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ORIGINAL REPORT

Phase III Study of Carboplatin and Paclitaxel Alone or With Sorafenib in Advanced Non–Small-Cell Lung Cancer

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See accompanying editorial on page 1810

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ABSTRACT

Purpose
This phase III, multicenter, randomized, placebo-controlled trial assessed the efficacy and safety of sorafenib, an oral multikinase inhibitor, in combination with carboplatin and paclitaxel in chemotherapy-naïve patients with unresectable stage IIIB or IV non–small-cell lung cancer (NSCLC).

Patients and Methods
Nine hundred twenty-six patients were randomly assigned to receive up to six 21-day cycles of carboplatin area under the curve 6 and paclitaxel 200 mg/m^2 (CP) on day 1, followed by either sorafenib 400 mg twice a day (n = 464, arm A) or placebo (n = 462, arm B) on days 2 to 19. The maintenance phase after CP consisted of sorafenib 400 mg or placebo twice a day. The primary end point was overall survival (OS); secondary end points included progression-free survival and tumor response.

Results
Overall demographics were balanced between arms; 223 patients (24%) had squamous cell histology. On the basis of a planned interim analysis, median OS was 10.7 months in arm A and 10.6 months in arm B (hazard ratio [HR] = 1.15; 95% CI, 0.94 to 1.41; P = .915). The study was terminated after the interim analysis concluded that the study was highly unlikely to meet its primary end point. A prespecified exploratory analysis revealed that patients with squamous cell histology had greater mortality in arm A than in arm B (HR = 1.85; 95% CI, 1.22 to 2.81). Main grade 3 or 4 sorafenib-related toxicities included rash (8.4%), hand-foot skin reaction (7.8%), and diarrhea (3.5%).

Conclusion
No clinical benefit was observed from adding sorafenib to CP chemotherapy as first-line treatment for NSCLC.

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INTRODUCTION

Platinum-based chemotherapy doublets remain the backbone systemic treatment option for patients with advanced non–small-cell lung cancer (NSCLC; wet stage IIIB and stage IV).[1] However, evidence from several randomized clinical trials[2-5] and systematic reviews[6,7] shows that cytotoxic chemotherapy has reached an efficacy plateau. To improve the survival of patients with advanced NSCLC, molecularly targeted drugs have been added to cytotoxic chemotherapy regimens.[8] Recently, bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), significantly improved survival of patients with advanced nonsquamous NSCLC when added to carboplatin and paclitaxel (CP).[9] Therapies targeting a single molecular target have demonstrated efficacy in first-, second-, and third-line treatment of advanced NSCLC.[9-11] However, several molecular pathways are implicated in lung carcinogenesis, and agents that inhibit several signaling pathways may theoretically provide increased therapeutic benefit.

Sorafenib inhibits several tyrosine kinase receptors, including VEGF receptor (R) 2, VEGFR-3, platelet-derived growth factor receptor β, FLT-3, and c-KIT.[12,13] In addition, sorafenib is a potent serine/threonine kinase inhibitor of C-Raf and B-Raf, proteins downstream of several growth factor receptors. Sorafenib has shown activity in preclinical

models of NSCLC[12] and in several phase I[14-17] and II[18,19] studies in patients with advanced NSCLC and has been safely combined with cytotoxic agents (including CP) in patients with a variety of tumors.[16,20] In a phase I study, sorafenib plus CP showed promising clinical activity in 15 patients with NSCLC, with a 79% disease control rate (complete response [CR] plus partial response [PR] plus stable disease).[21] Another recent phase I study of sorafenib plus CP reported an overall response rate (CR + PR) of 58% (95% CI, 28% to 85%), with one CR and six PRs in 12 evaluable Japanese patients with advanced NSCLC.[22]

On the basis of this evidence, a multicenter, randomized, placebo-controlled, phase III trial in NSCLC—Evaluation of Sorafenib, Carboplatin, and Paclitaxel Efficacy (ESCAPE)—was conducted to assess the efficacy and safety of adding sorafenib to CP in patients with unresectable stage IIIB (wet) or stage IV NSCLC.

PATIENTS AND METHODS

Patient Population

Chemotherapy-naïve patients (age ≥ 18 years) with a histologic or cytologic diagnosis of clinical stage IIIB (limited to malignant pleural or pericardial effusion) or stage IV NSCLC were eligible for the trial. Additional inclusion criteria included life expectancy ≥ 12 weeks; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and adequate bone marrow, liver, and renal function. Patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 3)[23] grade ≥ 2 pulmonary hemorrhage/bleeding, CTCAE grade ≥ 3 other hemorrhage/bleeding, or CTCAE grade more than 2 serious infections within 4 weeks of the first dose of study drug were excluded from the trial. Patients diagnosed with active severe cardiac disease; relevant cardiac ventricular arrhythmias requiring antiarrhythmic therapy; uncontrolled hypertension; known brain metastases; HIV infection or chronic hepatitis B or C; thromboembolic events within the past 6 months; history of bleeding diathesis or coagulopathy; or a serious nonhealing wound, ulcer, or bone fracture were also excluded from the study.

Study Design

Patients who met eligibility criteria were randomly assigned to sorafenib plus CP (arm A) or placebo plus CP (arm B), with stratification factors including ECOG PS (0 *v* 1), geographic region (North America, Northern/Western Europe, and Australia *v* South America, Eastern Europe, and the Asia-Pacific region), histologic subtype (squamous *v* other histologies), and disease stage (IIIB with effusion *v* stage IV). Histologic/cytologic diagnosis was not centrally reviewed. All patients received paclitaxel (200 mg/m^2 intravenously over 2.5 to 4 hours) first and carboplatin (area under the curve = 6 intravenously over 15 to 60 minutes) immediately after on day 1 of a 21-day cycle during the chemotherapy phase. Because sorafenib can be safely combined with CP as long as sorafenib treatment is interrupted during CP administration,[16] patients received either sorafenib (400 mg orally twice a day) or matching placebo (oral placebo tablets twice a day) on days 2 through 19. In the case of tumor stabilization or response after six cycles of treatment, patients received maintenance treatment with sorafenib or placebo twice a day until progression or occurrence of intolerable toxicity.

Patients provided written consent before participation in the trial. All sponsors and investigators were required to abide by Good Clinical Practice,

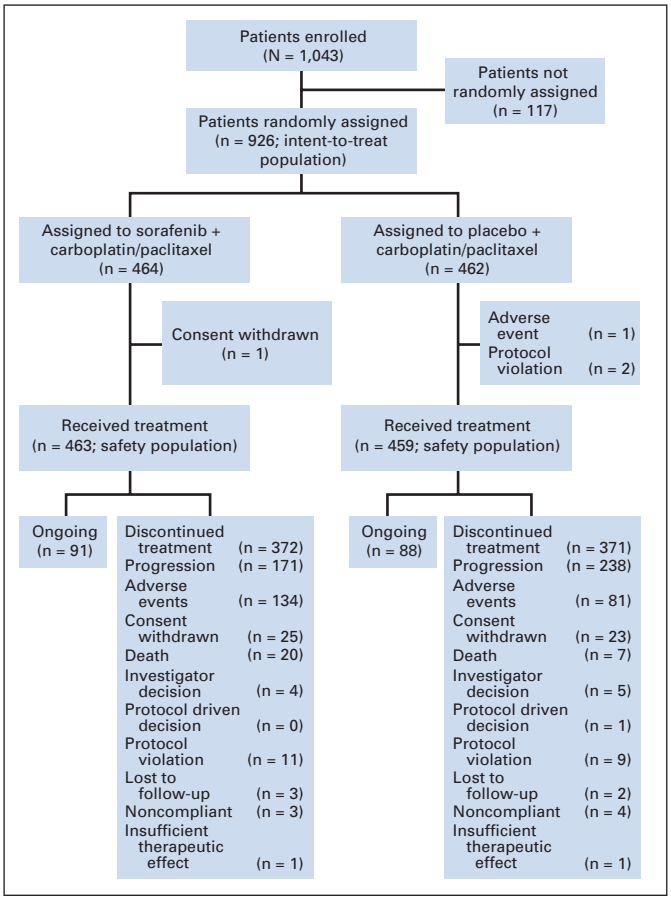

Fig 1. Summary of patient disposition.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Arm A: Sorafenib Plus CP (n = 464) No. of Patients	%	Arm B: CP Alone (n = 462) No. of Patients	%
Age, years				
Median	62.0		63.0	
Range	34-86		34-82	
≥ 65	185	40	196	42
Male	293	63	288	62
Race				
White	406	88	396	86
Black	18	4	13	3
Asian	21	5	21	5
Hispanic	11	2	21	5
Other	7	2	11	2
ECOG PS				
0	190	41	188	41
1	274	59	274	59
Past or present smoker	388	84	397	86
Stage at study entry				
IIIB	44	9	47	10
IV	420	91	415	90
Histology				
Adenocarcinoma	263	57	271	59
Large-cell carcinoma	23	5	30	6
Squamous cell carcinoma	109	23	114	25
Other*	69	15	47	10

Abbreviations: CP, carboplatin/paclitaxel; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Includes bronchoalveolar, undifferentiated, and neuroendocrine carcinoma and unspecified histology.

the Declaration of Helsinki principles, and local laws and regulations. The study was overseen by an ethics committee or institutional review board. An Independent Data Monitoring Committee (IDMC) provided a review of interim data to evaluate the ongoing safety and efficacy of the study.

Study End Points

The primary end point of the study was overall survival (OS), which was defined as the time from random assignment until death from any cause. Patients still alive at the time of analysis were censored at their last date of follow-up. Secondary end points included progression-free survival (PFS) and tumor response. PFS was defined as the time from random assignment until tumor progression (radiologic or clinical) or death. Patients without disease progression or alive at the time of analysis were censored at the last date of tumor evaluation. Tumor response and disease progression were assessed by an investigator review of computed tomography scans of the chest and abdomen performed at baseline, once every 6 weeks for the first 18 weeks of the study, and every 12 weeks thereafter. Best tumor responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST).[24] Safety was assessed based on the results of physical examinations, ECOG PS, vital signs, ECG data, weight, laboratory values, and adverse events (AEs) graded according to National Cancer Institute CTCAE (version 3)[23] up to 30 days after end of treatment.

Statistical Analysis

The study was designed to accrue approximately 900 patients to detect a clinically meaningful improvement in OS of 30% in patients with NSCLC treated with sorafenib plus CP (arm A) versus CP alone (arm B; hazard ratio [HR] = 0.769 for arm A over arm B). Assuming a one-sided overall $\alpha = .025$, 90% power, and a 1:1 random assignment ratio, with one planned interim analysis at approximately 307 events and one final analysis of OS, a total of 614 events (deaths) were required. For the primary efficacy analysis of OS, the two treatment arms were compared using a one-sided log-rank test with an overall $\alpha = .025$ stratified by ECOG PS, geographic region, histology, and disease stage. By the time data were available for the interim analysis (October 2007), 384 deaths had occurred, and all were included to determine the O'Brien-Fleming threshold for significance ($P = .0046$, one-sided). For the secondary efficacy analysis of PFS, the two treatment arms were compared in a similar way to the OS analyses. Preplanned prospective subgroup analyses of OS and PFS included age ($\geq$ *v* $<$ 65 years), disease stage (wet IIIB *v* IV), histologic subtype (squamous *v* other histologies), and smoking history (former/current *v* never smoker).

Safety analyses evaluated the rates of AEs, including relation to drug and seriousness, between treatment arms and were primarily descriptive in nature. All *P* values reported for AEs were computed using a two-sided, unadjusted Fisher's exact test and were used only to monitor for an adverse safety signal at a significance level of $P = .05$.

RESULTS

Patient Characteristics

A total of 1,043 patients were screened between February 2006 and May 2007 at 150 centers in 20 countries, 117 of whom did not meet the study criteria and 926 of whom were randomly assigned to treatment (n = 464 in arm A and n = 462 in arm B, defined as the intent-to-treat population; Fig 1). Of the 926 patients who were randomly assigned, 922 (n = 463 in arm A and n = 459 in arm B) received at least one dose of any one of the following treatments: carboplatin, paclitaxel, sorafenib, or placebo (safety population). Baseline demographic and disease characteristics of randomly assigned patients are listed in Table 1. The study included 223 patients (24%) with squamous cell histology.

Treatment

The median number of CP treatment cycles received was four (range, one to six cycles) in arm A and five (range, one to six cycles) in arm B. The median duration of treatment was 16.6 weeks (range, 0.1 to 69.9 weeks) in arm A and 17.9 weeks (range, 0.1 to 75.0 weeks) in arm B. Dose reductions and interruptions of sorafenib, paclitaxel, and carboplatin occurred at a higher rate in arm A than in arm B (Appendix Table A1, online only).

Efficacy

For the primary efficacy analysis, the median OS time in arm A was 10.7 months (95% CI, 9.1 to 13.9 months) compared with 10.6 months (95% CI, 9.6 to 12.0 months) in arm B, with an estimated HR of 1.15 (95% CI, 0.94 to 1.41; $P = .915$; Table 2, Fig 2). There was no statistically significant difference in OS between the two arms. On the basis of the monitoring guidelines for efficacy and futility at the interim analysis, the estimated HR crossed the prespecified futility

Table 2. OS and PFS

	Overall Population		Squamous Cell Histology		Other Histologies	
OS and PFS	Arm A: Sorafenib Plus CP (n = 464)	Arm B: CP Alone (n = 462)	Arm A: Sorafenib Plus CP (n = 109)	Arm B: CP Alone (n = 114)	Arm A: Sorafenib Plus CP (n = 355)	Arm B: CP Alone (n = 348)
OS						
Median, months	10.7	10.6	8.9	13.7	11.5	10.2
95% CI	9.1 to 13.9	9.6 to 12.0	6.3 to 13.9	9.6 to NE	9.7 to 14.8	9.1 to 11.5
Hazard ratio	1.15		1.85		0.98	
95% CI	0.94 to 1.41		1.22 to 2.81		0.78 to 1.23	
P	.915					
PFS						
Median, months	4.6	5.4	4.3	5.8	4.8	5.3
95% CI	4.3 to 5.3	4.4 to 5.8	3.7 to 5.8	4.2 to 6.4	4.3 to 5.8	4.3 to 5.7
Hazard ratio	0.99		1.31		0.91	
95% CI	0.84 to 1.16		0.94 to 1.83		0.76 to 1.09	
P	.433					

NOTE. Results based on the intent-to-treat population.
Abbreviations: OS, overall survival; PFS, progression-free survival; CP, carboplatin/paclitaxel; NE, not evaluable.

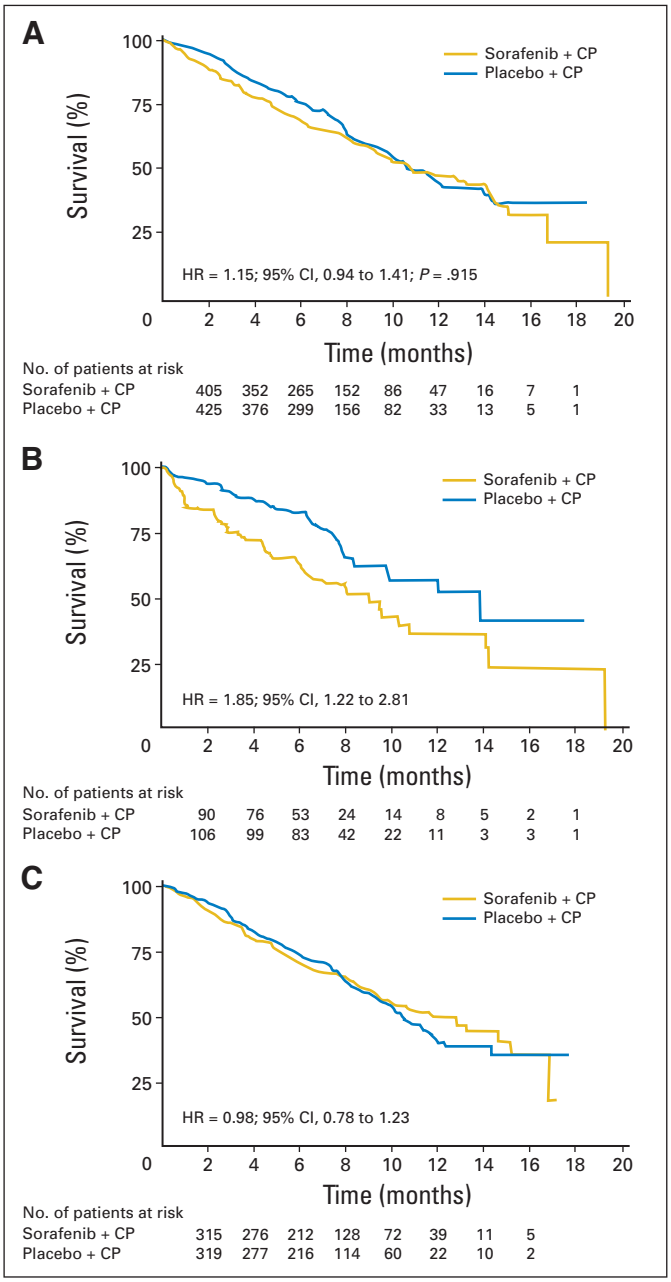

Fig 2. Kaplan-Meier overall survival curves for (A) overall patient population, (B) patients with squamous cell carcinoma, and (C) patients with other histologies. Analyses are based on the intent-to-treat population. CP, carboplatin/paclitaxel; HR, hazard ratio.

boundary, and the IDMC recommended early study termination. Furthermore, analysis of the secondary efficacy end point did not show a significant improvement in PFS in arm A compared with arm B. Patients in arm A had a median PFS of 4.6 months (95% CI, 4.3 to 5.3 months) compared with 5.4 months (95% CI, 4.4 to 5.8 months) in arm B (HR = 0.99; 95% CI, 0.84 to 1.16; $P = .433$). The overall response rate (CR + PR) by RECIST was 27.4% in arm A and 24.0% in arm B ($P = .1015$; Table 3). Clinical benefit as assessed by disease control rate (CR + PR + stable disease) was 50% and 56% in arms A and B, respectively.

Subgroup analyses of OS revealed that patients with squamous cell carcinoma in arm A had a shorter median OS (8.9 months; 95% CI, 6.3 to 13.9 months) than patients in arm B (13.6 months; 95% CI, 9.6 months to not estimable; HR = 1.85; 95% CI, 1.22 to 2.81; Fig 3). In subgroup analyses of PFS, the median PFS was lower in patients with squamous cell carcinoma in arm A (4.3 months; 95% CI, 3.7 to 5.8 months) than in arm B (5.8 months; 95% CI, 4.2 to 6.4 months; HR = 1.31; 95% CI, 0.94 to 1.83). However, patients with other histologies in arms A and B had comparable OS and PFS.

Safety

In arm A, 84% and 17% of patients reported drug-related AEs and drug-related serious AEs (SAEs), respectively (Table 4). In arm B, drug-related AEs and SAEs were reported by 68% and 9% of patients, respectively. Treatment discontinuation as a result of treatment-emergent and drug-related AEs occurred in 24% and 10% of patients, respectively, in arm A and in 17% and 5% of patients, respectively, in arm B. In general, AEs were manageable, only occasionally resulting in dose reductions, interruptions, or increased hospitalization. Drug-related grade ≥ 3 AEs were reported by 44% and 23% of patients in arms A and B, respectively ($P < .001$).

The rates of drug-related AEs and SAEs were comparable among histologies (Appendix Table A2, online only). In patients with squamous cell carcinoma, drug-related AEs and SAEs were reported in 77% and 14% of patients, respectively, in arm A and in 63% and 11% of patients, respectively, in arm B. Among patients with other histologies, drug-related AEs and SAEs were reported in 87% and 18% of patients, respectively, in arm A and in 70% and 8% of patients, respectively, in arm B.

The rate of drug-related hematologic AEs was similar in the two treatment arms, except for thrombocytopenia, which was significantly higher in arm A. Drug-related dermatologic AEs, including rash/desquamation, hand-foot skin reaction, and pruritus, occurred more frequently in patients in arm A (68%) than in patients in arm B (34%; $P < .001$), with a greater percentage of grade ≥ 3 events in arm A (18% *v* 2%, respectively; $P < .001$). Drug-related hypertension occurred in 12.5% of patients in arm A compared with 5.9% in arm B ($P < .001$), with grade ≥ 3 hypertension being reported more frequently in arm A (2.8% *v* 0.7%, respectively; $P = .02$). The rate of drug-related infections was higher in arm A (6.5%) than in arm B (2.2%; $P = .002$). Febrile neutropenia occurred in seven patients (1.5%) in arm A and two patients (0.4%; $P = .18$) in arm B. Three patients (0.6%) in arm A developed pneumonia, but none did in arm B ($P = .25$). Other important drug-related all-grade AEs in arm A versus B with less than 5% incidence included thrombosis/embolism (1.7% [1.5% were grade ≥ 3] *v* 1.1% [0.7% were grade ≥ 3], respectively; $P = .58$ for all-grade thrombosis/embolism) and dyspnea (1.9% [1.3% were grade ≥ 3] *v* 2.2% [none were grade ≥ 3], respectively; $P = .82$ for all-grade dyspnea). Drug-related cardiac ischemia was reported in one patient (0.2%) in each arm (grade 4 in arm A and grade 5 in arm B).

The rate of all drug-related hemorrhage/bleeding events was higher in arm A (10%) than in arm B (5%; $P = .004$). Ten patients (2.2%) in arm A and seven patients (1.5%) in arm B had pulmonary hemorrhage events that were considered drug related, of which five (1.1%) in each arm were grade ≥ 3. Overall, these events were comparable between treatment arms across patients with squamous cell carcinoma and patients with other histologies. Drug-related hemorrhage/bleeding events occurred in 12 patients (11%) with squamous

Table 3. Best Tumor Response

Response	Overall Population				Squamous Cell Histology				Other Histologies			
	Arm A: Sorafenib Plus CP (n = 464)		Arm B: CP Alone (n = 462)		Arm A: Sorafenib Plus CP (n = 109)		Arm B: CP Alone (n = 114)		Arm A: Sorafenib Plus CP (n = 355)		Arm B: CP Alone (n = 348)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Overall response rate*	127	27	111	24	27	25	40	35	100	28	71	20
Complete response	0	0	5	1	0	0	1	1	0	0	4	1
Partial response	127	27	106	23	27	25	39	34	100	28	67	19
Stable disease	213	46	221	48	49	45	43	38	164	46	178	51
Disease control rate†	231	50	260	56	46	42	68	60	185	52	192	55
Progressive disease	46	10	81	18	7	6	16	14	39	11	65	19
Not evaluated	78	17	49	11	26	24	15	13	52	15	34	10

NOTE. Results based on the intent-to-treat population.
Abbreviation: CP, carboplatin/paclitaxel.
*Complete response plus partial response.
†Disease control rate is defined as the proportion of patients who have a best response rating of complete response, partial response, or stable disease according to RECIST (Response Evaluation Criteria in Solid Tumors) that is maintained for at least 28 days from the first demonstration of that rating.

cell carcinoma and 35 patients (10%) with other histologies in arm A and in seven patients (6%) with squamous cell carcinoma and 16 patients (5%) with other histologies in arm B. Drug-related fatal hemorrhagic/bleeding events occurred in six patients (four patients in arm A and two patients in arm B). Four of these events (1.8%) were in patients with squamous cell carcinoma (two patients in arm A and two patients in arm B), and two (0.3%) were in patients with other histologies (one patient with adenocarcinoma and one patient with undifferentiated carcinoma; both in arm A). Overall, squamous cell histology was associated with a greater incidence of fatal bleeding events, irrespective of treatment allocation to arm A or B.

There were 136 deaths reported up to and within 30 days of the last dose of study drug as a result of an AE (mostly attributed to underlying disease); 86 deaths (19%) occurred in arm A, and 50 deaths (11%) occurred in arm B. Thirteen deaths (2.8%) in arm A and four deaths (0.9%) in arm B were considered to be drug related.

DISCUSSION

The addition of sorafenib to CP in chemotherapy-naïve patients with advanced NSCLC failed to show clinical benefit in this large, randomized, placebo-controlled trial. At the planned interim analysis, the IDMC recommended stopping the trial early because it was unlikely to meet the primary end point of improved OS in patients receiving sorafenib plus CP compared with CP alone. Efficacy results for OS, PFS, and best tumor response were similar across the two treatment

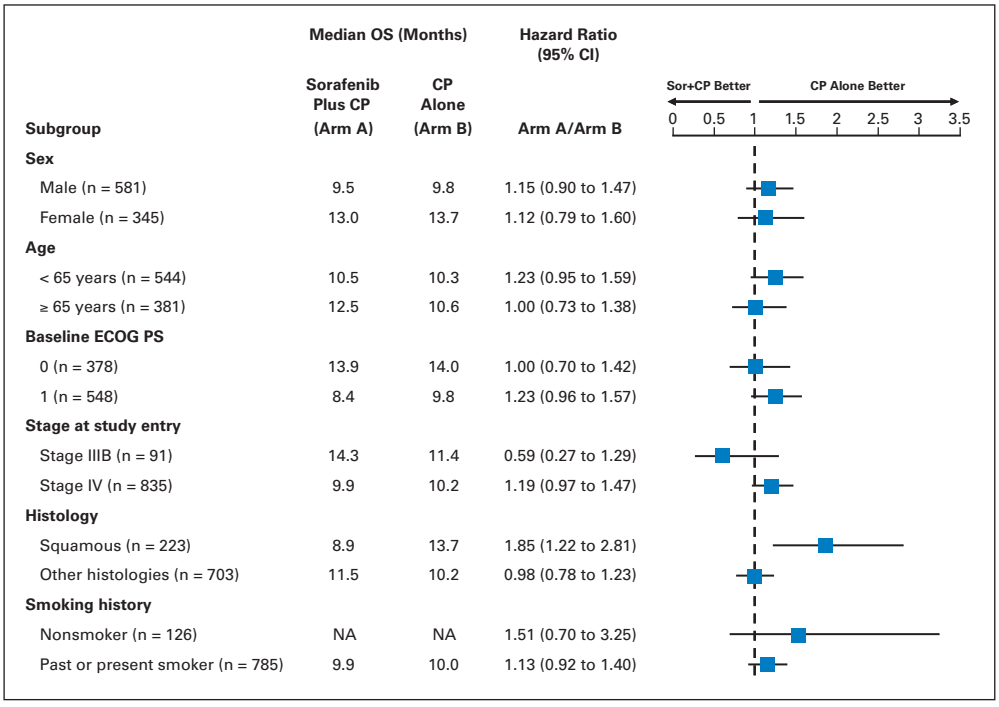

Fig 3. Overall survival (OS) by subgroups. Analyses are based on the intent-to-treat population. ECOG PS, Eastern Cooperative Oncology Group performance status; Sor, sorafenib; CP, carboplatin/paclitaxel; NA, not available/not assessable.

Table 4. Incidence Rates of Drug-Related AEs Occurring in ≥ 5% of Patients in Any Treatment Arm by Common Terminology Criteria for Adverse Events (version 3)

	Arm A: Sorafenib Plus CP (safety population, n = 436; squamous cell histology, n = 108; other histologies, n = 355)								Arm B: CP Alone (safety population, n = 459; squamous cell histology, n = 113; other histologies, n = 346)								
	All Grades		Grade 3		Grade 4		Grade 5*		All Grades		Grade 3		Grade 4		Grade 5†		
AE	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	P‡
Any drug-related AE	390	84	146	32	42	9	14	3	314	68	78	17	22	5	4	1	< .001
Squamous cell histology	83	77	28	26	10	9	3	3	71	63	20	18	5	4	2	2	.03
Other histologies	307	87	118	33	32	9	11	3	243	70	58	17	17	5	2	1	< .001
Any drug-related SAE	78	17	28	6	21	5	14	3	39	9	16	4	10	2	4	1	< .001
Squamous cell histology	15	14	6	6	5	5	3	3	12	11	6	5	1	1	2	2	.54
Other histologies	63	18	22	6	16	5	11	3	27	8	10	3	9	3	2	1	< .001
Hematologic																	
Neutropenia	42	9	21	5	17	4	0	0	32	7	14	3	13	3	0	0	.28
Thrombocytopenia	39	8	14	3	4	1	0	0	15	3	4	1	0	0	0	0	.001
Anemia	36	8	8	2	1	< 1	0	0	39	9	5	1	0	0	0	0	.72
Nonhematologic																	
Rash/desquamation	213	46	38	8	1	< 1	0	0	61	13	4	1	0	0	0	0	< .001
Diarrhea	129	28	16	4	0	0	0	0	59	13	8	2	1	< 1	0	0	< .001
HFSR	108	23	36	8	0	0	0	0	23	5	1	< 1	0	0	0	0	< .001
Fatigue	94	20	22	5	1	< 1	0	0	97	21	11	2	1	< 1	0	0	.81
Nausea	70	15	2	< 1	0	0	0	0	78	17	8	2	0	0	0	0	.47
Sensory neuropathy	66	14	12	3	0	0	0	0	61	13	8	2	0	0	0	0	.70
Hypertension	57	12	12	3	1	< 1	0	0	27	6	3	1	0	0	0	0	< .001
Pruritus	55	12	10	2	0	0	0	0	28	6	2	< 1	0	0	0	0	.003
Alopecia	49	11	0	0	0	0	0	0	56	12	0	0	0	0	0	0	.47
Anorexia	42	9	7	2	0	0	0	0	26	6	0	0	0	0	0	0	.06
Vomiting	40	9	1	< 1	0	0	0	0	34	7	7	2	0	0	0	0	.55
Oral mucositis	35	8	5	1	0	0	0	0	9	2	0	0	0	0	0	0	< .001
Dry skin	32	7	0	0	0	0	0	0	15	3	0	0	0	0	0	0	.02
Constipation	31	7	1	< 1	0	0	0	0	22	5	0	0	0	0	0	0	.26
Muscle pain	27	6	4	1	0	0	0	0	32	7	1	< 1	0	0	0	0	.50
Nose hemorrhage	24	5	1	< 1	0	0	0	0	10	2	0	0	0	0	0	0	.02

Abbreviations: CP, carboplatin/paclitaxel; AE, adverse event; SAE, serious adverse event; HFSR, hand-foot skin reaction.

*Grade 5 AEs in arm A included two lung hemorrhages and one case of pneumonitis in patients with squamous cell histology, one supraventricular tachycardia, one death not associated with a Common Terminology Criteria for Adverse Events term, disease progression not otherwise specified, one lung hemorrhage, one respiratory tract hemorrhage, one cerebral edema, one dyspnea, one respiratory insufficiency, two respiratory failures, one renal failure, and one pulmonary embolism in patients with other histologies.

†Grade 5 AEs in arm B included one lung hemorrhage and one bronchopulmonary hemorrhage in patients with squamous cell histology, one ventricular fibrillation, and one acute myocardial infarction in patients with other histologies.

‡*P* values for the comparison of AEs of all grades between the sorafenib plus CP arm (arm A) and the CP alone arm (arm B) were obtained using Fisher's exact test and used to monitor for adverse safety signals at a statistical significance level of $P = .05$.

arms. The incidence of drug-related AEs was higher in patients receiving sorafenib; however, with the exception of dermatologic AEs, hypertension, and diarrhea, most AEs were attributable to the underlying disease or cytotoxic chemotherapy. Dermatologic toxicities, such as hand-foot skin reaction, were generally manageable using dose modification and/or supportive treatment.[25]

Patients with squamous cell carcinoma receiving sorafenib plus CP had an increased risk of death and a decrease in PFS compared with patients receiving CP alone. The increased risk of death could not be attributed to an increase in AEs. Although the incidence of fatal bleeding events was greater in patients with squamous histology, there was no notable difference in the incidence of such events between treatment arms in this subgroup. Overall, these data suggest that squamous cell histology may be associated with a greater incidence of fatal bleeding events (including fatal pulmonary hemorrhage), irrespective of treatment. The median OS time with CP chemotherapy in patients with advanced NSCLC (including patients with squamous cell histology) has historically been 8 to 10 months.[2-5] The median OS time of 13.7 months seen in patients with squamous cell histology who received CP alone in this trial is much greater than expected for reasons that are not entirely clear.

Although an increased risk of fatal bleeding in patients with squamous cell carcinoma treated with bevacizumab[26] led to the exclusion of these patients from phase III studies testing its efficacy in combination with chemotherapy,[9,27] available data from phase I and II clinical trials of sorafenib in NSCLC did not suggest any increased risk of life-threatening bleeding events.[18,19] A recent phase III study investigating the multikinase inhibitor motesanib (AMG 706) plus CP versus CP alone in NSCLC reported a greater mortality rate in the motesanib plus CP arm, with an increased incidence of hemoptysis in

patients with squamous NSCLC.[28] In another recent phase III study, the combination of cisplatin plus pemetrexed was significantly less effective than cisplatin plus gemcitabine in patients with squamous cell NSCLC.[29]

The findings of the present study follow the challenging history of many molecularly targeted agents in combination with chemotherapy in NSCLC. Several molecular therapies, including erlotinib,[30-32] gefitinib,[33-35] cediranib (AZD2171),[36,37] lonafarnib (SCH66336),[38,39] and bexarotene[40,41] showed promising results in combination with chemotherapy in early drug development that could not be confirmed in subsequent randomized, placebo-controlled, phase III trials. In addition, bevacizumab failed to improve survival when administered in combination with gemcitabine and cisplatin in another phase III study (Avastin in Lung Cancer [AVAiL]).[27]

Several factors may contribute to negative results in randomized trials of targeted therapies in combination with chemotherapy in advanced NSCLC, including the choice of platinum-doublet regimen, the inclusion of patients with squamous cell carcinoma, or specific disease characteristics, such as specific biomarkers. The backbone CP chemotherapy used in this trial was recently evaluated with sorafenib in refractory advanced melanoma with disappointing results,[20] leading to speculation that sorafenib could alter the pharmacokinetics of CP, thereby impairing the efficacy of the combined regimen compared with CP alone. However, recent phase I trials of sorafenib plus CP have reported that coadministration of the three drugs had no impact on their respective pharmacokinetics.[16,22]

Unfortunately, there are no proven biomarkers for selecting patients with NSCLC who would benefit from antiangiogenic therapy, despite active research and a bounty of candidate markers. Indeed, there are conflicting reports about the utility of pretreatment VEGF levels as a predictive biomarker in patients with NSCLC treated with antiangiogenic therapy,[42-44] although data have suggested that bioavailable, rather than circulating, VEGF may provide the most predictive value.[45] In the Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) study, a novel biomarker-based approach is being assessed for selecting individualized targeted therapy for advanced NSCLC and identifying blood-based biomarkers as surrogates.

Despite the disappointing results reported here, there is evidence supporting the activity of sorafenib monotherapy in second- and late-line NSCLC from a single-arm, second-line, phase II study[18] and a randomized, placebo-controlled, third-line discontinuation phase II study.[19] Sorafenib monotherapy continues to be evaluated as a third- and fourth-line treatment in patients with advanced NSCLC in a large phase III study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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