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17-Feb-2025

Trial 2013-002625-35, CALGB80802

Phase III Randomized Study Of Sorafenib Plus Doxorubicin Versus Sorafenib In Patients With Advanced Hepatocellular Carcinoma (HCC)

Clinical Trial Results:
This trial was sponsored by Cancer Trials Ireland in Europe however was led and sponsored by NCI in the US. The trial never opened in the EU. Due to differences in the reporting of specific data fields in the US and EU, certain details required for validation of trial results in EudraCT are not available to us (some examples thereof are participants per country, breakdown of ages, number of occurrences of each SAE and AE). The attached article by Abou-Alfa et al and the downloaded results from the ClinicalTrials.gov website are the full extent of results available to us for the trial.

We as sponsor are therefore posting a PDF file of results incl. a justification.

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JAMA Oncology | Original Investigation

Assessment of Treatment With Sorafenib Plus Doxorubicin vs Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma
Phase 3 CALGB 80802 Randomized Clinical Trial

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IMPORTANCE Previous communication has reported significant improvement in overall survival (OS) when using doxorubicin plus sorafenib in the treatment of advanced hepatocellular cancer (HCC).

OBJECTIVE To determine if doxorubicin added to sorafenib therapy improves OS, with stratification for locally advanced and metastatic disease.

DESIGN, SETTING, AND PARTICIPANTS This unblinded randomized phase 3 clinical trial was led by Alliance in collaboration with Eastern Cooperative Oncology Group–American College of Radiology Imaging Network, Canadian Cancer Trials Group, and Southwest Oncology Group. It was launched in February 2010 and completed in May 2015; data were also analyzed during this time frame. Patients with histologically proven advanced HCC, no prior systemic therapy, Child-Pugh grade A score, Eastern Cooperative Oncology Group performance status of 0 to 2 (later amended to 0-1), and adequate hematologic, hepatic, renal, and cardiac function were eligible. The OS primary end point had a final analysis planned with 364 events observed among 480 total patients with 90% power to detect a 37% increase in median OS.

INTERVENTIONS OR EXPOSURES Patients received either 60 mg/m^2 of doxorubicin every 21 days plus 400 mg of sorafenib orally twice daily or the sorafenib alone, adjusted to half doses for patients with bilirubin levels of 1.3 to 3.0 mg/dL.

MAIN OUTCOMES AND MEASURES The primary end point was OS, and progression-free survival (PFS) was a secondary end point.

RESULTS Of 356 patients included in the study, the mean (SD) age was 62 (10.1) years, and 306 (86.0%) were men. Although it was planned to include 480 patients, the study was halted after accrual of 356 patients (180 patients treated with doxorubicin plus sorafenib and 176 with sorafenib alone) with a futility boundary crossed at a planned interim analysis. Median OS was 9.3 months (95% CI, 7.3-10.8 months) in the doxorubicin plus sorafenib arm and 9.4 months (95% CI, 7.3-12.9 months) in the sorafenib alone arm (hazard ratio, 1.05; 95% CI, 0.83-1.31). The median PFS was 4.0 months (95% CI, 3.4-4.9 months) in the doxorubicin plus sorafenib arm and 3.7 months (95% CI, 2.9-4.5 months) in the sorafenib alone arm (hazard ratio, 0.93; 95% CI, 0.75-1.16). Grade 3 or 4 neutropenia and thrombocytopenia adverse events occurred in 61 (36.8%) and 29 (17.5%) patients, respectively, being treated with doxorubicin plus sorafenib vs 1 (0.6%) and 4 (2.4%) patients treated with sorafenib.

CONCLUSIONS AND RELEVANCE This multigroup study of the addition of doxorubicin to sorafenib therapy did not show improvement of OS or PFS in patients with HCC.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT01015833

Supplemental content

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JAMA Oncol. 2019;5(11):1582-1588. doi:10.1001/jamaoncol.2019.2792
Published online September 5, 2019. Corrected on October 10, 2019.

The tyrosine kinase inhibitor sorafenib was shown in 2 randomized phase 3 clinical trials to lead to superior overall survival (OS) compared with placebo in the treatment of patients with advanced hepatocellular carcinoma (HCC).[1,2] Doxorubicin has also been considered an effective systemic therapy for HCC.[3] A phase 1 clinical trial proved the feasibility and tolerability of sorafenib in combination with doxorubicin.[4] A randomized, double-blind, phase 2 study of doxorubicin plus sorafenib and doxorubicin plus placebo followed and demonstrated a significant improvement in OS with doxorubicin plus sorafenib.[5] Cancer and Leukemia Group B (CALGB), now part of the Alliance for Clinical Trials in Oncology, designed CALGB 80802 to determine if doxorubicin plus sorafenib improved survival compared with the single agent sorafenib in the treatment of advanced HCC.

Key Points

Question Does adding doxorubicin to sorafenib therapy improve overall survival in patients with advanced hepatocellular cancer?

Findings This phase 3 clinical trial randomized 356 eligible patients to treatment with doxorubicin plus sorafenib vs sorafenib alone. Results demonstrated no difference in median overall survival (9.3 months for the doxorubicin plus sorafenib arm and 9.4 months for the sorafenib arm).

Meaning The addition of doxorubicin to sorafenib therapy did not improve overall survival and resulted in higher toxicity; the combination of doxorubicin and sorafenib should not be used for the treatment of advanced hepatocellular cancer.

Methods

This Alliance-led National Clinical Trials Network multigroup trial was approved by the institutional review boards at all sites and/or the National Cancer Institute (NCI) central institutional review board and was registered at ClinicalTrials.gov (NCT01015833). The study was conducted in accordance with the US Department of Health and Human Services guidelines. Written informed consent was obtained from all patients. The Alliance Data and Safety Monitoring Board (DSMB) reviewed this trial semiannually for toxic effects and scheduled interim efficacy analyses. The trial protocol is available in Supplement 1.

Patients' Eligibility

Patients with measurable, histologically proven, locally advanced (with disease not amenable to curative interventions) or metastatic HCC who had received no prior systemic therapy for HCC were eligible. Patients with known central nervous system tumors, including brain metastases, were ineligible. In view of the differing causes and backgrounds of HCC, ethnicity was reported by participants. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2 (later amended to 0-1), Child-Pugh grade A score status, an absolute neutrophil count of 1500/mm^3 or greater, a platelet count of 75 × 10^9/L or greater, a hemoglobin level of 8.5 g/dL or greater, and a prothrombin time–international normalized ratio of 1.7 or less. Patients who were therapeutically anticoagulated were allowed to participate provided that no prior evidence of underlying abnormality in prothrombin time–international normalized ratio existed. Adequate hepatic (bilirubin, ≤3 mg/dL; alanine transaminase and aspartate aminotransferase, ≤5 × upper limit of normal) and renal (serum creatinine, ≤1.5 × upper limit of normal or creatinine clearance, ≥60 cc/min) function were required.

Any hypertension must have been well controlled (<140/90 mm Hg). Patients with known history of congestive heart failure greater than New York Heart Association class II, cardiac arrhythmias requiring antiarrhythmic therapy other than beta blockers or digoxin, or myocardial infarction within 6 months prior to study entry were not eligible. Patients were required to have an absolute left ventricular ejection fraction (LVEF) of 45% or greater or the normal lower limit of the specific institution at which they were seen.

Patients could have had prior liver-directed treatment provided there was a measurable target lesion that had not been subjected to local therapy and/or progressed since last treatment. Such therapy must have been completed 4 or more weeks prior to study entry. Patients having undergone liver transplantation were not eligible.

Current antiviral therapy was allowed except for interferon. Patients with known HIV were not eligible.

Treatment and Dose Modifications

All patients received sorafenib and were randomly assigned on a 1:1 basis to receive doxorubicin or not using a permuted block allocation procedure.[6] Randomization was stratified by extent of disease (locally advanced vs metastatic). Hepatitis status (no hepatitis, hepatitis B, hepatitis C, or hepatitis B and C) was considered as a covariate. Patients received either 60 mg/m^2 of doxorubicin intravenously every 21 days (1 cycle) for a maximum total dose of 360 mg/m^2, plus 400 mg of sorafenib orally twice daily or 400 mg of sorafenib orally twice daily alone. Three dose reductions were allowed for doxorubicin (45, 30, and 22.5 mg/m^2) and 2 for sorafenib (400 mg daily and 400 mg every other day) for drug-related toxic effects based on the NCI Common Toxicity Criteria, version 4.0.

Patients with bilirubin levels between 1.3 and 3.0 mg/dL received either 30 mg/m^2 of doxorubicin intravenously every 21 days for a maximum of 360 mg/m^2 plus 400 mg of sorafenib orally once daily or 400 mg of sorafenib orally once daily.[7] Only 1 dose reduction was allowed for doxorubicin (22.5 mg/m^2) and sorafenib (400 mg every other day) for drug-related toxic effects.

After the maximal doxorubicin dose, patients continued treatment with single-agent sorafenib. In approved circumstances when a patient was benefitting from therapy and continued to have normal ejection fraction, treatment with doxorubicin was allowed up to a maximum total dose of 450 mg/m^2, following which sorafenib could be continued as a single agent. Cardiac function was followed with multigated acquisition scans obtained at baseline before start of doxorubicin therapy and every 3 cycles, then every cycle after the cumulative dose reached 360 mg/m^2. Patients were removed from protocol therapy in cases of clinical heart failure (eg, left ventricular systolic dysfunction

≥ grade 3) or LVEF value decline by a relative 20% from baseline (eg, a decline in LVEF from 55% to 44%).

Specific sorafenib dose modifications were implemented for hypertension (eTable 1 in Supplement 2). Specific sorafenib dose modifications were used for hand-foot skin reaction, palmar-plantar erythrodysesthesia (eTable 2 in Supplement 2),[8] and for hepatic toxicity (eTable 3 in Supplement 2).

If dose reductions beyond the lowest dose level were required, or either agent was held for more than 3 weeks, all protocol therapy was to be discontinued.

Disease Assessments and Follow-up

Patients were evaluated at the start of every cycle. Imaging was performed every 2 cycles. Posttreatment survival and progression follow-up was conducted every 3 months for 1 year, then every 6 months until 3 years after registration. Survival follow-up was conducted through available means, including but not limited to clinic visits, phone calls, and death reports.

Statistical Methods

Efficacy analysis was based on an intent-to-treat principle with all eligible patients belonging to the treatment arm in which they were randomized. The primary outcome measure was OS, defined as the time from the date of randomization to the date of death due to any cause. Patients who were alive at the primary analysis time were censored at the time they were last known to be alive. Assuming a median OS of 10.7 months in the sorafenib alone group, 480 patients enrolled over 2 years and followed up for 15 months were required to achieve 90% power to detect a 37% increase in median OS in the sorafenib plus doxorubicin arm (ie, 10.7-14.7 months; hazard ratio [HR], 0.73), using stratified log-rank test at a 1-sided significance level of α = .05. A total of 364 deaths were expected at the time of the final analysis. Formal interim analyses for OS began when 15% of expected events were observed and subsequently occurred every 6 months. Futility interim analyses based on the OS end point were conducted using a confidence interval approach. The Lan-DeMets boundaries[9] and O'Brien-Fleming[10] analogue were used to test the superiority and futility hypotheses at each interim (1-sided α = .05). A preplanned early-stopping analysis based on progression-free survival (PFS) was conducted when 130 events were observed, which provided 90% power to detect a 50% increase in median PFS (ie, 4.0-6.0 months in the sorafenib alone and sorafenib plus doxorubicin arms, respectively [HR, 0.66]), at a 1-sided significance level α = .15. If PFS was not statistically superior on the sorafenib plus doxorubicin arm vs the sorafenib alone arm at α = .15, the trial would have closed to further accrual. Cardiac toxicity was monitored by a formal statistical plan among patients randomized to treatment with sorafenib plus doxorubicin beginning when 33 patients were enrolled on the combination treatment arm and subsequently every 6 months coinciding with Alliance DSMB meetings. Cardiac toxicity was defined as the development of a grade 3 or higher decrease in ejection fraction per Common Terminology Criteria for Adverse Events, version 4.0.

Secondary end points were PFS, time to progression (TTP), and response by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.[11] The PFS was defined as time from randomization to disease progression or death due to any cause. The TTP was measured from randomization to documented disease progression, and patients who died without progression were censored at time of death. For both PFS and TTP, patients lost to follow-up were censored at the date of their most recent disease assessment (or contact).

The Kaplan-Meier method was used to estimate the distributions of time-to-event end points.[12] Stratified log-rank test was used to compare time-to-event end points between treatment groups.[13-15] A stratified Cox proportional hazards regression model was used to estimate HRs and 95% CIs.[16] For all analyses regarding time-to-event end point (eg, log-rank test and Cox model), extent of disease (locally advanced vs metastatic) was included as the stratification factor for controlling confounding effect. Hepatitis status was considered as a covariate. A $P < .05$ level was considered statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson (G.K.A.) following Alliance policies. All analyses were based on the study database frozen on December 19, 2017. Analyses were performed by using SAS, version 9.4 (SAS Institute Inc.).

Correlative Studies

A series of correlative studies were planned and are being completed. These include the evaluation of tumor necrotic areas using a new volumetric method of assessing nonviable tumor as a correlate for response,[17] the effect of sorafenib on hepatitis C viral titers, quasispecies in patients with virologic failure, and correlation with radiologic evaluation. Results from these studies will be reported separately.

Results

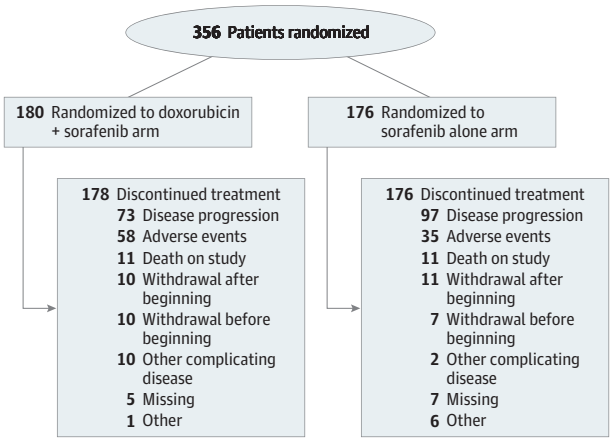
Study Population

Patient enrollment began February 15, 2010, and was halted on May 21, 2015, per recommendation of the DSMB after the fifth interim analysis demonstrated a low probability that OS of the combination group would surpass that of the sorafenib alone group. A total of 356 patients were enrolled from Alliance, Eastern Cooperative Oncology Group (now part of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network), National Cancer Institute of Canada (now Canadian Cancer Trials Group), and Southwest Oncology Group sites. All results are based on an intent-to-treat population of 356 patients (**Figure 1**). A total of 180 patients were randomized to the doxorubicin plus sorafenib arm and 176 to the sorafenib alone arm. All patients were evaluated for the toxicity analysis. Baseline demographic and disease characteristics of randomized patients are summarized in **Table 1** and were similar between the 2 study arms.

Dose and Duration of Therapy

In the doxorubicin plus sorafenib arm, the median total dose of doxorubicin administered was 237.5 mg (range, 0-1036 mg) given over a median of 3 cycles (range, 1-22 cycles), and the median daily dose of sorafenib was 433 mg (range, 19-895 mg). In the sorafenib arm, the mean daily dose was 495 mg (range, 38-994 mg). The median duration of treatment was 8.9 weeks

Figure 1. Cohort Flowchart



(range, 0.6-71.3 weeks) in the doxorubicin plus sorafenib arm and 11.7 weeks (range, 0.6-223.4 weeks) in the sorafenib arm.

Overall Survival

A total of 302 deaths (154 in the doxorubicin plus sorafenib arm and 148 in the sorafenib alone arm) were observed after a median follow-up of 36.1 months. The median OS was 9.3 months (95% CI, 7.3-10.8 months) in patients treated with doxorubicin plus sorafenib compared with 9.4 months (95% CI, 7.3-12.9 months) among those who received sorafenib alone. The stratified HRs were 1.05 (95% CI, 0.83-1.31; P = .68) and 1.03 (95% CI, 0.82-1.29; P = .83) without and with adjustment by hepatitis status, respectively (**Figure 2**A).

Progression-Free Survival

The preplanned PFS interim analysis was completed per protocol in July 2013 after the first 170 patients were enrolled and 130 PFS events were observed. At that time, median PFS for patients randomized to the doxorubicin plus sorafenib arm was 4.5 months (95% CI, 2.6-6.0 months) and median PFS for patients randomized to the sorafenib alone arm was 3.5 months (95% CI, 2.6-5.0 months). The 1-sided log-rank P value was .12, which is significant at α = .15 level. This satisfied the preplanned threshold for activity of the doxorubicin plus sorafenib arm, and the study continued accrual. With updated database information available as of December 2017, the median PFS was 4.0 months (95% CI, 3.4-4.9 months) among patients treated with doxorubicin plus sorafenib compared with 3.7 months (95% CI, 2.9-4.5 months) among those who received sorafenib alone. The HR estimated by Cox model was 0.93 (95% CI, 0.75-1.16) with stratified log-rank test (P = .54) (Figure 2B).

Time to Progression

The Kaplan-Meier estimate of the median TTP was 4.7 months (95% CI, 4.1-5.6 months) in patients treated with doxorubicin plus sorafenib compared with 4.2 months (95% CI, 3.4-5.4 months) for those who received sorafenib alone. The HR estimated by Cox model was 0.92 (95% CI, 0.71-1.18) with log-rank test (P = .49).

Table 1. Patient Demographics and Disease Characteristics by Treatment Arm

Characteristic	No. (%) Doxorubicin Plus Sorafenib (n = 180)	Sorafenib (n = 176)
Age, median (range), y	62.0 (21.0-80.0)	61.5 (30.0-85.0)
Gender		
Male	153 (85.0)	153 (86.9)
Female	27 (15.0)	23 (13.1)
Race		
Unknown	3 (1.7)	6 (3.4)
White	121 (67.2)	118 (67.0)
Black or African American	24 (13.3)	26 (14.8)
Asian	27 (15.0)	23 (13.1)
American Indian or Alaska Native	2 (1.1)	1 (0.6)
Not reported	3 (1.7)	2 (1.1)
ECOG performance status		
0	65 (36.1)	70 (39.8)
1	111 (61.7)	100 (56.8)
2	4 (2.2)	6 (3.4)
Extent of disease		
Locally advanced	75 (41.7)	75 (42.6)
Metastatic	105 (58.3)	101 (57.4)
Hepatitis status		
Missing	81 (45.0)	86 (48.9)
None	36 (20.0)	37 (21.0)
Hepatitis B	16 (8.9)	17 (9.7)
Hepatitis C	38 (21.1)	32 (18.2)
Hepatitis B and C	9 (5.0)	4 (2.3)
Histologic grade		
Missing	3	5
Grade cannot be assessed	33 (18.6)	39 (22.8)
Well differentiated	41 (23.2)	39 (22.8)
Moderately differentiated	68 (38.4)	58 (33.9)
Poorly differentiated	35 (19.8)	31 (18.1)
Undifferentiated	0	4 (2.3)
Baseline AFP, median (range), ng/mL	137.0 (0.0-514 014.0)	134.4 (0.0-494 082.0)
Prior therapy		
Surgery	47 (26.6)	51 (29.5)
Locoregional therapy	33 (18.6)	33 (19.1)
Adjuvant	4 (2.3)	1 (0.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein.

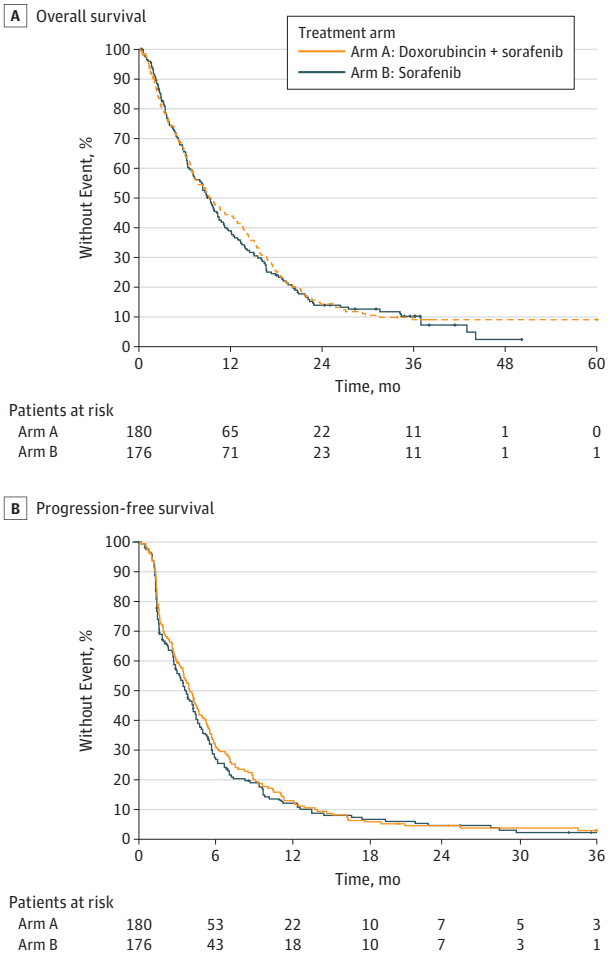
Response Rate

There was 1 complete response in the doxorubicin plus sorafenib arm. Partial response was noted in 14 (9.3%) patients in the doxorubicin plus sorafenib arm, and 8 (5.4%) in the sorafenib alone arm (χ^2_4, 3.21; P = .52). **Table 2** shows the detailed RECIST response data. There was no significant difference in tumor response between the doxorubicin plus sorafenib and sorafenib alone arms.

Toxic Events

Grade 3 or 4 neutropenia and thrombocytopenia occurred in 61 (36.8%) and 29 (17.5%) patients, respectively, being treated with doxorubicin plus sorafenib vs 1 (0.6%) and 4 (2.4%) patients, respectively, taking sorafenib; nonhematologic ad-

Figure 2. Overall and Progression-Free Survival



A, The median overall survival was 9.3 months in patients treated with doxorubicin plus sorafenib compared with 9.4 months among those treated with sorafenib alone. B, The median progression-free survival was 4.0 months among patients treated with doxorubicin plus sorafenib compared with 3.7 months among those treated with sorafenib alone.

verse events were comparable (138 [83.1%] and 118 [76.9%] patients, respectively). Observed nonhematologic grade 3 and 4 toxicities that occurred with an incidence of more than 4% in at least one arm included fatigue (21 [12.6%] patients in the doxorubicin plus sorafenib arm, and 17 [10.1%] in the sorafenib only arm), hypertension (8 [4.8%] and 23 [13.6%] patients), hand-foot skin reaction (22 [13.3%] and 24 [14.2%] patients), nausea (11 [6.6%] and 12 [7.1%] patients), mucositis (15 [9.0%] and 4 [2.4%] patients), abdominal pain (8 [4.8%] and 14 [8.3%] patients), and diarrhea (12 [7.2%] and 12 [7.1%] patients) (eTable 4 in Supplement 2).

Grade 3 and 4 cardiac toxic events were limited to patients in the doxorubicin plus sorafenib arm. Left ventricular systolic dysfunction and decreased ejection fraction rates were noted in 5 (3.0%) and 8 (4.8%) patients taking doxorubicin plus sorafenib, respectively.

Of 46 deaths (22 in the doxorubicin plus sorafenib arm and 24 in the sorafenib arm), 7 in the doxorubicin plus sorafenib arm, and 3 in the sorafenib arm, were possibly related to treatment.

Table 2. Observed Treatment Responses (RECIST 1.1) by Regimen

Characteristic	No. (%) Doxorubicin Plus Sorafenib (n = 180)	Sorafenib (n = 176)
Missing, No.	30	28
Complete response	1 (0.7)	0
Partial response	14 (9.3)	8 (5.4)
Stable disease	85 (56.7)	89 (60.1)
Progressive disease	44 (29.3)	47 (31.8)
Not evaluable	6 (4.0)	4 (2.7)

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors, version 1.1.

Discussion

This phase 3 randomized clinical trial evaluating the addition of doxorubicin to sorafenib in the treatment of advanced HCC is a landmark study. It represents, to our knowledge, the first US national effort of a phase 3 clinical trial for advanced HCC that was led by the Alliance National Clinical Trials Network group collaborating successfully with Eastern Cooperative Oncology Group-American College of Radiology Imaging Network, Canadian Cancer Trials Group, and Southwest Oncology Group. This is also to our knowledge the first published product of collaborative work of the NCI Hepatobiliary Task Force that was established around the same time with oversight from the NCI Gastrointestinal Cancer Steering Committee.

This study demonstrates that the addition of doxorubicin to sorafenib treatment does not improve OS and also strongly suggests that doxorubicin does not have a role as a systemic therapy for patients with advanced HCC.[18] This also substantiates a previous finding that the addition of doxorubicin to therapy does not improve outcomes when combined with locoregional intrahepatic embolization.[19]

The experimental arm was designed following the results from a randomized phase 2 trial[3] that combined doxorubicin and sorafenib based on laboratory evidence of the deactivation of the multidrug resistance pathway by the Ras/Raf/MEK/ERK pathway[20] and bFGF-mediated activation of Raf-1 promoting the formation of antiapoptotic Raf-1 and ASK1 complex, induced by anthracyclines.[21,22] The OS for those on sorafenib monotherapy was in the expected range (9.4 months), but the patients receiving the doxorubicin and sorafenib combination had a survival of just 9.3 months; that contrasts with the OS of 13.7 months in the cohort of patients treated with doxorubicin and sorafenib in the preceding randomized phase 2 trial.[5]

Although this study, like almost every other contemporary study in HCC, was restricted to patients who could have no worse than Child-Pugh grade A cirrhosis, HCC is a very heterogeneous disease, and similar patient populations can have very different outcomes (eg, the SHARP North American/European and the Asia-Pacific sorafenib phase III trials).[1,2]

After 130 (of the planned 480) patients experienced disease progression, a statistically significant difference in PFS favoring the doxorubicin plus sorafenib arm was mandatory for the study to continue accrual. The study met that metric, yet with continued accrual, OS did not prove to be any better when accrual was complete.

The doxorubicin plus sorafenib combination can be added to a long list of phase 2 treatments in any cancer that were not sustained in phase 3 trials. Beyond the possible confounders listed above, it appears that the toxicity of doxorubicin was a major factor despite the observed adverse events of both doxorubicin and sorafenib as previously noted,[3] with an observed and expected increase in the rates of grade 3 or greater adverse events for the doxorubicin plus sorafenib arm compared with the sorafenib alone arm. The increased rate of doxorubicin-associated cardiac toxic events in this study was not unexpected, and it is unclear whether it was attributable to a sorafenib-induced increase in doxorubicin area under the curve or to other factors.[23]

Limitations

Regardless of the outcome, this study has certain limitations. Raf inhibition of sorafenib may play a limited role compared with other attributes of the drug that would not necessarily support the combination. It is also a reminder of the criticality of phase 3 trials in the setting of promising phase 2 data.[5] Despite the detailed descriptors of the study population with Child-Pugh scores, further details delineating portal vein thrombosis among others would have been helpful. The relatively low median daily dose of sorafenib and starting dose based on bilirubin level may also explain the poor outcome of the study.

Conclusions

Despite the negative outcomes of this study, the data obtained from patients enrolled in the sorafenib control arm are of key importance. They will help provide insights into a series of correlative research questions that are being studied that will provide data pertinent to patients with HCC. Ongoing planned analyses include a prospective evaluation of radiographic tumor necrosis for association with treatment response building on prior studies,[17,24] studies of hepatitis C viral load and quasispecies changes on therapy, and baseline platelets level and correlation with biology and outcome,[18] as described in the methods section.

The study is timely considering the continued rising incidence of HCC in the United States[25] and the critical need for better treatments for patients with advanced HCC.

ARTICLE INFORMATION

Accepted for Publication: May 10, 2019.

Published Online: September 5, 2019. doi:10.1001/jamaoncol.2019.2792

Correction: This article was corrected on October 10, 2019, to correct Dr Harding's middle initial.

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Statistical analysis: Abou-Alfa, Shi, Niedzwiecki, Kavan, Zemla, O'Reilly.
Obtained funding: Abou-Alfa, Schwartz, Bertagnolli, O'Reilly, Venook.
Administrative, technical, or material support: Abou-Alfa, Knox, Goel, Lammers, Bekaii-Saab, Rajdev, El Dika, Zemla, Potaracke, Schwartz, Goldberg, Bertagnolli, O'Reilly, Venook.
Study supervision: Abou-Alfa, Knox, Lammers, Tam, El-Khoueiry, Suga, Schwartz, Goldberg, Bertagnolli, O'Reilly, Venook.
Other—enrolled patients: Kaubisch.

Conflict of Interest Disclosures: Dr Abou-Alfa reports receiving grants and personal fees from Bayer during the conduct of the study; receiving grants and personal fees from Bristol-Myers Squibb, AstraZeneca, Exelixis, and Eli Lilly, as well as personal fees from Merck and Eisai outside of the submitted work; and was issued a patent (PCT/US2014/031545). Dr Bekaii-Saab reported receiving personal fees from Imugene, Immuneering, Exelixis, Armo, AbbVie, Glenmark, Amgen, and Merck outside of the submitted work; consulting fees from Bayer, Bristol-Myers Squibb, Amgen, Merck, Array BioPharma, Celgene, Incyte, Ipsen, Pfizer, and Genentech/Roche; and research grants from Bayer. Dr El-Khoueiry reports receiving grants from SWOG during the conduct of the study; personal fees from Bristol-Myers Squibb, Bayer, AstraZeneca, Novartis, Genentech/Roche, Merck, Eisai, Exelixis, CytomX, Pieris, EMD Serono, Pfizer, and Agenus; and grants from Astex and AstraZeneca. Dr Harding reports receiving grants from Bristol-Myers Squibb, as well as personal fees from Bristol-Myers Squibb, Eli Lilly, CytomX, and Eisai outside of the submitted work. Dr Kavan reports receiving grants from Jewish General Hospital during the conduct of the study and grants from Bayer outside of the submitted work. Dr Kelley reports receiving grants from Alliance National Clinical Trial Network during the conduct of the study; grants from AstraZeneca, Bristol-Myers Squibb, Bayer, Agios, Adaptimmune, Exelixis, Eli Lilly, Merck, Novartis, QED, and Taiho; and personal fees from Genentech/Roche outside of the submitted work. Dr Knox reports receiving grants from Merck and personal fees from Bristol-Myers Squibb and AstraZeneca outside of the submitted work. Dr Lammers reports receiving personal fees from Pfizer, Merck, Teva, and Sanofi-Aventis outside of the submitted work. Dr Meyerhardt reports receiving personal fees from Ignyta, Taiho, Array BioPharma, and Genentech/Roche outside of the submitted work. Dr O'Reilly reports receiving grants and personal fees from Bristol-Myers Squibb and AstraZeneca, as well as personal fees from Merck outside of the submitted work. Dr Schwartz reported receiving grants from Merck, Novartis, and GlaxoSmithKline, as well as personal fees from Genentech/Roche outside of the submitted work. Dr Tam reports receiving funding from the Canadian Clinical Trials Group during the conduct of the study and grants from Bayer outside of the submitted work. Dr Tan reports receiving grants from the Alliance CALGB Cooperative Group during the conduct of the study. Dr Venook reports receiving grants from the National Cancer Institute during the conduct of the study. No other disclosures were reported.

Funding/Support: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health (U10CA180821 and U10CA180882 to the Alliance

for Clinical Trials in Oncology; U10CA077202, U10CA180820, U10CA180830, U10CA189859, U10CA180888, and UG1CA189821). The work was also supported in part by Bristol-Myers Squibb and Sanofi.

Role of the Funder/Sponsor: The National Cancer Institute of the National Institutes of Health reviewed and approved the design and conduct of the study. Bristol-Myers Squibb and Sanofi had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Meeting Presentation: These data were previously presented at the American Society of Clinical Oncology Annual Meeting; June 3–7; Chicago, Illinois.

Data Sharing Statement: See Supplement 3.

Additional Contributions: The authors thank the following investigators and institutions who participated in this study: Kendrith Rowland and the Carle Cancer Center NCI Community Oncology Research Program in Urbana, Illinois (UG1CA189861); Gary Schwartz and the Columbia University Minority Underserved NCORP in New York, New York (UG1CA189960); Howard Gross and the Dayton NCI Community Oncology Research Program in Dayton, Ohio (UG1CA189957); Gregory Masters and the Delaware/Christiana Care NCI Community Oncology Research Program in Newark, Delaware (UG1CA189819); Bret Friday and the Essentia Health NCI Community Oncology Research Program in Duluth, Minnesota (UG1CA189812); Jeffrey Berenberg and the Hawaii Minority Underserved NCORP in Honolulu, Hawaii (UG1CA189804); James Wade and they Heartland Cancer Research NCORP in Decatur, Illinois (UG1CA189830); Jeffrey Kirshner and the Hematology Oncology Associates of Central New York–East Syracuse in East Syracuse, New York; the Hematology Oncology Associates of Ohio and Michigan PC; Robert Behrens and the Iowa-Wide Oncology Research Coalition NCORP in Des Moines, Iowa (UG1CA189816); the Kansas City CCOP; Steven Alberts and the Mayo Clinic LAPS in Rochester, Minnesota (U10CA180790); Filipa Lynce and the MedStar Georgetown University Hospital in Washington, DC; Philip Lammers and the Meharry Medical College in Nashville, Tennessee; Michael Morris of the Memorial Sloan Kettering Cancer Center LAPS in New York, New York (U10CA180791); Daniel Anderson and the Metro Minnesota Community Oncology Research Consortium in Saint Louis Park, Minnesota (UG1CA189863); Jeffrey Giguere and the NCORP of the Carolinas (Greenville Health System NCORP) in Greenville, South Carolina (UG1CA189972); John Ellerton and the Nevada Cancer Research Foundation NCORP in Las Vegas, Nevada (UG1CA189829); Zoneddy Dayao and the New Mexico Minority Underserved NCORP in Albuquerque, New Mexico (UG1CA189856); the Northern Indiana Cancer Research Consortium in South Bend, Indiana; Daniel Budman and the Northwell Health NCORP in Lake Success, New York (UG1CA189850); John Cole and the Ochsner NCI Community Oncology Research Program in New Orleans, Louisiana (UG1CA189870); Claire Verschraegen and The Ohio State University Comprehensive Cancer Center LAPS in Columbus, Ohio (U10CA180850); Ellis Levine and the Roswell Park Cancer Institute LAPS in Buffalo, New York (U10CA180866); Preston Steen and the Sanford NCI Community Oncology Research Program of the North Central Plains in Sioux Falls, South Dakota (UG1CA189825); Marvin Feldman and the Sinai Hospital of Baltimore in Baltimore, Maryland; James Atkins and the Southeast Clinical Oncology Research Consortium NCORP in Winston-Salem, North Carolina (UG1CA189858); Charalambos Andreadis and the UCSF Medical Center–Mount Zion in San Francisco, California; Thomas Shea and the UNC Lineberger Comprehensive Cancer Center LAPS in Chapel Hill, North Carolina (U10CA180838); Hedy Kindler and the University of Chicago Comprehensive Cancer Center LAPS in Chicago, Illinois (U10CA180836); John Quigley and the University of Illinois in Chicago, Illinois; Laith Abushahin and the University of Iowa/Holden Comprehensive Cancer Center in Iowa City, Iowa; Bruce Peterson and the University of Minnesota/Masonic Cancer Center in Minneapolis, Minnesota; Puja Nistala and the University of Missouri Ellis Fischel Cancer Center in Columbia, Missouri; Apar Ganti and the University of Nebraska Medical Center in Omaha, Nebraska; Adam Asch and the University of Oklahoma Health Sciences Center LAPS in Oklahoma City, Oklahoma (U10CA180798); Steven Ades and the University of Vermont College of Medicine in Burlington, Vermont; Nancy Bartlett and the Washington University Siteman Cancer Center LAPS in St Louis, Missouri (U10CA180833); Scott Tagawa and the Weill Medical College of Cornell University in New York, New York; and Shaker Dakhil and the Wichita NCI Community Oncology Research Program in Wichita, Kansas (UG1CA189808).

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Completed

Sorafenib Tosylate With or Without Doxorubicin Hydrochloride in Treating Patients With Locally Advanced or Metastatic Liver Cancer

ClinicalTrials.gov ID NCT01015833

Sponsor National Cancer Institute (NCI)

Information provided by National Cancer Institute (NCI) (Responsible Party)

Last Update Posted 2022-08-04

Results Posted Tab

Results Overview

Conditions

Advanced Adult Hepatocellular Carcinoma | Recurrent Hepatocellular Carcinoma | Stage III Hepatocellular Carcinoma AJCC v7 | Stage IIIA Hepatocellular Carcinoma AJCC v7

Intervention/Treatment

- Drug: Doxorubicin Hydrochloride

- Other: Laboratory Biomarker Analysis
- Other: Pharmacogenomic Study
- Drug: Sorafenib Tosylate

Other Study ID Numbers

- NCI-2011-01989
- NCI-2011-01989 (Registry Identifier) (REGISTRY: CTRP (Clinical Trial Reporting Program))

Study Design

Allocation: Randomized
Interventional Model: Parallel Assignment
Masking: Single (Investigator)
Primary Purpose: Treatment

Results Point of Contact

Name/Title: Ghassan Abou-Alfa, MD
Organization: Memorial Sloan-Kettering Cancer Center
Phone: 646-888-4184
Email: abou-alg@mskcc.org

Enrollment (Actual)

356

Study Type

Interventional

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates

First Submitted
2009-11-17

First Posted (Estimated)
2009-11-18

Results Reporting Dates

Results First Submitted
2017-12-01

Results First Posted
2018-05-02

Study Record Updates

Last Update Posted
2022-08-04

Last Verified
2022-08

Participant Flow

Recruitment Details

[Not Specified]

Pre-assignment Details

[Not Specified]

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.

Period Title: **Overall Study**

Started	180	176
Completed	167	171
Not Completed	13	5

Reason Not Completed

Death	1	0
Withdrawal by Subject	3	2
Adverse Event	0	1
Physician Decision	2	0
Symptomatic deterioration	0	1
Other	5	1
Motor Vehicle Accidents	1	0
Did not start treatment	1	0

Baseline Characteristics

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progression unacceptable toxicity.
Overall Number of Baseline Participants	180	176
Baseline Analysis Population Description	[Not Specified]	

Expand all / Collapse all

Age, Continuous

Median (Full Range) | Unit of measure: years

Number Analyzed	180 participants	176 participants
	62 (22 to 81)	62 (31 to 85)

Sex: Female, Male

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	180 participants	176 participants
Female	27 15.0%	23 13.1%
Male	153 85.0%	153 86.9%

Region of Enrollment

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	180 participants	176 participants
Canada	32 17.8%	29 16.5%
United States	148 82.2%	147 83.5%

Outcome Measures

Expand all / Collapse all

1. Overall Survival

Type: Primary | Time Frame: Up to 3 years

Description	Overall survival is defined as the time from study entry to death from any cause. The median OS was estimated using the Kaplan-Meier method.
Time Frame	Up to 3 years
Analysis Population Description	[Not Specified]

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.
Overall Number of Participants Analyzed	180	176
Median (95% Confidence Interval) | Unit of Measure: month	8.9 (7.1 to 10.8)	10.5 (7.6 to 13.8)

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate), Arm II (Sorafenib Tosylate)
Comments	[Not Specified]
Type of Statistical Test	Superiority
Comments	[Not Specified]

Statistical Test of Hypothesis

P-Value	0.24
Comments	[Not Specified]
Method	t-test, 1 sided

Comments	[Not Specified]

Method of Estimation

Estimation Parameter	Hazard Ratio (HR)
Estimated Value	1.06
Confidence Interval	(2-Sided) 95% 0.8 to 1.4
Estimation Comments	[Not Specified]

2. Incidence of Toxicities, as Assessed by National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Type: Secondary | Time Frame: Up to 3 years

Description	Toxicity is defined as a grade 3 or higher adverse events that is classified as either possibly, probably, or definitely related to study treatment. The assignment of attribution to study treatment and grade (or degree of severity) of the adverse event are classified using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The percentage of patients with a maximum grade 3 or higher adverse event at least possibly related to the study treatment are reported below.
Time Frame	Up to 3 years
Analysis Population Description	[Not Specified]

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.
Overall Number of Participants Analyzed	180	176
Fatigue *Measure Type: Number | Unit of Measure: percentage of patients	10	7
Hypertension *	3	13
White blood cells *	11	0
Neutrophils *	33	0
Platelets *	14	1
Hand Foot Syndrome *	10	14

vival

Frame: Up to 3 years

Progression free survival is defined as the time from study entry to earliest date of disease progression. Progression is defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).

Up to 3 years

[Not Specified]

* Measure Type: Number | Unit of Measure: percentage of patients

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.
Overall Number of Participants Analyzed	180	176
Median (95% Confidence Interval) | Unit of Measure: months	4.0 (3.2 to 5.0)	3.9 (2.9 to 4.8)

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate), Arm II (Sorafenib Tosylate)
Comments	[Not Specified]
Type of Statistical Test	Superiority
Comments	[Not Specified]

Statistical Test of Hypothesis

P-Value	0.98
Comments	[Not Specified]
Method	t-test, 1 sided

Comments	[Not Specified]

Method of Estimation

Estimation Parameter	Hazard Ratio (HR)
Estimated Value	0.9
Confidence Interval	(2-Sided) 95% 0.72 to 1.2
Estimation Comments	[Not Specified]

4. Time to Progression (TTP)

Type: Secondary | Time Frame: Up to 3 years

Description	Time to Progression (TTP) is defined as the time from on study to progression. Progression is defined by the RECIST criteria as Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression). Median and 95% confidence intervals are provided for each arm below.
Time Frame	Up to 3 years
Analysis Population Description	[Not Specified]

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.
Overall Number of Participants Analyzed	180	176
Median (95% Confidence Interval) | Unit of Measure: months	4.1 (3.25 to 5.00)	3.8 (2.92 to 4.50)

5. Best Overall Response Rate

Type: Secondary | Time Frame: Up to 3 years

Description	Best Overall Response Rate is defined as is the best response recorded from the start of the treatment until disease progression/recurrence. Complete Response: Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm. Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression). Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.
Time Frame	Up to 3 years

Analysis Population Description	Patients who started treatment and had follow-up assessments were included in this analysis.	
Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.
Overall Number of Participants Analyzed	150	150
Measure Type: Number | Unit of Measure: percentage of patients	7.3	3.3

Adverse Events

Time Frame
Up to 3 years.

Adverse Event Reporting Description
Each CTCAE term is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). All graded AEs are reported for patients who completed the study. Serious AE (SAE) reports may include any secondary serious or non-serious events considered related to the primary event (the reason for filing an expedited report); collectively, these events are referred to as Expedited AEs, and appear in the SAE table.

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
Arm/Group Description	Patients receive 60 mg/m2 doxorubicin hydrochloride IV on day 1 and 400 mg sorafenib tosylate PO QD or BID on days 1-21. Treatment repeats every 21 days for 6 courses in the absence of disease progression or unacceptable toxicity. After 6 courses, patients may continue to receive sorafenib tosylate PO QD or BID in the absence of disease progression or unacceptable toxicity.	Patients receive 400 mg sorafer tosylate PO QD or BID on days 1 Courses repeat every 21 days in absence of disease progressior unacceptable toxicity.

All-Cause Mortality

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)	Arm II (Sorafenib Tosylate
	Affected / at Risk (%)	Affected / at Risk (%)
Total	12/167 (7.19%)	16/171 (9.36%)

Serious Adverse Events

Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)		Arm II (Sorafenib Tosylate	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Even
Total	71/167 (42.51%)		57/171 (33.33%)	
Blood and lymphatic system disorders				
Anemia †1	9/167 (5.39%)	10	4/171 (2.34%)	5
Febrile neutropenia †1	7/167 (4.19%)	8	0/171 (0.00%)	0
Leukocytosis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Spleen disorder †1	0/167 (0.00%)	0	1/171 (0.58%)	1

Thrombotic thrombocytopenic purpura †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Cardiac disorders				
Atrial fibrillation †1	3/167 (1.80%)	3	1/171 (0.58%)	1
Cardiac disorder †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Chest pain - cardiac †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Left ventricular systolic dysfunction †1	3/167 (1.80%)	3	0/171 (0.00%)	0
Myocardial infarction †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Palpitations †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Sinus bradycardia †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Sinus tachycardia †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Endocrine disorders				
Hypothyroidism †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Eye disorders				
Conjunctivitis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Gastrointestinal disorders				
Abdominal distension †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Abdominal pain †1	22/167 (13.17%)	24	28/171 (16.37%)	33
Anal mucositis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Ascites †1	3/167 (1.80%)	3	2/171 (1.17%)	2
Colitis †1	2/167 (1.20%)	2	0/171 (0.00%)	0
Constipation †1	1/167 (0.60%)	1	0/171 (0.00%)	0

Diarrhea †1	27/167 (16.17%)	28	13/171 (7.60%)	15
Dyspepsia †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Dysphagia †1	3/167 (1.80%)	3	0/171 (0.00%)	0
Esophageal ulcer †1	1/167 (0.60%)	2	0/171 (0.00%)	0
Esophageal varices hemorrhage †1	1/167 (0.60%)	1	4/171 (2.34%)	4
Esophagitis †1	2/167 (1.20%)	3	0/171 (0.00%)	0
Gastric hemorrhage †1	0/167 (0.00%)	0	2/171 (1.17%)	2
Gastrointestinal disorders - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hemorrhoidal hemorrhage †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Lower gastrointestinal hemorrhage †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Mucositis oral †1	17/167 (10.18%)	17	4/171 (2.34%)	4
Nausea †1	34/167 (20.36%)	36	24/171 (14.04%)	29
Pancreatitis †1	2/167 (1.20%)	2	0/171 (0.00%)	0
Rectal hemorrhage †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Rectal mucositis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Upper gastrointestinal hemorrhage †1	1/167 (0.60%)	1	3/171 (1.75%)	4
Vomiting †1	4/167 (2.40%)	4	6/171 (3.51%)	6
General disorders				
Death NOS †1	4/167 (2.40%)	4	7/171 (4.09%)	7
Edema limbs †1	1/167 (0.60%)	1	0/171 (0.00%)	0

Edema trunk †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Fatigue †1	49/167 (29.34%)	56	32/171 (18.71%)	38
Fever †1	2/167 (1.20%)	2	1/171 (0.58%)	1
Localized edema †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Multi-organ failure †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Non-cardiac chest pain †1	0/167 (0.00%)	0	2/171 (1.17%)	2
Pain †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Sudden death NOS †1	1/167 (0.60%)	1	2/171 (1.17%)	2
Hepatobiliary disorders				
Cholecystitis †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Gallbladder obstruction †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Hepatic failure †1	3/167 (1.80%)	3	1/171 (0.58%)	1
Hepatic hemorrhage †1	0/167 (0.00%)	0	2/171 (1.17%)	2
Hepatobiliary disorders - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	2
Immune system disorders				
Anaphylaxis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Infections and infestations				
Abdominal infection †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Bone infection †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Infections and infestations - Other, specify †1	3/167 (1.80%)	3	1/171 (0.58%)	1

Lung infection †1	6/167 (3.59%)	6	0/171 (0.00%)	0
Peritoneal infection †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Rash pustular †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Sepsis †1	5/167 (2.99%)	5	2/171 (1.17%)	2
Skin infection †1	2/167 (1.20%)	2	2/171 (1.17%)	3
Urinary tract infection †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Wound infection †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Injury, poisoning and procedural complications				
Fall †1	0/167 (0.00%)	0	2/171 (1.17%)	2
Fracture †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Wound complication †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Investigations				
Activated partial thromboplastin time prolonged †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Alanine aminotransferase increased †1	3/167 (1.80%)	3	3/171 (1.75%)	3
Alkaline phosphatase increased †1	3/167 (1.80%)	3	4/171 (2.34%)	4
Aspartate aminotransferase increased †1	4/167 (2.40%)	4	6/171 (3.51%)	6
Blood bilirubin increased †1	8/167 (4.79%)	9	7/171 (4.09%)	7

Creatinine increased †1	3/167 (1.80%)	3	0/171 (0.00%)	0
Ejection fraction decreased †1	3/167 (1.80%)	3	1/171 (0.58%)	1
Haptoglobin decreased †1	1/167 (0.60%)	1	0/171 (0.00%)	0
INR increased †1	2/167 (1.20%)	2	1/171 (0.58%)	1
Leukocyte count decreased †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Lipase increased †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Lymphocyte count decreased †1	6/167 (3.59%)	6	2/171 (1.17%)	3
Neutrophil count decreased †1	31/167 (18.56%)	32	0/171 (0.00%)	0
Platelet count decreased †1	35/167 (20.96%)	38	20/171 (11.70%)	24
Weight loss †1	2/167 (1.20%)	2	1/171 (0.58%)	1
White blood cell decreased †1	10/167 (5.99%)	10	0/171 (0.00%)	0
Metabolism and nutrition disorders				
Anorexia †1	5/167 (2.99%)	5	4/171 (2.34%)	4
Dehydration †1	14/167 (8.38%)	14	5/171 (2.92%)	5
Hyperglycemia †1	2/167 (1.20%)	2	2/171 (1.17%)	2
Hyperkalemia †1	4/167 (2.40%)	4	1/171 (0.58%)	1
Hypernatremia †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hypoalbuminemia †1	4/167 (2.40%)	4	1/171 (0.58%)	1
Hypokalemia †1	2/167 (1.20%)	2	0/171 (0.00%)	0

Hypomagnesemia † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hyponatremia † 1	10/167 (5.99%)	10	4/171 (2.34%)	4
Hypophosphatemia † 1	4/167 (2.40%)	4	1/171 (0.58%)	1
Metabolism and nutrition disorders - Other, specify † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Serum phosphate decreased † 1	1/167 (0.60%)	1	0/171 (0.00%)	0

Musculoskeletal and connective tissue disorders

Back pain † 1	1/167 (0.60%)	1	1/171 (0.58%)	1
Bone pain † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Generalized muscle weakness † 1	1/167 (0.60%)	1	1/171 (0.58%)	1
Myalgia † 1	1/167 (0.60%)	1	0/171 (0.00%)	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify † 1	1/167 (0.60%)	1	3/171 (1.75%)	3
Treatment related secondary malignancy † 1	2/167 (1.20%)	2	0/171 (0.00%)	0

Nervous system disorders

Amnesia † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Headache † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Intracranial hemorrhage † 1	0/167 (0.00%)	0	1/171 (0.58%)	1

Nervous system disorders - Other, specify † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Seizure † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Syncope vasovagal † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Psychiatric disorders				
Anxiety † 1	1/167 (0.60%)	1	1/171 (0.58%)	1
Confusion † 1	1/167 (0.60%)	1	2/171 (1.17%)	2
Renal and urinary disorders				
Acute kidney injury † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hematuria † 1	2/167 (1.20%)	2	1/171 (0.58%)	1
Urogenital disorder † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea † 1	4/167 (2.40%)	4	4/171 (2.34%)	4
Epistaxis † 1	1/167 (0.60%)	1	3/171 (1.75%)	3
Hypoxia † 1	1/167 (0.60%)	1	1/171 (0.58%)	1
Pulmonary edema † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Sore throat † 1	1/167 (0.60%)	2	0/171 (0.00%)	0
Skin and subcutaneous tissue disorders				
Alopecia † 1	2/167 (1.20%)	2	0/171 (0.00%)	0
Erythema multiforme † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Palmar-plantar erythrodysesthesia syndrome † 1	13/167 (7.78%)	16	10/171 (5.85%)	11

Pruritus †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Rash maculo-papular †1	1/167 (0.60%)	1	2/171 (1.17%)	2
Scalp pain †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Skin ulceration †1	3/167 (1.80%)	3	3/171 (1.75%)	3
Stevens-Johnson syndrome †1	1/167 (0.60%)	1	0/171 (0.00%)	0

Vascular disorders

Hypertension †1	21/167 (12.57%)	25	16/171 (9.36%)	17
Hypotension †1	2/167 (1.20%)	2	1/171 (0.58%)	1
Thromboembolic event †1	0/167 (0.00%)	0	3/171 (1.75%)	3

† Indicates events were collected by systematic assessment

1 Term from vocabulary, MedDRA 12

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	0%			
Arm/Group Title	Arm I (Doxorubicin Hydrochloride, Sorafenib Tosylate)		Arm II (Sorafenib Tosylate	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Even
Total	146/167 (87.43%)		151/171 (88.30%)	

Blood and lymphatic system disorders

Anemia †1	10/167 (5.99%)	11	8/171 (4.68%)	8
Blood and lymphatic system disorders -	0/167 (0.00%)	0	1/171 (0.58%)	2

Other, specify † 1				
Febrile neutropenia † 1	5/167 (2.99%)	7	0/171 (0.00%)	0
Hemoglobin decreased † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hemolysis † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Thrombotic thrombocytopenic purpura † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Cardiac disorders				
Atrial fibrillation † 1	1/167 (0.60%)	5	0/171 (0.00%)	0
Chest pain - cardiac † 1	0/167 (0.00%)	0	2/171 (1.17%)	3
Left ventricular failure † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Left ventricular systolic dysfunction † 1	7/167 (4.19%)	7	0/171 (0.00%)	0
Sinus bradycardia † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Supraventricular tachycardia † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Ventricular tachycardia † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Ear and labyrinth disorders				
Hearing impaired † 1	0/167 (0.00%)	0	1/171 (0.58%)	4
Endocrine disorders				
Hypothyroidism † 1	5/167 (2.99%)	14	4/171 (2.34%)	18
Eye disorders				
Conjunctivitis † 1	1/167 (0.60%)	1	0/171 (0.00%)	0

Eye disorders - Other, specify † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Eye pain † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Gastrointestinal disorders				
Abdominal distension † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Abdominal pain † 1	59/167 (35.33%)	156	75/171 (43.86%)	205
Anal fistula † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Ascites † 1	3/167 (1.80%)	3	2/171 (1.17%)	2
Bloating † 1	0/167 (0.00%)	0	1/171 (0.58%)	1
Constipation † 1	1/167 (0.60%)	1	5/171 (2.92%)	6
Dental caries † 1	1/167 (0.60%)	2	0/171 (0.00%)	0
Diarrhea † 1	68/167 (40.72%)	203	73/171 (42.69%)	256
Dry mouth † 1	0/167 (0.00%)	0	2/171 (1.17%)	2
Dyspepsia † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Esophageal ulcer † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Esophageal varices hemorrhage † 1	0/167 (0.00%)	0	1/171 (0.58%)	2
Esophagitis † 1	2/167 (1.20%)	2	0/171 (0.00%)	0
Gastroesophageal reflux disease † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hemorrhoids † 1	1/167 (0.60%)	1	0/171 (0.00%)	0
Mucositis oral † 1	54/167 (32.34%)	126	31/171 (18.13%)	45
Nausea † 1	59/167 (35.33%)	167	64/171 (37.43%)	179
Oral pain † 1	1/167 (0.60%)	1	0/171 (0.00%)	0

Upper gastrointestinal hemorrhage †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Vomiting †1	5/167 (2.99%)	5	5/171 (2.92%)	5
General disorders				
Chills †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Edema limbs †1	4/167 (2.40%)	6	2/171 (1.17%)	2
Fatigue †1	111/167 (66.47%)	427	104/171 (60.82%)	407
Fever †1	1/167 (0.60%)	1	2/171 (1.17%)	2
Gait disturbance †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Localized edema †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Malaise †1	1/167 (0.60%)	1	1/171 (0.58%)	2
Non-cardiac chest pain †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Pain †1	4/167 (2.40%)	5	2/171 (1.17%)	2
Hepatobiliary disorders				
Hepatic failure †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hepatic hemorrhage †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hepatobiliary disorders - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Infections and infestations				
Cecal infection †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Gum infection †1	1/167 (0.60%)	2	0/171 (0.00%)	0
Lung infection †1	0/167 (0.00%)	0	1/171 (0.58%)	1

Papulopustular rash †1	1/167 (0.60%)	2	1/171 (0.58%)	1
Periorbital infection †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Rash pustular †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Tooth infection †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Upper respiratory infection †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Urinary tract infection †1	2/167 (1.20%)	2	1/171 (0.58%)	2
Injury, poisoning and procedural complications				
Dermatitis radiation †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Fracture †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Investigations				
Alanine aminotransferase increased †1	6/167 (3.59%)	7	6/171 (3.51%)	10
Alkaline phosphatase increased †1	5/167 (2.99%)	6	9/171 (5.26%)	13
Aspartate aminotransferase increased †1	12/167 (7.19%)	15	15/171 (8.77%)	25
Blood bilirubin increased †1	9/167 (5.39%)	10	10/171 (5.85%)	14
CD4 lymphocytes decreased †1	1/167 (0.60%)	3	0/171 (0.00%)	0
Creatinine increased †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Ejection fraction decreased †1	14/167 (8.38%)	29	0/171 (0.00%)	0

Electrocardiogram QT corrected interval prolonged †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Leukocyte count decreased †1	3/167 (1.80%)	4	0/171 (0.00%)	0
Lipase increased †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Lymphocyte count decreased †1	8/167 (4.79%)	15	9/171 (5.26%)	20
Neutrophil count decreased †1	58/167 (34.73%)	110	11/171 (6.43%)	69
Platelet count decreased †1	67/167 (40.12%)	199	62/171 (36.26%)	348
Weight loss †1	1/167 (0.60%)	1	4/171 (2.34%)	6
White blood cell decreased †1	11/167 (6.59%)	13	1/171 (0.58%)	1
Metabolism and nutrition disorders				
Anorexia †1	6/167 (3.59%)	8	11/171 (6.43%)	16
Blood glucose increased †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Dehydration †1	1/167 (0.60%)	1	2/171 (1.17%)	3
Hypercalcemia †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hyperglycemia †1	9/167 (5.39%)	12	9/171 (5.26%)	11
Hyperkalemia †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Hypermagnesemia †1	1/167 (0.60%)	3	0/171 (0.00%)	0
Hypernatremia †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hyperuricemia †1	1/167 (0.60%)	2	0/171 (0.00%)	0
Hypoalbuminemia †1	2/167 (1.20%)	2	2/171 (1.17%)	3

Hypocalcemia †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Hypoglycemia †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Hypokalemia †1	3/167 (1.80%)	7	2/171 (1.17%)	2
Hypomagnesemia †1	3/167 (1.80%)	3	0/171 (0.00%)	0
Hyponatremia †1	7/167 (4.19%)	13	11/171 (6.43%)	16
Hypophosphatemia †1	6/167 (3.59%)	15	11/171 (6.43%)	16
Metabolism and nutrition disorders - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Serum albumin decreased †1	2/167 (1.20%)	2	0/171 (0.00%)	0
Serum phosphate decreased †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Serum potassium decreased †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Serum sodium decreased †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Musculoskeletal and connective tissue disorders				
Arthralgia †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Arthritis †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Back pain †1	0/167 (0.00%)	0	3/171 (1.75%)	7
Chest wall pain †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Generalized muscle weakness †1	2/167 (1.20%)	2	1/171 (0.58%)	1
Muscle weakness upper limb †1	1/167 (0.60%)	1	0/171 (0.00%)	0

Musculoskeletal disorder †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Myalgia †1	0/167 (0.00%)	0	1/171 (0.58%)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	5
Nervous system disorders				
Dysgeusia †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Encephalopathy †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Headache †1	1/167 (0.60%)	2	1/171 (0.58%)	1
Paresthesia †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Peripheral sensory neuropathy †1	1/167 (0.60%)	1	2/171 (1.17%)	3
Psychiatric disorders				
Confusion †1	0/167 (0.00%)	0	2/171 (1.17%)	2
Depression †1	2/167 (1.20%)	2	2/171 (1.17%)	3
Insomnia †1	2/167 (1.20%)	2	2/171 (1.17%)	2
Renal and urinary disorders				
Chronic kidney disease †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hematuria †1	5/167 (2.99%)	10	4/171 (2.34%)	5
Respiratory, thoracic and mediastinal disorders				
Cough †1	1/167 (0.60%)	2	0/171 (0.00%)	0

Dyspnea †1	1/167 (0.60%)	1	6/171 (3.51%)	8
Epistaxis †1	7/167 (4.19%)	8	12/171 (7.02%)	16
Hiccups †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hypoxia †1	1/167 (0.60%)	2	0/171 (0.00%)	0
Sore throat †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Skin and subcutaneous tissue disorders				
Alopecia †1	3/167 (1.80%)	5	1/171 (0.58%)	2
Dry skin †1	0/167 (0.00%)	0	3/171 (1.75%)	5
Erythema multiforme †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hand-and-foot syndrome †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Nail discoloration †1	1/167 (0.60%)	2	0/171 (0.00%)	0
Palmar-plantar erythrodysesthesia syndrome †1	57/167 (34.13%)	197	68/171 (39.77%)	215
Pruritus †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Rash acneiform †1	1/167 (0.60%)	1	0/171 (0.00%)	0
Rash maculo-papular †1	6/167 (3.59%)	7	3/171 (1.75%)	3
Scalp pain †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Skin and subcutaneous tissue disorders - Other, specify †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Skin disorder †1	0/167 (0.00%)	0	1/171 (0.58%)	3

Skin ulceration †1	8/167 (4.79%)	16	7/171 (4.09%)	9
Vascular disorders				
Flushing †1	0/167 (0.00%)	0	1/171 (0.58%)	1
Hypertension †1	49/167 (29.34%)	172	68/171 (39.77%)	316
Hypotension †1	1/167 (0.60%)	1	1/171 (0.58%)	1
Thromboembolic event †1	3/167 (1.80%)	15	0/171 (0.00%)	0
Thrombosis †1	1/167 (0.60%)	1	0/171 (0.00%)	0

† Indicates events were collected by systematic assessment

1 Term from vocabulary, MedDRA 12

Limitations and Caveats

[Not Specified]

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor

National Cancer Institute (NCI)

Investigators

- Principal Investigator: Ghassan K Abou-Alfa, Alliance for Clinical Trials in Oncology

Publications

From PubMed

These publications come from PubMed, a public database of scientific and medical articles. This list is automatically created by ClinicalTrials.gov Identifier (NCT Number), and these articles may or may not be about the study.

- Quintanilha JCF, Geyer S, Etheridge AS, Racioppi A, Hammond K, Crona DJ, Pena CE, Jacobson SB, Marmorino F, Rossini D, Cremolini C, Sanoff HK, Abou-Alfa GK, Innocenti F. KDR genetic predictor of toxicities induced by sorafenib and regorafenib. Pharmacogenomics J. 2022 Dec;22(5-6):251-257. doi: 10.1038/s41397-022-00279-3. Epub 2022 Apr 28. (https://pubmed.ncbi.nlm.nih.gov/35484400)
- Abou-Alfa GK, Shi Q, Knox JJ, Kaubisch A, Niedzwiecki D, Posey J, Tan BR Jr, Kavan P, Goel R, Lammers PE, Bekaii-Saab TS, Tam VC, Rajdev L, Kelley RK, El Dika I, Zemla T, Potaracke RI, Balletti J, El-Khoueiry AB, Harding JJ, Suga JM, Schwartz LH, Goldberg RM, Bertagnolli MM, Meyerhardt J, O'Reilly EM, Venook AP. Assessment of Treatment With Sorafenib Plus Doxorubicin vs Sorafenib Alone in Patients With Advanced Hepatocellular Carcinoma: Phase 3 CALGB 80802 Randomized Clinical Trial. JAMA Oncol. 2019 Nov 1;5(11):1582-1588. doi: 10.1001/jamaoncol.2019.2792. Erratum In: JAMA Oncol. 2019 Nov 1;5(11):1643. doi: 10.1001/jamaoncol.2019.4781. (https://pubmed.ncbi.nlm.nih.gov/31486832)

More Information

Record History

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed