Randomized Phase II Study of Carboplatin and Paclitaxel With Either Linifanib or Placebo for Advanced Nonsquamous Non–Small-Cell Lung Cancer

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A B S T R A C T

Purpose

Linifanib, a potent, selective inhibitor of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors, has single-agent activity in non–small-cell lung cancer (NSCLC). We evaluated linifanib with carboplatin and paclitaxel as first-line therapy of advanced nonsquamous NSCLC.

Patients and Methods

Patients with stage IIIB/IV nonsquamous NSCLC were randomly assigned to 3-week cycles of carboplatin (area under the curve 6) and paclitaxel (200 mg/m²) with daily placebo (arm A), linifanib 7.5 mg (arm B), or linifanib 12.5 mg (arm C). The primary end point was progression-free survival (PFS); secondary efficacy end points included overall survival (OS) and objective response rate.

Results

One hundred thirty-eight patients were randomly assigned (median age, 61 years; 57% men; 84% smokers). Median PFS times were 5.4 months (95% CI, 4.2 to 5.7 months) in arm A (n = 47), 8.3 months (95% CI, 4.2 to 10.8 months) in arm B (n = 44), and 7.3 months (95% CI, 4.6 to 10.8 months) in arm C (n = 47). Hazard ratios (HRs) for PFS were 0.51 for arm B versus A (*P* = .022) and 0.64 for arm C versus A (*P* = .118). Median OS times were 11.3, 11.4, and 13.0 months in arms A, B, and C, respectively. HRs for OS were 1.08 for arm B versus A (*P* = .779) and 0.88 for arm C versus A (*P* = .650). Both linifanib doses were associated with increased toxicity, including a higher incidence of adverse events known to be associated with VEGF/PDGF inhibition. Baseline plasma carcinoembryonic antigen/cytokeratin 19 fragments biomarker signature was associated with PFS improvement and a trend toward OS improvement with linifanib 12.5 mg.

Conclusion

Addition of linifanib to chemotherapy significantly improved PFS (arm B), with a modest trend for survival benefit (arm C) and increased toxicity reflective of known VEGF/PDGF inhibitory effects.

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INTRODUCTION

Platinum-based combination chemotherapy is associated with modest improvements in overall survival (OS) and quality of life for patients with advanced [non–small-cell lung cancer \(NSCLC\)](#).¹ Addition of the anti–vascular endothelial growth factor A (VEGF-A) monoclonal antibody bevacizumab to standard carboplatin-paclitaxel chemotherapy results in improved progression-free survival (PFS) and OS for patients with advanced NSCLC.² [Vascular endothelial growth factors \(VEGFs\)](#) are the key mediators of angiogenesis in NSCLC. VEGF-A is expressed by the vasculature of

most tumors, and its expression correlates with distant metastases and poor survival.³⁻⁶ [Platelet-derived growth factor \(PDGF\)](#) also plays an important role in tumor growth and has been associated with poor prognosis in patients with NSCLC.⁵ Linifanib (ABT-869) is an orally active, selective [receptor tyrosine kinase](#) inhibitor with half maximal inhibitory concentration values in the low nanomolar range for VEGF (FLT1, KDR, FLT4) and PDGF (PDGFR α and β , CSF-1R, KIT, FLT3) receptors.⁷ The breadth of its activity, potency, and selectivity against unrelated cellular kinases compares favorably with that of other small molecules targeting receptors of VEGF and PDGF.⁸ In preclinical

Fig 1. CONSORT diagram. DP, disease progression.

studies, linifanib potentiated carboplatin and paclitaxel activity in a number of tumor models, including NSCLC.^{8,9} Single-agent activity of linifanib in phase I and II clinical studies in patients with advanced NSCLC encouraged further evaluation of linifanib as a component of

therapy for these patients.^{10,11} In a multinational, open-label phase II trial, 139 patients with advanced NSCLC were randomly assigned to receive linifanib 0.1 or 0.25 mg/kg as second- or third-line therapy. Anticancer activity was observed, with a median PFS of 3.6 months

Table 1. Baseline Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Placebo (n = 47)		Linifanib 7.5 mg (n = 44)		Linifanib 12.5 mg (n = 47)		P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age, years							
Median	61.0		61.5		60.0		
Range	44 to 79		35 to 79		43 to 79		
< 65	30	63.8	31	70.5	34	72.3	.681
≥ 65	17	36.2	13	29.5	13	27.7	
Male	27	57.4	25	56.8	27	57.4	1.000
Race							.685
White	42	89.4	41	93.2	41	87.2	
Black	2	4.3	0	0	2	4.3	
Asian	2	4.3	3	6.8	2	4.3	
Other	1	2.1	0	0	2	4.3	
Country							.835
United States	13	27.7	13	29.5	11	23.4	
Outside of United States	34	72.3	31	70.5	36	76.6	
Smoker	39	83.0	39	88.6	38	80.9	.592
ECOG PS							.633
0	15	31.9	13	29.5	16	34.0	
1	32	68.1	31	70.5	31	66.0	
Histology							
Adenocarcinoma	42	89.4	40	95.2	40	85.1	
Large cell	0	0	2	5.3	3	6.4	
Other†	5	10.6	0	0	4	8.5	
Disease							.907
Locally advanced	4	8.5	2	4.8	2	4.3	
Metastatic	43	91.5	40	95.2‡	45	95.7	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

*P value for differences among treatment groups by Fisher's exact test.

†Other tumor types were classified as non-small-cell carcinoma (n = 3), bronchoalveolar carcinoma (n = 2), planocellular nonsquamous lung cancer (n = 2), squamous cell carcinoma (n = 1), and nonsquamous carcinoma (n = 1).

‡Two patients had missing data.

and OS of 9.0 months; objective response rate (ORR) and VEGF-related toxicities (eg, hypertension, proteinuria) seemed to be dose related.¹¹

On the basis of these observations, we conducted a randomized study to determine whether adding oral linifanib to carboplatin and paclitaxel can prolong PFS, compared with carboplatin and paclitaxel alone, in patients with NSCLC. Secondary objectives included evaluation of OS, 12-month survival rate, ORR, best percentage change in tumor size, and duration of response, as well as safety and tolerability of each treatment arm.

PATIENTS AND METHODS

Patient Population

Chemotherapy-naïve patients ≥ 18 years of age, with cytologically or histologically confirmed recurrent stage IIIB (pleural or pericardial effusion) or IV (metastatic) predominantly nonsquamous NSCLC not amenable to surgical resection or radiation with curative intent, were eligible. Other inclusion criteria were presence of measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 ; adequate bone marrow, renal, and liver function; and willingness to take adequate contraceptive mea-

sures. Patients were excluded if they received radiation therapy or major surgery ≤ 21 days before study entry, had untreated brain or meningeal metastases, were receiving a full therapeutic dose of anticoagulation therapy, or had a central thoracic tumor lesion as defined by location within the hilar structures; central nodal disease was allowed. Additional exclusion criteria included a history of significant cancer-related bleeding; proteinuria (grade > 1); uncontrolled hypertension; left ventricular ejection fraction less than 50%; history of myocardial infarction, stroke, or transient ischemic attack ≤ 6 months before study entry; antiretroviral therapy for HIV disease; another active malignancy within the past 5 years; severe GI disease that could interfere with drug absorption; or pregnancy or breastfeeding. The institutional review board at each participating institution approved the study protocol. The study was conducted following Good Clinical Practice guidelines, Declaration of Helsinki principles, and local laws and regulations. All patients provided written informed consent before participation. This trial is registered as NCT00716534 at <http://www.clinicaltrials.gov>.

Study Design and Assessments

This was a phase II, randomized, double-blind, placebo-controlled multicenter trial. An open-label lead-in cohort of patients ($n = 7$) established the tolerability of carboplatin (area under the plasma concentration-time curve [AUC] 6 mg/mL/min) and paclitaxel (200 mg/m²) administered intravenously on day 1 of an every-21-day cycle with once-daily linifanib 0.20 mg/kg

Fig 2. (A) Kaplan-Meier analysis of progression-free survival for all randomly assigned patients, based on 75 progression events. (B) Kaplan-Meier analysis of overall survival based on 90 survival events, performed with the 90th death event as the cutoff date.

starting on day 3 of cycle 1.¹² Eligible patients were randomly assigned to receive carboplatin and paclitaxel plus placebo, linifanib 7.5 mg, or linifanib 12.5 mg. Patients were stratified by ECOG PS and sex. Carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m²) were administered intravenously on day 1 of an every-21-day cycle, and linifanib (7.5 or 12.5 mg) or placebo was self-administered orally once daily on a continuous schedule. Carboplatin and paclitaxel were given to a maximum of six cycles or until criteria for discontinuation were met. Linifanib and placebo could be continued until disease progression, unacceptable toxicity, consent withdrawal, pregnancy, noncompliance, or investigator's decision to stop treatment.

Computed tomography scans of the chest and abdomen were performed for the investigator's assessment of tumor response by RECIST version 1.0¹³ at screening, after every two cycles, and at final visit. Safety was assessed throughout the study from day 1 to 30 days after the last dose of study drug. Severity of adverse events (AEs) was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. For AEs attributed to linifanib, treatment with linifanib could be interrupted for up to 21 days and/or its dose reduced by 2.5 mg; carboplatin and paclitaxel administration could continue as scheduled at the investigator's discretion. Carboplatin and paclitaxel were dose-reduced or delayed because of toxicity, according to the locally approved product label.

Biomarker Analysis

Patients were classified based on a biomarker signature profile of carcinoembryonic antigen (CEA) and soluble cytokeratin 19 fragments (CYFRA 21-1) identified in baseline plasma samples from 241 patients enrolled onto four prior randomized clinical trials of advanced lung cancer.^{11,14-16} Plasma samples collected before therapy were stored at ≤ -70°C until analyzed for quantitative assessment of CYFRA 21-1 and CEA and measured using ARCHITECT enzyme-linked immunosorbent assays (Abbott Diagnostics, Abbott Park, IL).

Statistical Analysis

A minimum of 75 PFS events was required to provide adequate precision in the hazard ratio (HR) estimate. Assuming a median PFS of 4.5 months in the placebo arm and 7.65 months in the linifanib arms, based on a total of 75 PFS events, the expected 95% CI for the estimated HR would be approximately 0.33 to 1.03. Each treatment group was compared separately with the placebo group. OS was analyzed using the date of the 90th survival event as the cutoff to better estimate the effect of adding linifanib to carboplatin-paclitaxel.

PFS was defined as the time from random assignment to radiographic or clinical progression or death. OS was defined as the time from random assignment to death or date last known alive. Distributions of PFS and OS were estimated using the Kaplan-Meier method. For both PFS and OS, pairwise comparisons between each linifanib dose group and the placebo group were assessed using the log-rank test stratified by baseline ECOG PS (0 v 1) and sex. Median times for PFS and OS and the corresponding 95% CIs were presented for each treatment group. In addition, Cox proportional hazards model, stratified by baseline ECOG and sex, was used to test for treatment effect. ORRs (proportion of patients with confirmed complete or partial response) were based on RECIST and compared between treatment arms using Fisher's exact test. Efficacy analyses were performed on the intent-to-treat population. The safety analyses included all patients who received at least one dose of linifanib or placebo.

RESULTS

Patient Characteristics

Between September 2009 and December 2010, 138 patients were randomly assigned to placebo (n = 47), linifanib 7.5 mg (n = 44), or linifanib 12.5 mg (n = 47) and defined as the intent-to-treat population. Among these patients, two in the 7.5-mg study arm did not receive at least one dose of linifanib and were excluded from safety and exposure analyses (Fig 1). Baseline characteristics (Table 1) were sim-

ilar among treatment arms with regard to age, sex, race, ECOG PS, smoking history, and extent of disease.

Treatment

Exposure to carboplatin and paclitaxel was similar among the three treatment arms; the median number of carboplatin and paclitaxel cycles was six (range, one to six cycles) for placebo and five (range, one to six cycles) for both the linifanib 7.5- and 12.5-mg study arms (Appendix Table A1, online only). Linifanib dose was reduced for 34% of patients in the 12.5-mg arm, compared with 14% in the 7.5-mg arm and 2% in the placebo arm, but dose-intensity of linifanib was more than 94% in both treatment arms (Appendix Table A1). Women in the linifanib arms received less chemotherapy (median, four cycles) than men in the linifanib arms. Women also received less linifanib than men in both the 7.5-mg (108 v 202 days, respectively) and 12.5-mg (97 v 147 days, respectively) arms.

Efficacy

Median PFS for the linifanib 7.5-mg arm was 252 days (95% CI, 127 to 328 days; 8.3 months; 95% CI, 4.2 to 10.8 months) compared with 164 days (95% CI, 127 to 174 days; 5.4 months; 95% CI, 4.2 to 5.7 months) for placebo (Fig 2). The HR (0.509; 95% CI, 0.283 to 0.917) stratified by PS and sex indicated a 49% decrease in risk of progression or death (P = .022; Table 2). In the linifanib 12.5-mg arm, median PFS

Table 2. Analysis of Secondary End Points

End Point*	Placebo (n = 47)	Linifanib 7.5 mg (n = 44)	Linifanib 12.5 mg (n = 47)
PFS			
Median, months	5.4	8.3	7.3
95% CI, months	4.2 to 5.7	4.2 to 10.8	4.6 to 10.8
HR†		0.509	0.640
P‡		.022	.118
OS			
Median, months	11.3	11.4	13.0
95% CI, months	8.8 to 17.0	6.6 to 14.8	8.3 to 18.9
HR†		1.075	0.888
P‡		.779	.650
12-Month survival rate, %	45	44	54
95% CI	30 to 58	29 to 59	40 to 68
ORR, %	25.5	43.2	31.9
95% CI	13.9 to 40.3	28.3 to 59.0	19.1 to 47.1
P§		.066	.500
Best % change in sum of target lesion sizes			
Median	-14.6	-37.2	-35.3
Range	-89.1-27.0	-100.0-6.7	-80.5-7.1
DOR, months			
Median	6.9	7.0	8.1
95% CI	3.0 to NR	5.6 to 9.6	6.8 to NR

Abbreviations: DOR, duration of response; ECOG Eastern Cooperative Oncology Group; HR, hazard ratio; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

*Analyses of PFS were performed with the 75th PFS event as the cutoff date. Analyses for OS and 12-month survival rate were performed with the 90th death event as the cutoff date.

†Stratified (by ECOG and sex), Cox proportional hazards model for comparison to placebo group.

‡Stratified (by ECOG and sex), log-rank test.

§Stratified (by ECOG and sex), Cochran-Mantel-Haenszel test.

Fig 3. (A) Forest plot of progression-free survival (PFS) by subgroup: 7.5 mg linifanib v placebo. (B) Forest plot of PFS by subgroup: 12.5 mg linifanib v placebo. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IVRS, interactive voice response system; US, United States.

was 221 days (95% CI, 140 to 330 days; 7.3 months; 95% CI, 4.6 to 10.8 months). Compared with patients receiving placebo, the HR (0.640; 95% CI, 0.366 to 1.190) stratified by PS and sex did not reach statistical significance ($P = .118$).

The risk for progression or death was reduced in most of the subgroup analyses for linifanib-treated patients compared with placebo-treated patients in both linifanib treatment arms (Fig 3). Interestingly, in the linifanib 7.5-mg arm, the HR for women was 0.932 (95% CI, 0.383 to 2.268), whereas for men, it was 0.340 (95% CI, 0.157 to 0.736). A similar difference between men and women was seen in the 12.5-mg arm. HR estimates for age, region, ECOG PS, and smoking history subgroups ranged from 0.468 to 0.632 and from 0.295 to 0.921 in the linifanib 7.5- and 12.5-mg arms, respectively.

Analyses of secondary end points are shown in Table 2. Objective responses were seen in 26% of patients receiving placebo, 43% receiving linifanib 7.5 mg, and 32% receiving linifanib 12.5 mg. Median best percentage changes in the sum of target lesion sizes were -15%, -37%, and -35% in the placebo, linifanib 7.5-mg, and linifanib 12.5-mg arms, respectively. Figure 4 shows the best percentage change from baseline in the sum of target lesions for each evaluable patient across study arms.

A modest improvement in OS was seen in the linifanib 12.5-mg arm; median survival durations were 343, 346, and 396 days (11.3, 11.4, and 13.0 months) in the placebo, linifanib 7.5-mg, and linifanib 12.5-mg arms, respectively (Fig 2B). Mean HR estimates for the subgroup analyses for differences in OS versus placebo ranged from 0.516

Fig 4. Waterfall plot showing the best percentage change from baseline in the sum of target lesions by treatment group.

to 1.346 for the linifanib 7.5-mg arm and from 0.523 to 1.921 for the linifanib 12.5-mg arm. The 12-month survival rate was also numerically greater in the linifanib 12.5-mg arm (54%) versus the placebo arm (45%; Table 2). More patients received second-line therapy in the placebo arm ($n = 26$) than in either the linifanib 7.5-mg ($n = 13$) or linifanib 12.5-mg ($n = 18$) arm.

Safety

Both doses of linifanib were associated with increased toxicity. Overall rates of severe and serious AEs were similar for linifanib 7.5 or 12.5 mg; however, some specific events characteristic of VEGF-directed therapy or combination chemotherapy were more common with the higher linifanib dose (Table 3). Common AEs ($\geq 10\%$) that were reported at a significantly higher rate ($P \geq .05$) in patients in either the linifanib 7.5- or 12.5-mg group compared with the placebo group were diarrhea, anemia, hypertension, dysphonia, decreased weight, and palmar-plantar erythrodysesthesia. Thrombocytopenia was the only grade 3 or 4 event that occurred with significantly greater frequency in linifanib-treated patients and was the most common reason for treatment interruption or dose reduction of carboplatin and paclitaxel. Thrombocytopenia, diarrhea, and palmar-plantar erythrodysesthesia were the most common reasons for interruption or reduction of linifanib. There were two AEs leading to death that were deemed possibly related to linifanib by the investigator (7.5 mg: respiratory failure, day 123 in a patient with brain metastases; 12.5 mg: neutropenic sepsis, day 144, in a patient with pneumonia, alternative etiology of chemotherapy-induced neutropenia).

Biomarkers

The CEA/CYFRA 21-1 biomarker signature of patients enrolled onto the trial was determined from the baseline plasma. In the linifanib treatment arms, a positive biomarker profile (CEA > 3 ng/mL; CYFRA 21-1 < 7 ng/mL) was associated with a significant improvement in PFS in both linifanib arms (7.5 mg: HR, 0.49; $P = .049$; 12.5 mg: HR, 0.38; $P = .029$) and a trend toward improved survival in the 12.5-mg arm (HR, 0.54; $P = .137$; Appendix Table A2, online only).

Table 3. Overall Safety and Adverse Events of Interest

Adverse Event	Treatment Group					
	Placebo (n = 47)		Linifanib 7.5 mg (n = 42)*		Linifanib 12.5 mg (n = 47)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Any adverse event	46	97.9	41	97.6	47	100
Any grade 3/4 adverse event	27	57.4	36†	85.7	34	72.3
Any serious adverse event	16	34.0	25†	59.5	25	53.2
Diarrhea						
Any grade	10	21.3	13	31.0	21†	44.7
Grade 3/4	1	2.1	1	2.4	4	8.5
Thrombocytopenia						
Any grade	7	14.9	13	31.0	19†	40.4
Grade 3/4	1	2.1	7†	16.7	14†	29.8
Anemia						
Any grade	9	19.1	17†	40.5	8	17.0
Grade 3/4	4	8.5	5	11.9	2	4.3
Hypertension						
Any grade	2	4.3	6	14.3	13†	27.7
Grade 3/4	1	2.1	2	4.8	5	10.6
Dysphonia						
Any grade	1	2.1	12†	28.6	7	14.9
Grade 3/4	0	0	0	0	1	2.1
Weight decrease						
Any grade	1	2.1	3	7.1	10†	21.3
Grade 3/4	0	0	1	2.4	1	2.1
PPE						
Any grade	0	0	3	7.1	8†	17.0
Grade 3/4	0	0	0	0	4	8.5
Hypothyroidism						
Any grade	0	0	3	7.1	5	10.6
Grade 3/4	0	0	0	0	0	0
Pneumothorax						
Any grade	0	0	4†	9.5	4	8.5
Grade 3/4	0	0	0	0	1	2.1
Oral candidiasis						
Any grade	0	0	4†	9.5	3	6.4
Grade 3/4	0	0	0	0	0	0

Abbreviation: PPE, palmar-plantar erythrodysesthesia.

*Two patients did not receive a dose of linifanib and were not included in the safety analysis.

†Fisher's exact test $P \leq .05$ for comparison with the placebo arm.

DISCUSSION

In the last decade, a number of targeted therapeutic strategies have been studied to improve the efficacy of chemotherapy in patients with advanced NSCLC. The only approach approved by the US Food and Drug Administration is the addition of bevacizumab, a VEGF-targeted monoclonal antibody, to chemotherapy for first-line therapy of patients with advanced nonsquamous NSCLC.

Since the demonstration of proof of concept with bevacizumab, several drugs that target the VEGF receptor have been evaluated in the first-line treatment of advanced NSCLC.¹⁷ Although activity has been

shown with these agents as monotherapy or in phase II studies in combination with chemotherapy, efficacy has not been established in phase III trials. A phase III study of sorafenib added to paclitaxel-carboplatin first-line chemotherapy showed no clinical benefit for patients with NSCLC.¹⁸ In another phase III trial, the addition of sorafenib to gemcitabine-cisplatin did not result in improvement of the primary end point of OS (HR, 0.98) but resulted in improvement in PFS (HR, 0.83) and time to progression (HR, 0.73).¹⁹ In a phase II/III trial, the addition of cediranib to paclitaxel and carboplatin improved response and PFS (HR, 0.77) but was associated with toxicity at a cediranib dose of 30 mg.²⁰ Decreasing the dose of cediranib to 20 mg with paclitaxel and carboplatin did not show PFS or OS benefit, and the study was terminated.²¹ Motesanib also failed to add any significant benefit to first-line therapy with paclitaxel and carboplatin in a phase III study based on the primary end point of OS (HR, 0.90).²² Further development of this class of agents has been seriously limited by the lack of predictive biomarkers.

Linifanib, with single-agent activity in patients with advanced NSCLC, demonstrated enhanced efficacy in combination with carboplatin and paclitaxel in the preclinical setting. These observations formed the basis for the current randomized phase II study with a major focus on identification of predictive biomarkers. A potentially predictive baseline signature combining established plasma tumor markers (CEA and CYFRA 21-1) was identified (McKeegan et al, manuscript in preparation). Increased levels of circulating CEA have been associated with brain metastases and poor survival in patients with advanced lung adenocarcinomas.²³ Increased circulating levels of CYFRA 21-1 have been associated with reduced survival in patients with squamous cell lung cancers.²⁴ An index based on levels of these markers has been reported to have prognostic value for patients with early-stage NSCLC.²⁵ In the previously reported study of linifanib in second- or third-line treatment of NSCLC, this biomarker signature was associated with OS improvement over linifanib monotherapy but no improvement in OS over other treatments.¹⁶ This biomarker signature was tested in this study and was found to be associated with significant PFS improvement with linifanib and a trend toward significant OS improvement at high dose, thus providing a potential new direction for further development of linifanib and other agents of this class.

Other key strengths of this study are that it was double-blinded and placebo-controlled. Linifanib was tolerated well, and the majority of toxicities were grade 1 or 2 in severity. There was a clinically significant 2- to 3-month improvement in PFS for the linifanib arms, which was statistically significant for the low-dose arm. There was a nonsignificant trend toward OS improvement for patients in the high-dose linifanib arm, although the study was not powered to detect a survival benefit. It may be important, in this regard, that more patients received second-line therapy in the placebo arm than in either linifanib arm. The carboplatin and paclitaxel exposures were similar across the three study arms. Therefore, the linifanib benefit was achieved without compromising exposure to carboplatin and paclitaxel.

AEs seemed to be dose-related, in particular, diarrhea, thrombocytopenia, hypertension, weight decrease, palmar-plantar erythrodysesthesia, and hypothyroidism. There was also a higher rate of grade 3 or 4 thrombocytopenia on the high-dose linifanib arm. Thrombocytopenia was the most common reason for dose interruption or reduction of linifanib, carboplatin, and paclitaxel. Compared with other VEGF receptor inhibitors in phase III studies with paclitaxel and

carboplatin, linifanib was associated with a higher rate of thrombocytopenia; comparable rates of diarrhea, hypertension, and skin toxicity; and less sensory neuropathy.^{18,20-22}

The reason for differential efficacy in PFS favoring men over women in this study is not apparent and may be a result of the limited study size, given that this sex difference was not seen in the OS analyses.²⁶ Similar sex differences have been seen in other trials combining angiogenesis inhibition with chemotherapy in lung cancer but not as consistent observations. In the bevacizumab pivotal trial, differential efficacy favoring men occurred for OS (HR, 0.70 v 0.98 for women)² but not for PFS (HR, 0.64 v 0.71 for women).²⁷ In the phase III trials of paclitaxel and carboplatin with sorafenib¹⁸ or motesanib,²² HRs for OS were similar for men and women. Sex differences may occur by chance or may be related to unmeasured prognostic factors. In this study, the finding that women had less exposure to both chemotherapy and linifanib than did men may have been contributing factors.

In summary, this study demonstrated the efficacy and manageable toxicity of adding linifanib to standard platinum-based chemotherapy in advanced nonsquamous NSCLC. In addition, the study identified a potential predictive biomarker signature that may allow better patient selection for these therapies. Although additional studies of linifanib in NSCLC are not currently planned, further evaluation of linifanib in patients with the identified biomarker signature is warranted. These findings are also of potential significance for other antiangiogenic agents presently under development for NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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GLOSSARY TERMS

non–small-cell lung cancer (NSCLC): a type of lung cancer that includes squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.

PDGF (platelet-derived growth factor): a family of proteins that exists in the A, B, C, or D forms. PDGF is involved in proliferation pathways, especially of mesenchymal cell types. PDGF forms homodimers (eg, AA, BB, CC, DD) or heterodimers (eg, AB), which interact with appropriate cellular receptors.

predictive biomarkers: measurements associated with response to or lack of response to a particular therapy.

receptor tyrosine kinase: transmembrane protein with intrinsic ability to transfer phosphate groups to tyrosine residues contained in cellular substrates. See *tyrosine kinase receptors*.

vascular endothelial growth factor receptor (VEGFR): transmembrane tyrosine kinase receptors to which the VEGF ligand binds. VEGFR-1 (also called FLT1) and VEGFR-2 (also called KDR/FLK1 [murine homologue]) are expressed on endothelial cells, whereas VEGFR-3 (also called FLT4) is expressed on cells of the lymphatic and vascular endothelium. VEGFR-2 is thought to be principally responsible for angiogenesis and for the proliferation of endothelial cells. Typically, most VEGFRs have seven extracellular immunoglobulin-like domains, responsible for VEGF binding, and an intracellular tyrosine kinase domain. See *VEGF (vascular endothelial growth factor)*.

vascular endothelial growth factor (VEGF): a cytokine that mediates numerous functions of endothelial cells including proliferation, migration, invasion, survival, and permeability. VEGF is also known as vascular permeability factor. VEGF naturally occurs as a glycoprotein and is critical for angiogenesis. Many tumors overexpress VEGF, which correlates with poor prognosis. VEGF-A, -B, -C, -D, and -E are members of the larger family of VEGF-related proteins.

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Appendix

Table A1. Study Drug Exposure			
Drug Exposure Factor	Placebo (n = 47)	Linifanib 7.5 mg (n = 42)*	Linifanib 12.5 mg (n = 47)
Treatment duration, days			
Median	159.0	153.0	126.0
Range	2.0-465.0	6.0-525.0	6.0-503.0
Dose-intensity, %			
Median	100.0	99.5	94.9
Range	63.4-119.5	60.3-104.6	51.9-100.0
Dose modifications			
No. of patients	35	23	22
%	74.5	54.8	46.8
Any dose interruption			
No. of patients	12	19	25
%	25.5	45.2	53.2
Any dose reduction			
No. of patients	1	6	16
%	2.1	14.3	34.0
Paclitaxel			
No. of cycles			
Median	6.0	5.0	5.0
Range	1.0-6.0	1.0-6.0	1.0-6.0
Six cycles			
No. of patients	28	19	20
%	59.6	45.2	43.5
Carboplatin			
No. of cycles			
Median	6.0	5.0	5.0
Range	1.0-6.0	1.0-6.0	1.0-6.0
Six cycles			
No. of patients	29	19	20
%	61.7	45.2	42.6

*Two patients did not receive a dose of linifanib and were not included in the exposure or safety analyses.

Table A2. Outcome of Patients With a Positive Baseline Biomarker Signature			
Outcome	Placebo (n = 19)	Linifanib 7.5 mg (n = 24)	Linifanib 12.5 mg (n = 26)
PFS			
Median, months	5.4	10.2	8.3
95% CI, months	1.5 to 6.9	3.9 to NR	4.8 to NR
HR*		0.49	0.38
P†		.049	.029
OS			
Median, months	11.3	12.5	17.4
95% CI, months	9.2 to 17.4	6.2 to NR	12.9 to NR
HR*		1.02	0.54
P†		.758	.137

Abbreviations: HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

*Adjusted for Eastern Cooperative Oncology Group performance status and sex.

†Stratified log-rank test; P value compared with placebo.