria</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01324076</td>
<td>TACE-2</td>
<td>III</td>
<td>412</td>
<td>Continuous: sorafenib + DEB chemoembolization vs DEB chemoembolization</td>
<td>Continuous: starting sorafenib or placebo immediately after chemoembolization</td>
<td>Child–Pugh class A disease (72% of patients) and Child–Pugh class B disease (28% of patients), respectively (P value not significant).</td>
<td>Primary: OS; secondary: PFS; safety</td>
</tr>
<tr>
<td>NCT01556490</td>
<td>STOP-90Y vs sorafenib</td>
<td>Sequential: sorafenib is started after 90Y treatment</td>
<td>Phase III/400</td>
<td>Unresectable advanced HCC, no main PV thrombosis</td>
<td>Sorafenib + 90Y vs sorafenib</td>
<td>ECOG PS 0/1; no extrahepatic spread; no prior radiofrequency, radiation therapy, or RT for HCC</td>
<td>Primary: OS; secondary: PFS; safety</td>
</tr>
</tbody>
</table>

**Definition of abbreviations:**

- **Barcelona Clinic Liver Cancer (BCLC):** A staging classification system for hepatocellular carcinoma (HCC) based on tumor stage, patient performance status, and presence of complications.
- **DEB:** Doxorubicin-eluting bead.
- **ECOG:** Eastern Cooperative Oncology Group.
- **HCC:** Hepatocellular carcinoma.
- **LRT:** Locoregional therapy.
- **OS:** Overall survival.
- **ORR:** Objective response rate.
- **PFS:** Progression-free survival.
- **QoL:** Quality of life.
- **PV:** Portal vein.
- **RT:** Radiation therapy.
- **SHARP:** Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol.
- **SIRT:** Selective internal radiation therapy.
- **TACE:** Transarterial chemoembolization.
- **TTUP:** Time to untreatable progression.
- **90Y:** Yttrium-90.

**Additional information:**

- Sorafenib is a multitargeted tyrosine kinase inhibitor that acts on Raf and platelet-derived growth factor receptor signaling pathways in addition to VEGF receptors. The mechanism(s) responsible for the observed survival benefit with sorafenib in the pivotal phase III studies have not been defined. In fact, neither the SHARP nor the Asia-Pacific positive survival findings can be definitively attributed to the anti-VEGF mechanism of sorafenib. In addition, the recent study by Sansonno and colleagues demonstrated a significant increase in survival for patients treated with sorafenib 1 month after chemoembolization, a time by which the VEGF surge should have subsided. Therefore, mechanisms other than anti-VEGF activity may contribute to clinical benefit observed with sorafenib in combination with transarterial chemoembolization.

- Several phase II and III trials evaluating sorafenib with LRT are ongoing and may resolve some of these outstanding issues with regard to combination therapy. A North American phase III study (National Clinical Trials [NCT] identifier 01004978) sponsored by ECOG and the National Cancer Institute will compare conventional/DEB...
chemoembolization with sorafenib versus conventional/DEB chemoembolization and placebo. University College London is sponsoring a European phase III trial (NCT identifier 01324076) of DEB chemoembolization with concurrent sorafenib or placebo to be conducted in approximately 412 patients with unresectable HCC and Child–Pugh class A cirrhosis. Finally, the international phase III Efficacy Evaluation of TheraSphere in Patients With Inoperable Liver Cancer will evaluate the safety and efficacy of sorafenib with or without concurrent radioembolization in 400 patients with HCC (NCT identifier 01556490).

In summary, the state of the science of transarterial chemoembolization combined with sorafenib continues to evolve. Several small studies (35,37,48,52,54,59) and two larger randomized controlled trials (43,47) have evaluated sorafenib with conventional chemoembolization or DEB chemoembolization; these have suggested that the combination is feasible and tolerable. Reported AEIs are predictable and manageable with dose reduction. However, whether sorafenib combined with conventional or DEB chemoembolization yields additive or synergistic efficacy benefits versus chemoembolization alone remains unclear. A randomized phase III study (42) demonstrated no added benefit of transarterial chemoembolization with sorafenib versus placebo; however, in this trial, sorafenib was administered past the time when the theoretical maximal effect would be expected. The randomized phase II SPACE trial showed that transarterial chemoembolization combined with sorafenib exhibited a trend for increased TTP versus transarterial chemoembolization alone ($P = .07$). The results of ongoing phase III trials will yield more information on whether sorafenib combined with conventional chemoembolization, DEB chemoembolization, or radioembolization provides added benefit versus single-therapy approaches.

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