

Doxorubicin Plus Sorafenib vs Doxorubicin Alone in Patients With Advanced Hepatocellular Carcinoma A Randomized Trial

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HEPATOCELLULAR CARCINOMA (HCC) is the sixth most common malignancy worldwide,¹ with approximately 600 000 new cases per year. Patients with unresectable or metastatic disease have a median survival of only a few months.² Despite the lack of a clear survival benefit, doxorubicin has become a routinely and widely used agent in the treatment of HCC.

Sorafenib, an oral multikinase inhibitor,³ has shown in a double-blind, randomized, phase 3 trial involving patients with advanced HCC and Child-Pugh A cirrhosis⁴ a statistically significant increase in median overall survival over placebo (10.7 months vs 7.9 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55-0.88; $P < .001$). Concurrently, a phase 1 study assessing the feasibility and tolerability of sorafenib in combination with doxorubicin for patients with solid tumors was ongoing.⁵ This study demonstrated a 21% area under the curve (AUC) increase of doxorubicin when

Context In a randomized phase 3 trial, 400 mg of sorafenib twice daily prolonged overall survival of patients with advanced hepatocellular carcinoma (HCC) and Child-Pugh A disease. In a phase 1 study, sorafenib combined with doxorubicin, 60 mg/m², was well tolerated by patients with refractory solid tumors. The combination of sorafenib and doxorubicin in patients with advanced HCC has not been evaluated in a phase 2 or 3 trial.

Objective To evaluate the efficacy and safety of doxorubicin plus sorafenib compared with doxorubicin alone in patients with advanced HCC and Child-Pugh A disease.

Design, Setting, and Patients In a double-blind phase 2 multinational study, conducted from April 2005 to October 2006, 96 patients (76% male; median age, 65 years [range, 38-82 years]) with advanced HCC, Eastern Cooperative Oncology Group performance status 0 to 2, Child-Pugh A status, and no prior systemic therapy were randomly assigned to receive 60 mg/m² of doxorubicin intravenously every 21 days plus either 400 mg of sorafenib or placebo orally twice a day. The date of the last patient's follow-up was April 2008.

Main Outcome Measure Time to progression as determined by independent review.

Results Following complete accrual, an unplanned early analysis for efficacy was performed by the independent data monitoring committee, so the trial was halted. The 2 patients remaining in the placebo group at that time were offered sorafenib. Based on 51 progressions, 63 deaths, and 70 events for progression-free survival, median time to progression was 6.4 months in the sorafenib-doxorubicin group (95% confidence interval [CI], 4.8-9.2), and 2.8 months (95% CI, 1.6-5) in the doxorubicin-placebo monotherapy group ($P = .02$). Median overall survival was 13.7 months (95% CI, 8.9-not reached) and 6.5 months (95% CI, 4.5-9.9; $P = .006$), and progression-free survival was 6.0 months (95% CI, 4.6-8.6) and 2.7 months (95% CI, 1.4-2.8) in these groups, respectively ($P = .006$). Toxicity profiles were similar to those for the single agents.

Conclusions Among patients with advanced HCC, treatment with sorafenib plus doxorubicin compared with doxorubicin monotherapy resulted in greater median time to progression, overall survival, and progression-free survival. The degree to which this improvement may represent synergism between sorafenib and doxorubicin remains to be defined. The combination of sorafenib and doxorubicin is not yet indicated for routine clinical use.

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administered concomitantly with sorafenib. However, this increase in AUC did not result in a substantial worsen-

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ing of toxicity over what would be expected from either compound administered individually. The 4 patients with HCC achieved prolonged stability of disease, and continued therapy for more than 1 year. Based on this background, we conducted a randomized, double-blind, phase 2 study of doxorubicin plus sorafenib and doxorubicin plus placebo.

METHODS

This was a multinational, double-blind, randomized, phase 2 trial involving patients with advanced HCC. The trial was approved by the human investigation committee at each center and was conducted in accordance with the US Department of Health and Human Services guidelines. Written informed consent was obtained from each patient.

Patient Eligibility

Patients were included if they had measurable, histologically proven, inoperable HCC; no prior systemic treatments for HCC; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; Child-Pugh A status; life expectancy of at least 12 weeks; and adequate hematologic (absolute neutrophil count of $\geq 1500/\mu\text{L}$, platelet count of $\geq 75 \times 10^3/\mu\text{L}$, hemoglobin of $\geq 8.5 \text{ g/dL}$), hepatic (bilirubin $\leq 3 \text{ mg/dL}$, alanine aminotransferase and aspartate aminotransferase $\leq 5 \times$ the upper limit of normal), renal (serum creatinine $\leq 1.5 \times$ the upper limit of normal), and cardiac function. The latter was evaluated with a 12-lead electrocardiogram and a multigated acquisition scan or echocardiography. Left ventricular ejection fraction had to be at least 45% or at least the normal limit. To convert bilirubin from mg/dL to $\mu\text{mol/L}$, multiply by 17.104.

Although prior local therapies such as alcohol injection, radiofrequency ablation, or bland hepatic artery embolization were allowed as long as there was evidence of progression of disease at the time of enrollment, patients with a history of prior transarterial chemoembolization were excluded. Patients who

had tumors of mixed histology or fibrolamellar variant, were pregnant or lactating, or who had psychological or social problems that were thought would likely adversely affect study participation were excluded.

Treatment and Dose Modifications

Patients received 60 mg/m^2 of doxorubicin intravenously every 21 days for a maximum of 360 mg/m^2 plus either 400 mg of sorafenib or placebo orally twice daily. If continued benefit and lack of toxicity were observed, patients were allowed to continue doxorubicin to 450 mg/m^2 . Following treatment with the combination of agents, patients continued with single-agent sorafenib or placebo until disease progression. A cycle of therapy was defined as 21 days for either the combination or single-agent therapy after doxorubicin was discontinued; however, treatment with sorafenib or placebo was continued without planned interruptions. Patients with baseline serum bilirubin concentration between 1.3 and 3 mg/dL were started with doxorubicin 30 mg/m^2 and were allowed 1 dose reduction to 22.5 mg/m^2 . Two dose reductions were allowed for doxorubicin (45 and 30 mg/m^2) and sorafenib plus placebo (400 mg daily, and 400 mg every other day), for drug-related toxicities (National Cancer Institute–Common Toxicity Criteria v3.0); otherwise, treatment continued until disease progression or an unacceptable drug-related toxicity was reached.

All patients who received 1 or more doses of any study medication were considered evaluable for safety and efficacy. For grade 3 or 4 hematologic and for grade 3 nonhematologic toxic effects believed to be potentially doxorubicin-related, the study drug was withheld until toxic effects improved to grade 2 or lower or grade 1 or lower, respectively. For grade 4 nonhematologic toxic effects believed to be potentially doxorubicin-related, therapy was discontinued and then 16 patients resumed treatment with a dose reduction. However, the study drug was discontinued if recovery time took 21 days or longer. For toxic effects that were

considered drug specific, the other drug was continued without interruption or dose modification. A modified toxicity scale (eTable 1 available at www.jama.com) was used for hand-foot skin reaction to facilitate interpretation, and specific dose modifications (eTable 2) were implemented.⁶ Grading criteria for left ventricular systolic dysfunction are shown in eTable 3. Management criteria of treatment-emergent hypertension are shown in eTable 4.

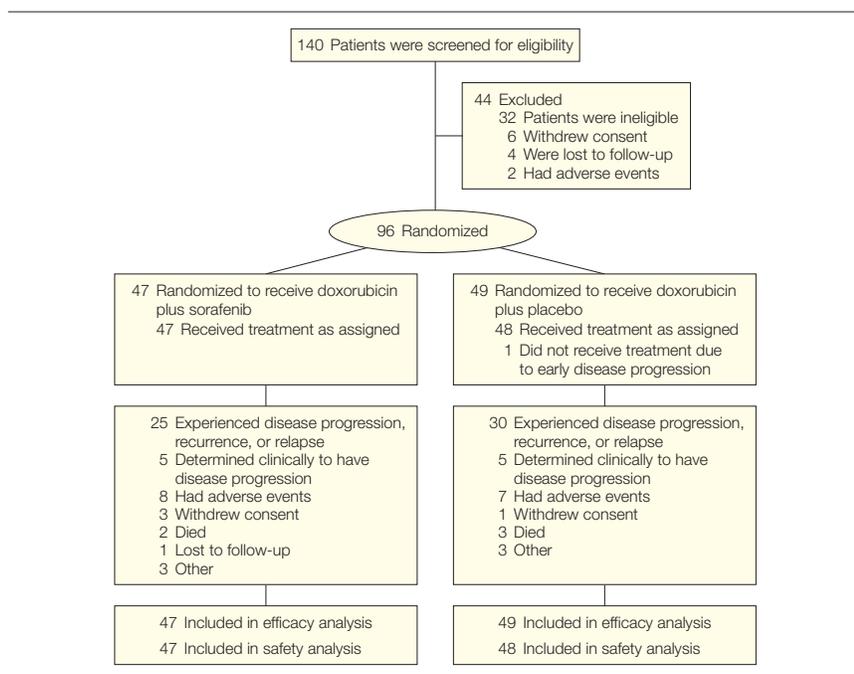
Randomization

This study enrolled 96 patients from 25 centers from April 2005 to October 2006. The date of the last follow-up was April 2008. All patients received doxorubicin and were randomly assigned on a 1 to 1 basis and in double-blind fashion to receive either oral sorafenib or matching oral placebo by using a unicentric randomization scheme, thus avoiding any allocation concealment issues. A randomization number was provided through a telephone interactive voice response system. Sorafenib and placebo tablets were identical in appearance to preserve blinding, and patients were to take an identical number of tablets and on the same schedule. Study tablets were labeled with a unique bottle number, which was assigned to a specific patient using the interactive response system. Randomization was stratified by presence vs absence of macroscopic vascular invasion, extrahepatic spread, or both.

Efficacy Analysis

Analyses were based on an intention-to-treat population. Time to progression was defined as the time from randomization to the first radiologically documented disease progression. Patients without tumor progression at the time of analysis or at time of death were censored at their last date of tumor evaluation.

Secondary efficacy variables included overall survival and progression-free survival, both of which were measured from the date of randomization. Overall survival definition was based on the date of death due to any cause, and

Figure 1. Enrollment and Outcomes

the progression-free survival definition was based on the first documented radiologic disease progression or death. For patients without documented death or progression at the time of analysis, time to death (overall survival) was censored at the last date of follow-up, and progression-free survival was censored at the last date of tumor evaluation.

Overall response rate was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0⁷ by blinded independent radiologic review. Overall response rate per RECIST was defined as the proportion of patients with the best tumor response achieved during treatment or within 30 days after termination of active therapy.

Statistical Analyses

The primary objective of this randomized phase 2 trial was to study the effect of doxorubicin plus sorafenib or doxorubicin plus placebo on time to progression. Median time to progression for patients with HCC treated with doxorubicin varies widely in the literature, but a value of 4 months was con-

sidered to be a reasonable approximation,⁸⁻¹⁰ and this value was used as the historical control for this trial. The planned sample size selected was 45 patients per treatment group, to be followed up until approximately 35 progressions had occurred. Each group had 80% power to detect a difference of 100% of the median time to progression, with a type I error rate of .10 for each group separately. The analysis was planned to occur when approximately 70 events had been reached.

An exploratory comparison between the 2 study groups for time to progression, overall survival, and progression-free survival was also planned. Kaplan-Meier survival curves were rendered for each group. All statistical computations were performed using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

The tests performed were 2-sided, and *P* values < .05 were considered statistically significant. The definition of time to progression allowed for patients who died before documented progression to be censored, for which death could have been related to progression. To account for the presence of

multiple competing risks (events other than the event of interest), we have performed a competing risk analysis^{11,12} in which progression counted as the primary event while deaths occurring before documented progression, adverse events, and other non-death-related events counted as separate competing risk events. A sensitivity analyses for progression-free survival was also performed, in which patients discontinuing study without documented progression were included as having had events at the subsequent tumor assessment they would have had if they had continued the trial.

A data monitoring committee was instituted for the study, consisting of an independent statistician, oncologist, and hepatologist. Safety review meetings were held according to the committee's charter. On the basis of the reported survival benefit of the interim results of the phase 3 trial of sorafenib vs placebo,¹ the committee performed an unplanned interim analysis for efficacy in February 2007. It stated that the results of the interim analysis of the current study, although immature, indicated that the patients randomized to receive doxorubicin plus placebo may be at a considerable disadvantage regarding efficacy, and thus advised the sponsor to discontinue this phase 2 trial. The study was therefore discontinued, and patients were unblinded. The 2 patients remaining in the placebo group were offered sorafenib.

RESULTS

Demographics

All results are based on 96 patients (FIGURE 1). Forty-seven patients were randomized to the doxorubicin-sorafenib group and 49 to the doxorubicin-placebo group. The safety-evaluable population included 95 patients because 1 patient never received treatment during the study due to early progression noted during screening. One patient in each cohort had fibrolamellar HCC. There were 3 protocol violations based on prior therapy: 2 patients had received transarterial chemoembolization and 1 pa-

tient, gemcitabine plus carboplatin. All 3 were in the doxorubicin-sorafenib group.

At baseline, patients in both groups were comparable, except for 15 of 47 patients (31.9%) assigned to receive doxorubicin plus sorafenib had well-differentiated tumors vs 4 of 49 (8.2%) of those receiving doxorubicin plus placebo (TABLE 1). The median size of target lesions used for RECIST criteria radiologic assessment was 66 mm (range, 38-82 mm) for the doxorubicin-sorafenib group and 65 mm (range, 38-81 mm) for the doxorubicin monotherapy group ($P = .49$).

Dose and Duration of Therapy

The median total dose of doxorubicin administered was 165 mg/m² (range, 30-420 mg/m²) given over a median of 4 cycles (range, 1-7 cycles) in the doxorubicin-sorafenib group and 120 mg/m² (range, 30-420 mg/m²) given over a median of 2 cycles (range, 1-9 cycles) in the doxorubicin-placebo group. The median daily dose of sorafenib was 570.1 mg (range, 111.1-950 mg) and the weight of the placebo, 762.8 mg (range, 17.9-904.3 mg).

The median duration of treatment was 5.7 cycles (range, 0.2-21 cycles) in the doxorubicin-sorafenib group and 2.7 cycles (range, 0.6-18.4 cycles) in the doxorubicin monotherapy group.

Time to Progression

There were 51 total time-to-progression events (24, doxorubicin plus sorafenib vs 27, doxorubicin plus placebo) available, representing 73% of the approximated 70 events that were initially required for the final analysis. Time to progression was a median of 6.4 months (95% CI, 4.8-9.2) for patients who received doxorubicin plus sorafenib and 2.8 months (95% CI, 1.6-5) for those who received doxorubicin plus placebo (FIGURE 2). Although the median time to progression for those in the combined treatment group exceeded the prespecified historical comparator of 4 months, it did not meet the prespecified statistical hypothesis. However, in the exploratory analysis com-

paring the 2 groups, the hazard ratio was 0.5 (95% CI, 0.3-0.9), representing a 50% reduction in the risk of progression in patients treated with doxorubicin plus sorafenib compared with reduction of risk progression in those treated with doxorubicin plus placebo ($P = .02$). In the competing risk analysis, the cumulative incidence of progression at 4 months was 26% (95% CI, 23%-29%) for the doxorubicin-sorafenib group vs 55% (95% CI, 53%-57%) for the doxorubicin-placebo group ($P = .12$).

Survival

Sixty-three patients died: 25 in the doxorubicin-sorafenib group; 38 in the doxorubicin-placebo group. Median overall survival was 13.7 months (95% CI, 8.9-not reached) among patients treated with doxorubicin plus sorafenib vs 6.5 months (95% CI, 4.5-9.9) among those who received doxorubicin plus placebo. Based on an exploratory analysis comparing the 2 groups, the hazard ratio was 0.49 (95% CI, 0.3-0.8), representing a 51% reduction in the risk of death in patients

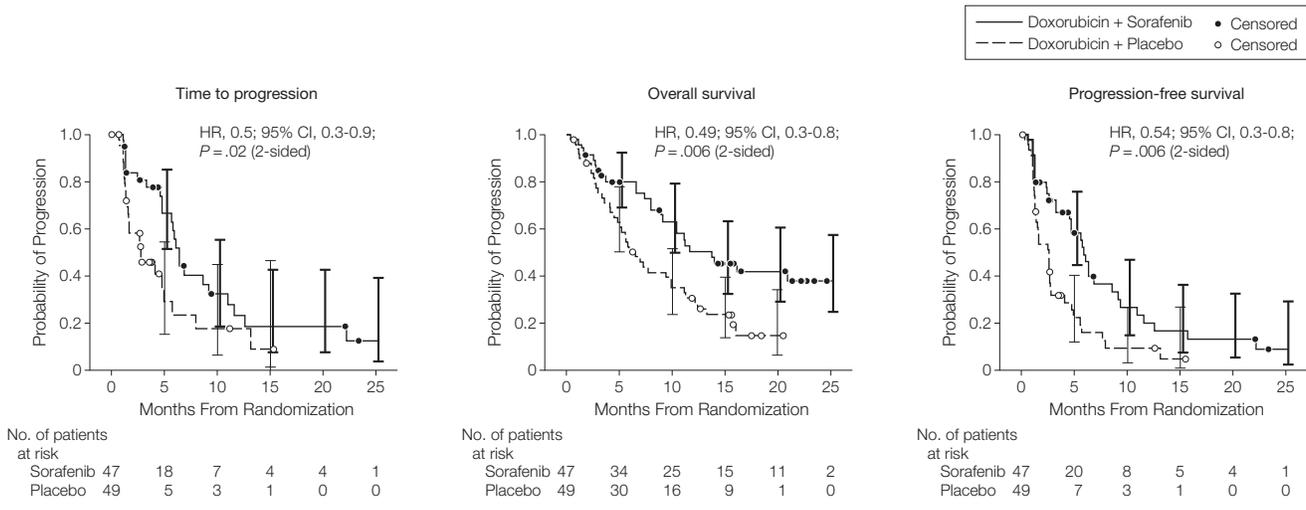
Table 1. Baseline Demographic and Disease Characteristics of Randomized Patients

Characteristic	Doxorubicin Plus Sorafenib (n = 47)	Doxorubicin Plus Placebo (n = 49)
Sex, No. (%)		
Men	31 (66.0)	42 (85.7)
Women	16 (34.0)	7 (14.3)
Age, median (range), y	66 (38-82)	65 (38-81)
ECOG performance status, No. (%)		
0-1	40 (85.1)	41 (83.7)
2	4 (8.5)	3 (6.1)
3	0	1 (2)
Missing	3 (6.4)	4 (8.2)
Positive hepatitis status, No. (%)		
Hepatitis B	3 (6.4)	7 (14.3)
Hepatitis C	10 (21.3)	7 (14.3)
Patients by region, No. (%)		
North America	30 (64)	27 (55)
Europe	15 (32)	18 (37)
Asia	0	2 (4)
South America	2 (4)	2 (4)
Child-Pugh score, No. (%)		
A	47 (100)	47 (95.9)
B	0	2 (4.1)
Tumor burden, No. (%)		
Macroscopic vascular invasion	13 (27.8)	16 (32.4)
Extrahepatic disease	24 (51.1)	32 (79.6)
Cancer grade at initial diagnosis, No. (%) ^a		
Well-differentiated	15 (31.9)	4 (8.2)
Moderately well-differentiated	15 (31.9)	15 (30.6)
Poorly differentiated	5 (10.6)	8 (16.3)
Undifferentiated	0	1 (2.0)
Not assessable/missing	12 (25.5)	21 (42.9)
Baseline AFP >ULN, No. (%)		
Yes	27 (57.4)	35 (71.4)
No	9 (19.1)	8 (16.3)
Missing	11 (23.4)	6 (12.2)
Prior therapy, No. (%)		
Surgery	11 (23.4)	11 (22.5)
Local therapy	4 (8.4)	3 (6.1)
Radiation therapy	3 (6.4)	2 (4.1)
Size of measurable disease by RECIST at baseline, median (range), mm	66 (38-82)	65 (38-81)

Abbreviations: AFP, α -fetoprotein; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

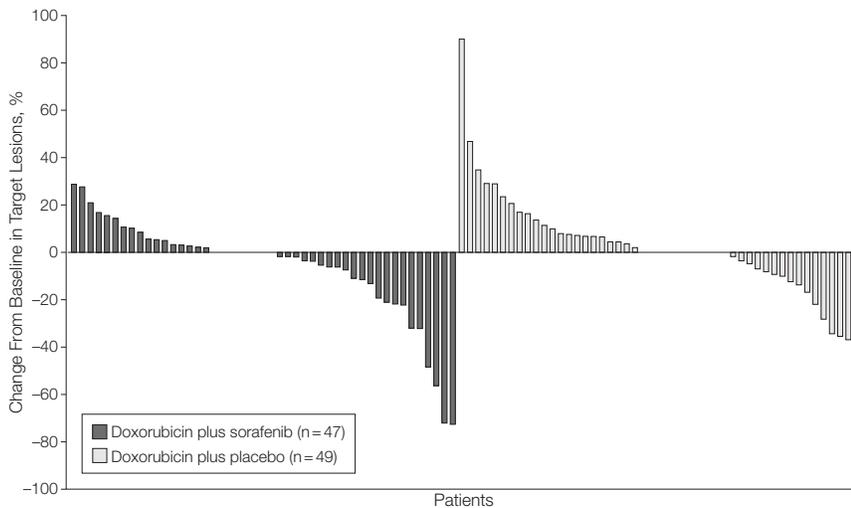
^aBased on the American Joint Committee on Cancer staging.

Figure 2. Exploratory Kaplan Meyer Curves Showing Time to Progression and Survival by Group



Error bars indicate 95% confidence intervals, and HR indicates hazard ratio.

Figure 3. Maximum Percentage Change in Size of Target Lesions by Patient



Each bar represents 1 patient. Eight patients in the doxorubicin plus sorafenib group had 0% change, and 11 in the doxorubicin plus placebo group had 0% change in size of tumor lesions.

treated with doxorubicin and sorafenib vs doxorubicin and placebo (P = .006).

Progression-Free Survival

The number of total progression-free survival events was 70: 32 in the doxorubicin-sorafenib group and 38 in the doxorubicin-placebo group. The median progression-free survival was 6 months (95% CI, 4.6-8.6) among pa-

tients treated with doxorubicin plus sorafenib vs 2.7 months (95% CI, 1.4-2.8) among those who received doxorubicin plus placebo. An exploratory comparison of the 2 groups showed the estimated hazard ratio to be 0.54 (95% CI, 0.3-0.8), representing a 46% reduction in the risk of progression or death among patients treated with doxorubicin plus sorafenib vs doxorubicin plus placebo (P = .006). The sensitivity analyses for

progression-free survival in which patients leaving the study without documented progression were included as having had events at the subsequent tumor assessment they would have had if continuing the trial showed similar results of median progression-free survival of 5.7 months (95% CI, 3.3-6.4) among patients treated with doxorubicin plus sorafenib vs 2.7 months (95% CI, 1.6-2.9) for doxorubicin plus placebo.

Response Rate

Based on independent radiologic assessment, there were 2 partial responses (4%) in the doxorubicin-sorafenib group and 1 complete response (2%) in the doxorubicin-placebo group. A waterfall plot analysis was performed on patients with evaluable scans to determine the magnitude of reduction in the size of target lesions (FIGURE 3). It demonstrated tumor shrinkage in a greater proportion of patients treated with doxorubicin plus sorafenib (62%) than in those treated with doxorubicin plus placebo (29%).

Toxicity

The most common grade 3 or 4 drug-related adverse events are shown in

TABLE 2. Grade 3 and 4 toxic effects included fatigue ($\approx 6\%$ of patients in each group) and hand-foot skin reaction (6.4% of patients in the doxorubicin-sorafenib group). Other grade 3 or 4 adverse events in the doxorubicin-sorafenib and doxorubicin-placebo groups, respectively, were diarrhea (10.6% vs 6.3); and neutropenia ($\approx 38\%$ vs 31.1). Most toxic effects occurred at a rate expected with the individual agents alone.^{3,10}

All-grade, treatment-emergent left-ventricular systolic dysfunction occurred in 19% of patients who received doxorubicin plus sorafenib vs 2% of those who received doxorubicin plus placebo. Of these, 1 patient (2%) with no cardiac history in the doxorubicin-sorafenib group and none in the doxorubicin-placebo group experienced grade 3 to 4 left ventricular dysfunction. Hypertension and bleeding, which are adverse events frequently attributed to anti-vascular endothelial growth factor (anti-VEGF) therapy and are thought to represent class effects, were also noted. All-grade, treatment-emergent hypertension was reported for 8 patients (17.0%) treated with doxorubicin plus sorafenib and for none who received doxorubicin plus placebo. These events were limited to grade 1 (2 events) and grade 2 (6 events). Only 1 patient received antihypertensive medication at any time during the study, and no dose-limiting hypertension was seen. Nine patients (19.1%) in the doxorubicin-sorafenib group and 5 (10.2%) in the doxorubicin-placebo group experienced any-grade, treatment-emergent bleeding events. Grade 3 and 4 treatment-related bleeding events occurred in 2 patients in the doxorubicin-sorafenib group, both of which were gastrointestinal bleeds.

Death within 30 days of starting study medication occurred in 5 patients (11%) in the doxorubicin-sorafenib group and in 10 patients (21%) in the doxorubicin-placebo group. Of these 15 patients, the cause of death was reported as progression of HCC in 9 (2 in the doxorubicin-sorafenib group and 7 in the doxorubicin-placebo group). Among the other 3

Table 2. Grade 3 or 4 Drug-Related Adverse Events in at Least 5% of Randomized Patients

Adverse Event ^a	No. (%) of Patients			
	Doxorubicin Plus Sorafenib (n = 47)		Doxorubicin Plus Placebo (n = 49)	
	3	4	3	4
All events	15 (31.9)	15 (31.9)	13 (27.1)	16 (33.3)
Constitutional symptoms	3 (6.4)	0	3 (6.3)	0
Fatigue	3 (6.4)	0	3 (6.3)	0
Dermatology/skin	5 (10.6)	0	0	0
Hand-foot skin reaction	3 (6.4)	0	0	0
Gastrointestinal	10 (21.3)	0	9 (18.8)	0
Nausea	3 (6.4)	0	0	0
Vomiting	3 (6.4)	0	0	0
Diarrhea	5 (10.6)	0	4 (8.3)	0
Dehydration	0	0	3 (6.3)	0
Hematologic	8 (17.0)	13 (27.7)	9 (18.8)	15 (31.3)
Neutropenia	5 (10.6)	13 (27.7)	6 (12.5)	15 (31.3)
Leukopenia	6 (12.8)	0	0	0
Infection	0	0	4 (8.3)	0
Febrile neutropenia	0	0	3 (6.3)	1 (2.1)
Pain	3 (6.4)	0	0	0

^aNational Cancer Institute–Common Terminology Criteria for Adverse Events version 3.0 category/term.

patients who received doxorubicin plus sorafenib, serious adverse events leading to death were liver dysfunction¹ and cardiac ischemia or myocardial infarction.² Among the other 3 patients who received doxorubicin plus placebo, 2 had serious adverse events leading to death (febrile neutropenia and thrombosis, thrombus, or embolism).

COMMENT

An improvement in median time to progression, overall survival, and progression-free survival was noted in patients treated with doxorubicin plus sorafenib compared with those who received single-agent doxorubicin. At the time of this trial's design and accrual, doxorubicin was the accepted standard control group for randomized trials involving HCC. Subsequent data have established sorafenib as a new standard treatment for advanced HCC and an appropriate control regimen for HCC trials.⁴ The lack of a comparative sorafenib standard group in our trial precludes any assessment of potential synergism between doxorubicin and sorafenib. Thus, whether doxorubicin contributed significantly to the out-

come or whether the benefit seen in the doxorubicin-sorafenib group was the result of sorafenib alone, cannot be determined from the results of this trial.

There are several hypotheses that may support a possible synergism between sorafenib and doxorubicin. Inhibition of the Ras/Raf/MEK/ERK pathway may prevent activation of the multidrug resistance pathway.¹³ Raf-1–dependent basic fibroblast growth factor–mediated protection of endothelial cells has been noted in response to stress-mediated apoptosis.^{14–16} Basic fibroblast growth factor–mediated activation of Raf-1 promotes the formation of a complex between Raf-1 and apoptosis signal-regulating kinase 1 at the mitochondrial level, leading to inhibition of apoptosis signal-regulating kinase 1 activity and prevention of stress-mediated apoptosis, which can be induced by anthracyclines such as doxorubicin. Anthracyclines have also been described as modulators of angiogenesis,¹⁷ possibly providing an additive rather than a synergistic role in this setting.

Adverse effects of doxorubicin plus sorafenib were essentially additive and

similar to what would be expected for each drug used as a single agent. Although most occurrences of left-ventricular systolic dysfunction were asymptomatic, the increased incidence with the combination necessitates further careful investigation. It is not clear whether increased doxorubicin-associated cardiac toxicity in this study is attributable to a sorafenib-induced increase in doxorubicin AUC. The median cumulative dose of doxorubicin was limited to 165 mg/m²; thereby making the number of cardiac events concerning. In future trials evaluating the combination of doxorubicin and sorafenib, cardiac function should be monitored carefully.

The competing risk analysis we performed illustrates a potential limitation of time to progression as a primary study end point. However the confirmatory sensitivity analysis for progression-free survival and the overall survival confirm the positive outcome of the study.

Responses as defined by RECIST were infrequent, but this result was not unexpected given the low absolute response rates observed with both agents in HCC trials.^{1,6,8-10,18,19} Moreover, sorafenib has been shown to stabilize HCC with a tumoral central necrosis phenomenon that has been observed in patients with HCC treated with sorafenib alone.²⁰ This interesting phenomenon, the clinical relevance of which remains undefined, could be the result of a synergistic effect between sorafenib and doxorubicin. Further research in this area is warranted.

In summary, among patients with advanced HCC, treatment with sorafenib doxorubicin compared with doxorubicin plus placebo resulted in greater median time to progression, overall survival, and progression-free survival. The degree to which this improvement may represent synergism between sorafenib and doxorubicin remains to be defined. This trial has served as the basis for the ongoing phase 3 trial of sorafenib plus doxorubicin vs sorafenib alone.²¹

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Author Contributions: Dr Abou-Alfa had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Abou-Alfa, Johnson, Knox, Davidenko, Lacava, Leung, Gansukh, Saltz.

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Drafting of the manuscript: Abou-Alfa, Capanu, Saltz. **Critical revision of the manuscript for important intellectual content:** Abou-Alfa, Johnson, Knox, Capanu, Davidenko, Lacava, Leung, Gansukh, Saltz.

Statistical analysis: Abou-Alfa, Capanu, Gansukh, Saltz. **Administrative, technical, or material support:** Gansukh.

Study supervision: Abou-Alfa, Saltz.

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Online-Only Material: eTables 1 through 4 and are available at www.jama.com.

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