Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Webposting Clinical Trial Results Synopsis

Study Sponsor:	Bayer Healthcare Pharmaceuticals Inc.	
Study Number:	11546	NCT00108953
Study Phase:	Phase 2	
Study Title:	A randomized, placebo-controlled study of sorafenib in combination with doxorubicin versus doxorubicin in patients with advanced hepatocellular carcinoma.	
Therapeutic Area:	Advanced hepatocellular carcinoma (HCC)	
Name of Test Product:	Nexavar®	
Active Ingredient:	Sorafenib/BAY 43-9006 Combination therapy: sorafenib + doxorubicin	
Dosage:	All subjects were to receive doxorubicin 60 mg/m^2 IV infusion every 21 days for 6 cycles (18 weeks). Dose reductions were permitted to predefined levels if subjects were randomized with elevated bilirubin levels prior to Cycle 1 (half of the normal doxorubicin dose, ie, 30 mg/m^2) or for adverse events related to study treatment. In the event of doxorubicin dose reduction, the number of cycles could be increased until the maximum cumulative dose of 360 mg/m^2 was administered. However, at the discretion of the investigator, doxorubicin treatment could be continued beyond the maximum cumulative dose of 360 mg/m^2 but was not to exceed 450 mg/m^2. Sorafenib (Nexavar®, BAY-43 9006) was administered orally at a dose of 400 mg (2 x 200 mg tablets) twice daily; 2 dose reductions to predefined levels of 400 mg once daily (od) and 400 mg every other day were permitted for adverse events related to study treatment.	
Reference Therapy:	Monotherapy: placebo + doxorubicin	
Dosage:	See above: Active Ingredient, Dosage	
Placebo:	Placebo tablets matching in appearance were administered orally twice daily (bid).	
Route of Administration:	Doxorubicin was administered as intravenous (IV) infusion. Sorafenib and sorafenib matching placebo tablets were administered orally.	
Treatment Duration:	Treatment was continued until death or until a criterion for stopping the therapy was met. Treatment beyond radiological and symptomatic progression was allowed upon request of the treating investigator. The treatment period (not fixed in time but ended by any event) was followed by a follow-up period.	
Study Period:	Date of first subject's first visit:	13 April 2005
	Date of last subject's last contact:	11 April 2008
Methodology:	• Multi-center • Multinational • Randomized • Double-blind • Placebo-controlled: sorafenib + doxorubicin (combination) versus placebo + doxorubicin (monotherapy)	
Study Site:	This multinational study was conducted at 25 active centers in 6 countries/regions: Argentina, Canada, Hong Kong, Russia, the United Kingdom, and the United States.	
Main Inclusion Criteria:	Subjects with advanced HCC, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2, Child-Pugh status A, who had not received prior systemic anti-cancer treatment for HCC were to be enrolled in the study. Advanced HCC in this study was defined as unresectable and/or metastatic HCC. Eligible subjects were to have a life expectancy of at least 12 weeks.	

Study Objectives:	Overall: • To evaluate the safety and efficacy of sorafenib + doxorubicin versus placebo + doxorubicin in subjects with advanced HCC Primary: • To evaluate time to progression (TTP) Secondary: • To evaluate overall survival (OS) • To evaluate progression-free survival (PFS) • To evaluate time to symptomatic progression (TTSP) • To evaluate duration of response • To evaluate time to response (TTR) per Response Evaluation Criteria in Solid Tumors (RECIST) criteria • To evaluate overall best tumor response rate (RR) • To evaluate overall disease control rate (DCR)
Evaluation Criteria	Efficacy (Primary): • The primary focus is on time to progression (TTP) defined as the time from randomization to the first documented disease progression (radiological only) with sorafenib plus doxorubicin, compared with doxorubicin alone. Subjects without tumor progression at the time of analysis were censored at their last date of tumor evaluation.
	Efficacy (Secondary): • Overall survival (OS) was measured from the date of randomization until the date of death due to any cause. For subjects alive or lost to follow-up at the time of analysis, time to death was censored at their last date of follow-up. • Progression-free survival (PFS) was defined as the time from randomization to the first documented radiological disease progression or death (if death occurred earlier than progression). For subjects without documented progression or death at the time of analysis, PFS was censored at the last date of tumor evaluation. • Time to symptomatic progression (TTSP) was defined as the time from randomization to first documented symptomatic progression. For subjects who had not progressed symptomatically at the time of analysis, TTSP was censored at the date of their last Functional Assessment of Cancer Therapy Hepatobiliary Symptom Index-8 (FHSI-8) assessment. • Duration of response was defined as the time from the first documented objective response (CR, PR) to disease progression or death (if death occurs earlier than progression). Subjects who had not progressed or died at the time of analysis were censored at the date of their last tumor assessment. For subjects failing to achieve an objective response, overall response duration was assigned value zero. • Time to response (TTR) was defined as the time from the date of randomization to the date that an objective tumor response (CR or PR) is first documented according to the RECIST tumor response criteria. Response must subsequently be confirmed at least 4 weeks later. For subjects failing to achieve an objective response and did not progress during the trial, time to objective response was censored at their last date of tumor evaluation. • Overall best tumor response rate was defined as the proportion of subjects with the best tumor response (confirmed PR and CR) achieved during treatment or within 30 days after termination of active therapy and confirmed according to RECIST criteria. These are based on changes in only the largest diameter of the tumor lesions. • Overall disease control rate (DCR) defined as the proportion of subjects who had a best response rating of CR, PR or stable disease that was maintained for at least 28 days from the first demonstration of that rating.

	Safety: The population for safety analyses included all subjects who had received at least 1 dose of study medication prior to the data cut off date. Safety variables included adverse events graded according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0, laboratory changes (hematology and clinical chemistry), changes in vital signs (blood pressure, heart rate, respiratory rate, temperature) and electrocardiogram (ECG). Study visits for evaluation of safety occurred every 3 weeks during the treatment period; safety was also evaluated during screening and at the end of treatment visit. The Data Monitoring Committee (DMC) held safety review meetings approximately every 6 months after initiation of enrollment. The study data were reviewed for clinically important differences between the treatment groups in serious adverse events, toxicities and deaths.
Statistical Methods:	Efficacy (Primary): The primary efficacy endpoint of this study was TTP; TTP for subjects without tumor progression at the time of analysis was censored at their last date of tumor evaluation. The 2 treatment groups were compared using a log rank test stratified by tumor burden. .The medians TTP and their 80% and 95% confidence intervals (CIs) were calculated using Kaplan-Meier estimates. The Hazard ratio 'sorafenib + doxorubicin' over 'placebo + doxorubicin' was estimated with its CI according the Cox proportional hazard model with tumor burden as covariate. All randomized subjects (ITT population) were included in the primary analysis. Efficacy (Secondary): For the secondary time-to-event variables were analyzed in the same way as the primary variables. For each treatment group, the FHSI-8 scores were summarized by cycle for the observed values and changes from baseline using descriptive statistics. A graph of average score changes from baseline by visit for each treatment group was generated to see whether a time trend existed. In addition, response rates based on the 2-point minimally important difference (MID) and most conservative estimate of the MID (4-point change) were compared between treatment groups by cycle. Safety: Statistical summaries were provided by treatment group for treatment duration, average daily dose taken, and percentage of planned dose received. Subjects with dose reduction or interruption, subjects with dose delay, and the number of dose reductions/interruptions/delays per subject were also summarized. All adverse events and hematological/biochemical toxicities based on laboratory measurements were summarized by treatment group and NCI-CTCAE Version 3.0 worst grade. The incidence of deaths, drug-related adverse events, treatment-emergent serious adverse events, and adverse events leading to discontinuation of investigational product and/or withdrawal from the study were summarized.
Number of Subjects:	Of 140 subjects screened, 96 were randomized (last subject on 12 Oct 2006) and were valid for the efficacy analyses (intent-to-treat [ITT] population). 95 received at least one dose of study medication and were valid for the safety analyses. Of the 96 subjects in the ITT population, 49 were randomized to placebo + doxorubicin and 47 to sorafenib + doxorubicin and completed the treatment period. Of those randomized to placebo + doxorubicin and sorafenib + doxorubicin, respectively, 45 and 40 subjects entered the follow-up period, and 12 and 11 subjects completed it. The study had been prematurely terminated by the sponsor because positive results were obtained in another sorafenib trial (Phase 3 study #100554). The results are considered not conclusive due to a lot of censored data.

Results Summary — Subject Disposition and Baseline

Of the 96 randomized subjects (ITT population), 73 were men and 23 women. In the ITT population the median age was 65 years, with age ranging from 38 to 82 years. The baseline characteristics by treatment group are given in Table 1. Randomization was stratified according to "tumor burden". Stratification and prognostic criteria were balanced between the 2 treatment arms.

Table 1: Subject baseline characteristics (ITT population)

Demographic and clinical baseline features		Placebo + doxorubicin (N = 49)	Sorafenib + doxorubicin (N = 47)
Age – median (range)		65 (38 – 81)	66 (38 – 82)
Sex – n	Female	7	16

	Male	42	31
ECOG Performance Status – n	Grade 0	16	22
	Grade 1	25	18
	Grade 2	3	4
	Grade 3	1	0
	Missing	4	3
Child-Pugh score – n	5 (Child-Pugh A)	28	30
	6 (Child-Pugh A)	19	17
	7 (Child-Pugh B)	2	0
Tumor burden: Macroscopic vascular invasion – n	Yes	13	16
	No	33	32
	Missing	1	1
Tumor burden: Extrahepatic spread – n	Yes	32	24
	No	17	23

Results Summary — Efficacy

At the third safety review carried out by an independent DMC, when efficacy data were also presented for the first time, the DMC, on the ground of the Phase 3 positive results, recommended early termination of this trial. Moreover, encouraging preliminary results for TTP, the primary endpoint of study #11546, were detected: TTP resulted significantly longer in the combination treatment arm (sorafenib + doxorubicin). On these grounds, the study was stopped early and subjects still ongoing on placebo were switched to sorafenib.

Primary efficacy:

Analysis of efficacy based on these 38 disease progression events (18 in the sorafenib + doxorubicin arm and 20 in the placebo + doxorubicin arm) that had occurred as of 11 Apr 2008 showed that combination treatment with sorafenib + doxorubicin significantly prolonged TTP (the primary endpoint of the study), as compared with placebo + doxorubicin. The TTP analysis was based on blinded assessment of radiological scans by independent radiological review, taking into account only radiological progressions. The median TTP and estimated hazard ratio based on independent radiological review are given in Table 2. This is a clinically meaningful and statistically significant improvement in TTP, supporting a clinically meaningful improvement in TTP for subjects treated with sorafenib + doxorubicin compared to those treated with placebo + doxorubicin.

Table 2: Time to progression (TTP) based on independent radiological review (ITT population)

Time to event	Placebo + doxorubicin (N = 49)	Sorafenib + doxorubicin (N = 47)
Total failed	20	18
Total censored	29	29
Median TTP (days)	147	263
95% CI for median	66, 244	146, 384
Hazard ratio [*P* value]	0.60 [0.0765]	
95% CI for hazard ratio	0.30; 1.22	

TTP includes only radiologically-determined disease progression.

Hazard ratio: 'sorafenib + doxorubicin' / 'placebo + doxorubicin'

Abbreviations: TTP – time to progression, ITT – intent-to-treat, CI – confidence interval

Secondary efficacy:

The median TTP based on investigator assessment was 83 days (2.7 months) for subjects who received placebo + doxorubicin versus 186 days (6.1 months) for subjects treated with sorafenib + doxorubicin ($P = 0.0161$).

Analysis of secondary efficacy endpoints revealed that sorafenib + doxorubicin also significantly prolonged OS compared with placebo + doxorubicin. Median OS was 199 days (6.5 months) in subjects randomized to placebo + doxorubicin and 418 days (13.8 months) in subjects randomized to sorafenib + doxorubicin. The estimated hazard ratio for survival ('sorafenib + doxorubicin'

over 'placebo + doxorubicin') was 0.52 (P = 0.006952). Also, in this case, the addition of sorafenib to doxorubicin provides subjects on treatment with a meaningful benefit in terms of overall survival. These data are consistent with the results of study #100554 and confirm sorafenib to be the first systemic treatment which clearly demonstrates a survival advantage in subjects with HCC.

The overall disease control rate (DCR) as assessed by independent review was 63.8% in the sorafenib + doxorubicin group versus 30.6% in the placebo + doxorubicin group. At 6 months from the start of study treatment, the PFS rate was 54% for sorafenib + doxorubicin (80% CI: 0.43%, 0.64%) and 27% for placebo + doxorubicin (80% CI: 0.18%, 0.36%).

These and other secondary efficacy endpoints are summarized in Table 3.

In summary, efficacy data from this blinded, placebo-controlled study clearly demonstrated clinically and statistically significant prolongation of TTP and OS in subjects with HCC treated with sorafenib + doxorubicin. These results support the broad applicability of sorafenib-based therapy in subjects with advanced HCC.

Table 3: Secondary efficacy endpoints (ITT population)

Time to event or percent of subjects		Placebo + doxorubicin (N = 49)	Sorafenib + doxorubicin (N = 47)
Overall survival	– median days (95% CI)	199 (148, 302)	418 (317, NE)
	– hazard ratio [P value]	0.52 [0.007]	
Progression-free survival	– median days (95% CI)	85 (71, 172)	242 (140, 312)
	– hazard ratio [P value]	0.61 [0.018]	
Time to symptomatic progression	– median days (95% CI)	152 (110, 180)	208 (85, 317)
	– hazard ratio [P value]	0.65 [0.038]	
Duration of response	– median days (95% CI)	68 (NE)	199 (NE)
Time to response	– median days (95% CI)	40 (NE)	134 (NE)
Overall best tumor response rate	– percentage of subjects	2.0	4.3
Overall disease control rate	– percentage of subjects	30.6	63.8

Hazard ratio: 'sorafenib + doxorubicin' / 'placebo + doxorubicin'

Abbreviations: ITT – intent-to-treat, CI – confidence interval, NE – not estimable

Results Summary — Safety

Doxorubicin has a well-characterized safety profile, the main features of which are myelosuppression and cardiotoxicity. Leucopenia and/or neutropenia are the predominant manifestation of hematological toxicity. Other commonly recognized side-effects of doxorubicin are associated with gastrointestinal, dermatologic, and metabolic toxicities. This placebo-controlled study provided an opportunity to discriminate between toxicities associated with sorafenib and events usually associated with doxorubicin as well as possible synergistic additive toxicities of the combination.

Overall, 16 subjects (33.3%) in the placebo + doxorubicin group and 18 subjects (38.3%) in the sorafenib + doxorubicin group discontinued study medication because of adverse events, including events associated with disease progression. Of these 34 subjects, 4 in the placebo + doxorubicin group and 2 in the sorafenib + doxorubicin group discontinued due to progressive disease.

The dosage of doxorubicin was reduced in 54% of subjects receiving placebo + doxorubicin and 64% of those receiving sorafenib + doxorubicin; this was due to adverse events in 85% and 97% of these subjects respectively. Likewise, dosing with doxorubicin was interrupted in 21% of subjects receiving placebo + doxorubicin and 21% of those receiving sorafenib + doxorubicin; this was due to adverse events in 50% and 100% of these subjects, respectively.

The dosage of study drug was reduced in 58% of subjects receiving placebo + doxorubicin and 77% of those receiving sorafenib + doxorubicin; this was due to adverse events in 86% and 97% of these subjects respectively. Likewise, dosing with study drug was interrupted in 54% of subjects receiving placebo + doxorubicin and 72% of those receiving sorafenib + doxorubicin; this was due to adverse events in 92% and 97% of these subjects respectively.

A brief summary of adverse events is given in Table 4. The overall incidence of Grade 3 and 4 events was similar in both treatment groups; Grade 3 or 4 adverse events reported at a higher incidence (ie, in at least 4 more subjects) in sorafenib + doxorubicin subjects than in placebo + doxorubicin subjects were neutropenia and leukopenia that was not associated with infection; vomiting, and elevated transaminases, which were not unexpected adverse events, based on the well characterized safety profile of doxorubicin.

Dermatology/skin adverse events overall were common in both treatment groups, but were more frequent in the sorafenib + doxorubicin group (placebo + doxorubicin group: 31 subjects [64.6%]; sorafenib + doxorubicin group: 37 subjects [78.7%]). The most common individual event was alopecia, the incidence of which was very similar in both treatment groups and may be attributed to doxorubicin. There was also a higher incidence (ie, in at least 6 more subjects) of Grade 3 dermatological events, especially hand-foot skin reaction (placebo + doxorubicin group: 2 subjects [4.2%]; sorafenib + doxorubicin group: 14 subjects [29.8%]), known to be associated with sorafenib treatment. However, none of the dermatologic events were classed as serious, none were above Grade 3 in

severity, and there were no discontinuations due to dermatological toxicities.

Gastrointestinal events were the most common overall (placebo + doxorubicin group: 41 subjects [85.4%]; sorafenib + doxorubicin group: 45 subjects [95.7%]); the incidence of nausea and constipation was similar in both treatment groups, and may well have been attributable to doxorubicin; however anorexia, vomiting and diarrhea were more common with sorafenib + doxorubicin treatment. None of the events were above Grade 3 in severity.

Left ventricular systolic dysfunction (LVSD) was found in 9 subjects (19.1%), in the sorafenib + doxorubicin group, and in 1 subject (2.1%) in the placebo + doxorubicin group. In the sorafenib + doxorubicin group 5 subjects had a NCI-CTCAE Grade of 1, and 3 subjects of Grade 2, and only 1 subject had Grade 3 LVSD; the only subject in the placebo + doxorubicin group with LVSD had Grade 2.

The incidences of treatment-emergent non-serious adverse events by NCI-CTC event categories (and NCI-CTC terms) in ≥20% of subjects of either treatment arm are given in Table 5. The incidences of all treatment-emergent serious adverse events by NCI-CTC event categories (and NCI-CTC terms) are given in Table 6.

Table 4: Incidence rates of adverse events (Safety population)

Number (%) of subjects with event	Placebo + doxorubicin (N = 48)	Sorafenib + doxorubicin (N = 47)
Treatment emergent adverse events (including serious)	48 (100)	47 (100)
Treatment emergent adverse events (excluding serious)	48 (100)	47 (100)
Drug-related treatment emergent adverse events (including serious)	42 (87.5)	43 (91.5)
Treatment emergent adverse events leading to discontinuation [a]	16 (33.3)	18 (38.3)
Treatment emergent serious adverse events	20 (41.7)	19 (40.4)
Drug-related treatment emergent serious adverse events	7 (14.6)	11 (23.4)
Deaths within 30 days of receiving study drug [b]	10 (20.8)	5 (10.6)
Deaths prior to cut-off (last subject's last visit) [c]	37 (77.1)	24 (51.1)

[a] Of these subjects, 4 in the placebo + doxorubicin group and 2 in the sorafenib + doxorubicin group were reported to have stopped study treatment because of progressive disease and 5 because of death (3 in placebo + doxorubicin group and 2 in sorafenib + doxorubicin)

[b] During study treatment, or within 30 days after the last dose of study medication.

[c] An additional 2 subjects who were not randomized to treatment and one additional subject (11546-12004001) who was randomized to the placebo + doxorubicin group but did not receive any study medication died prior to the data cut-off date.

Table 5: Incidence rates of non-serious adverse events by NCI CTC event category / term in at least 20% of subjects (Safety population)

Number (%) of subjects with event	Placebo + doxorubicin (N = 48)	Sorafenib + doxorubicin (N = 47)
Number of subjects with at least 1 of these events	44 (91.7)	47 (100)
Blood/bone marrow, any event	36 (75.0)	35 (74.5)
Neutrophils	29 (60.4)	31 (66.0)
Hemoglobin	14 (29.2)	15 (31.9)
Leukocytes	9 (18.8)	10 (21.3)
Cardiac general, any event	7 (14.6)	16 (34.0)
Constitutional symptoms, any event	36 (75.0)	43 (91.5)
Fatigue	32 (66.7)	39 (83.0)
Insomnia	8 (16.7)	13 (27.7)
Gastrointestinal, any event	41 (85.4)	45 (95.7)
Nausea	27 (56.3)	27 (57.4)
Constipation	21 (43.8)	21 (44.7)

Anorexia	14 (29.2)	24 (51.1)
Diarrhea	12 (25.0)	25 (53.2)
Vomiting	10 (20.8)	17 (36.2)
Mucositis (functional/symptomatic), oral cavity	14 (29.2)	11 (23.4)
GI – other	7 (14.6)	13 (27.7)
Mucositis (clinical exam), oral cavity	6 (12.5)	10 (21.3)
Taste alteration	5 (10.4)	10 (21.3)
Hemorrhage/bleeding, any event	5 (10.4)	12 (25.5)
Infection, any event	16 (33.3)	15 (31.9)
Lymphatics, any event	14 (29.2)	16 (34.0)
Edema: limb	13 (27.1)	15 (31.9)
Metabolic/laboratory, any event	24 (50.0)	27 (57.4)
Bilirubin (hyperbilirubinemia)	15 (31.3)	15 (31.9)
AST	7 (14.6)	11 (23.4)
Neurology, any event	13 (27.1)	17 (36.2)
Dizziness	3 (6.3)	10 (21.3)
Pain, any event	27 (56.3)	39 (83.0)
Pain, abdomen nos	14 (29.2)	18 (38.3)
Pain, back	7 (14.6)	14 (29.8)
Pulmonary/upper respiratory, any event	18 (37.5)	23 (48.9)
Cough	9 (18.8)	13 (27.7)
Dermatology/skin, any event	31 (64.6)	37 (78.7)
Alopecia	25 (52.1)	24 (51.1)
Rash/desquamation	8 (16.7)	18 (38.3)
Hand-foot skin reaction	2 (4.2)	14 (29.8)
Dry skin	4 (8.3)	10 (21.3)

The table gives NCI CTC V3 event categories ("any event") (in alphabetical order) and associated CTCAE terms (by frequency), as applicable to ≥20 subjects. The incidences include all CTC grades.

Abbreviations: GI – gastrointestinal, AST – aspartate aminotransferase (also known as SGOT), nos – not otherwise specified

Table 6: Incidence rates of serious adverse events by NCI CTC event category / term (Safety population)

Number (%) of subjects with event	Placebo + doxorubicin (N = 48)	Sorafenib + doxorubicin (N = 47)
Blood/bone marrow, any event	1 (2.1)	3 (6.4)
Neutrophils	0 (0.0)	2 (4.3)
Hemoglobin	1 (2.1)	1 (2.1)
Cardiac arrhythmia, any event	1 (2.1)	2 (4.3)
Supraventricular arrhythmia, atrial fibrillation	1 (2.1)	1 (2.1)
Supraventricular arrhythmia, sinus tachycardia	0 (0.0)	1 (2.1)
Cardiac general	1 (2.1)	2 (4.3)
Cardiac ischemia/infarction	0 (0.0)	2 (4.3)
Hypotension	1 (2.1)	0 (0.0)

Death, any event [a]	10 (20.8)	3 (6.4)
Death not associated with CTCAE term, disease progression nos	10 (20.8)	3 (6.4)
Constitutional symptoms, any event	1 (2.1)	1 (2.1)
Fever	1 (2.1)	0 (0.0)
Fatigue	0 (0.0)	1 (2.1)
Gastrointestinal, any event	5 (10.4)	4 (8.5)
Dehydration	2 (4.2)	2 (4.3)
Diarrhea	2 (4.2)	1 (2.1)
Vomiting	0 (0.0)	3 (6.4)
Mucositis (clinical exam), oral cavity	1 (2.1)	1 (2.1)
Nausea	0 (0.0)	2 (4.3)
Constipation	0 (0.0)	1 (2.1)
Ileus	0 (0.0)	1 (2.1)
Hemorrhage/bleeding, any event	0 (0.0)	2 (4.3)
Hemorrhage, GI, stomach	0 (0.0)	1 (2.1)
Hemorrhage, GI, upper GI nos	0 (0.0)	1 (2.1)
Hepatobiliary/pancreas, any event	1 (2.1)	1 (2.1)
Liver dysfunction	0 (0.0)	1 (2.1)
Hepatobiliary – other	1 (2.1)	0 (0.0)
Infection, any event	7 (14.6)	4 (8.5)
Febrile neutropenia	5 (10.4)	1 (2.1)
Infection with normal ANC, skin (cellulitis)	0 (0.0)	2 (4.3)
Infection (documented clinically), blood	0 (0.0)	1 (2.1)
Infection (documented clinically), kidney	0 (0.0)	1 (2.1)
Infection (documented clinically), lung (pneumonia)	1 (2.1)	0 (0.0)
Infection (documented clinically), skin (cellulites)	0 (0.0)	1 (2.1)
Infection with normal ANC, soft tissue nos	1 (2.1)	0 (0.0)
Metabolic/laboratory, any event	1 (2.1)	5 (10.6)
Hyperkalemia	0 (0.0)	2 (4.3)
Lipase	1 (2.1)	1 (2.1)
Bilirubin (hyperbilirubinemia)	0 (0.0)	1 (2.1)
Hypercalcemia	0 (0.0)	1 (2.1)
Neurology, any event	1 (2.1)	0 (0.0)
Neurology – other	1 (2.1)	0 (0.0)
Pain, any event	2 (4.2)	4 (8.5)
Pain, back	1 (2.1)	2 (4.3)
Pain, abdomen nos	1 (2.1)	2 (4.3)
Pain, chest/thorax nos	0 (0.0)	1 (2.1)
Pain, liver	0 (0.0)	1 (2.1)
Pulmonary/upper respiratory, any event	1 (2.1)	3 (6.4)
Dyspnea (shortness of breath)	1 (2.1)	2 (4.3)
Hiccoughs	0 (0.0)	1 (2.1)

Vascular, any event	1 (2.1)	2 (4.3)
Thrombosis/thrombus/embolism	1 (2.1)	1 (2.1)
Artery injury, visceral	0 (0.0)	1 (2.1)

[a] Outcome of event: death

The table gives NCI CTC V3 event categories ("any event") (in alphabetical order) and associated CTCAE terms (by frequency).

The incidences include all CTC grades.

Abbreviations: GI – gastrointestinal, nos – not otherwise specified, ANC – absolute neutrophil count

None of the subjects had clinically relevant deterioration of the left ventricular ejection fraction (LVEF). The deterioration of LVEF from cycle to cycle was from 0% to maximum of 19%, and there were no ECG findings which were possibly correlated to LVSD. None of these 9 subjects died due to cardiac events.

Subjects treated with sorafenib + doxorubicin were found to have an increased incidence of high blood pressure (8 subjects [17.0%] versus 2 subjects [4.2%] receiving placebo + doxorubicin) but in no case was this above Grade 2 severity.

Adverse events under the NCI-CTCAE category hemorrhage/bleeding were reported in 12 subjects (25.5%) in the sorafenib + doxorubicin and 5 subjects (10.4%) in the placebo + doxorubicin groups. Two of these (both in the sorafenib + doxorubicin group) were serious adverse events (Grade 3 and 4); in both subjects the underlying disease and concomitant medication (platelet aggregation inhibitor and vitamin K antagonist) indicated a higher predisposition for bleeding complications without any correlation to the study drug.

The overall incidence of neurological adverse events was low, and was equally common in both treatment groups. None were above Grade 2 in severity with sorafenib + doxorubicin and none were serious or resulted in discontinuation. The incidence of sensory neuropathy was only slightly higher with sorafenib + doxorubicin (3 subjects [6.3%] in the placebo + doxorubicin group and 4 subjects [14.9%] in the sorafenib + doxorubicin group).

Grade 3 or 4 biochemistry laboratory events occurring at a higher incidence (ie, in at least 3 more subjects) with sorafenib + doxorubicin treatment were elevated transaminases. Clinical pancreatitis was not reported in this study.

Hypophosphatemia was slightly less common with sorafenib + doxorubicin treatment, although a slight increase in lipase was observed in this treatment group.

Conclusion(s)

In conclusion, the results of this randomized, placebo-controlled, Phase 2 study #11546 demonstrate the combinability of sorafenib with doxorubicin in patients with HCC. The safety of the combination is predictable and manageable. The efficacy results for TTP, PFS and OS, albeit based on a limited number of events, do confirm the activity of sorafenib in HCC, a fact that has already been demonstrated with a clear survival benefit in the randomized monotherapy Phase 3 study #100554.

Study #11546, however, does not provide evidence of an increased efficacy of sorafenib in HCC through the addition of doxorubicin. The efficacy of the control arm with doxorubicin alone – when compared to historical controls as well as the study #100554 – appears negligible.

Publication(s)

Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol. 2006;24(26): 4293-4300. PMID:16908937

Abou-Alfa GK, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. JAMA. 2010 Nov 17;304(19):2154-60. PMID:21081728

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Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Nexavar
Brand/Trade Name(s) ex-US	Nexavar
Generic Name	Sorafenib
Main Product Company Code	BAY43-9006
Other Company Code(s)	BAY54-9085
Chemical Description	**(1)** 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-**(2)** 4-(4-{3.[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide
Other Product Aliases	Sorafenib tosylate

Date of last Update/Change: 28 Apr 2012