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ORIGINAL REPORT

Phase II Study of Cisplatin Plus Etoposide and Bevacizumab for Previously Untreated, Extensive-Stage Small-Cell Lung Cancer: Eastern Cooperative Oncology Group Study E3501

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ABSTRACT

Purpose
To investigate the efficacy and safety of bevacizumab plus cisplatin and etoposide in patients with extensive-stage disease, small-cell lung cancer (ED-SCLC).

Patients and Methods
In this phase II trial, 63 patients were treated with bevacizumab 15 mg/kg plus cisplatin 60 mg/m^2 and etoposide 120 mg/m^2, which was followed by bevacizumab alone until death or disease progression occurred. The primary end point was the proportion of patients alive at 6 months without disease progression (ie, progression-free survival [PFS]). Secondary end points included overall survival (OS), objective response rate, and toxicity. Correlative studies were performed to explore the relationship between baseline and changes in plasma vascular endothelial growth factor (VEGF), soluble cell adhesion molecules (ie, vascular cell adhesion molecule [VCAM], intercellular cell adhesion molecule [ICAM], and E-selectin) and basic fibroblast growth factor and outcome.

Results
The 6-month PFS was 30.2%, the median PFS was 4.7 months, and OS was 10.9 months. The response rate was 63.5%. The most common adverse event was neutropenia (57.8%). Only one patient had grade 3 pulmonary hemorrhage. Patients who had high baseline VCAM had a higher risk of progression or death compared with those who had low baseline VCAM levels. No relationships between outcome and any other biomarkers were seen.

Conclusion
The addition of bevacizumab to cisplatin and etoposide in patients with ED-SCLC results in improved PFS and OS relative to historical controls who received this chemotherapy regimen without bevacizumab. This regimen appears to be well tolerated and has minimal increase in toxicities compared with chemotherapy alone. Baseline VCAM levels predicted survival, but no other relationships among treatment, biomarkers, and outcome were identified.

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INTRODUCTION

Small-cell lung cancer (SCLC) is a highly aggressive disease that accounts for 12% to 15% of the 213,380 new occurrences of lung cancer anticipated in the United states in 2008.[1] Patients are categorized as having limited-stage disease, defined as disease that is confined to the ipsilateral hemithorax that can be encompassed within a tolerable radiation port, or extensive-stage disease (ED), defined as the presence of overt metastatic disease by imaging or physical examination.[2] Two thirds of patients are diagnosed with ED at presentation.[3] Despite the development of novel cytotoxic drugs and so-called targeted therapies, the therapeutic approach to SCLC has been stagnant for more than 2 decades. Standard treatment for ED-SCLC remains cisplatin and etoposide (PE), a regimen that yields a median survival of approximately 9 months and a 5-year survival of less than 1%.[4-6]

Angiogenesis is a fundamental event in tumor growth and metastatic discrimination. Vascular endothelial growth factor (VEGF) is a key regulator of angiogenesis. The VEGF/VEGF-receptor axis is composed of multiple ligands and receptors with overlapping and distinct ligand-receptor binding specificities, cell-type expression, and function. The well-established role of VEGF in the pathogenesis of human cancers has led to the development of agents that selectively target this pathway. Bevacizumab is a

humanized, monoclonal antibody against VEGF. The addition of bevacizumab to standard chemotherapy with paclitaxel and carboplatin in patients with advanced non-squamous, non–small-cell lung cancer (NSCLC) in Eastern Cooperative Oncology Group (ECOG) study ECOG 4599 resulted in a significant increase in overall survival (OS) compared with chemotherapy alone.[7] Elevated VEGF expression is associated with a poor prognosis in SCLC.[8] On the basis of this knowledge, ECOG initiated a phase II trial in which bevacizumab was combined with PE in patients with ED-SCLC. The primary end point was PFS at 6 months. Secondary end points included OS, objective response rate, and toxicity.

Correlative studies were performed to explore the relationship between baseline and changes in plasma VEGF, soluble cell adhesion molecules (ie, vascular cell adhesion molecule [VCAM], intercellular cell adhesion molecule [ICAM], and E-selectin) and basic fibroblast growth factor (bFGF) and outcome in this cohort of patients. The rationale for selection of these molecules was based on their roles in angiogenesis and metastases. The serum or plasma concentrations of soluble ICAM, VCAM, and E-selectin in patients with a variety of malignancies are associated with disease progression or prognosis.[9-11] The primary target of bevacizumab is the endothelial cell; therefore, we hypothesized that damage and/or apoptosis of vascular endothelial cells would be associated with release of endothelial cell specific markers into plasma (ie, ICAM, VCAM, and E-Selectin).

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically or cytologically confirmed ED-SCLC were eligible. Additional eligibility requirements included age 18 years or older; measurable disease as defined by RECIST (Response Evaluation Criteria in Solid Tumors); an ECOG performance status (PS) of 0 to 2; neutrophil count $\geq$ 1,500 μL; platelets $\geq$ 100,000 μL; international normalized ratio, bilirubin, and creatinine $\leq$ 1.5 mg/dL; and proteinuria by dipstick or urinalysis $\leq$ 1+ or 24-hour urine for protein $\leq$ 1 g. Exclusion criteria included prior chemotherapy, immunotherapy, or biologic therapy for lung cancer; nonhealing wound, ulcer, or bone fracture, or major surgical procedure within 28 days of treatment; or minor surgery or needle biopsies within 7 days of treatment. Patients with symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmias, significant peripheral arterial disease, thrombotic or hemorrhagic disorders, recent (within 6 months) arterial thromboembolic events, a history of gross hemoptysis ($\geq$ one-half teaspoon bright red blood), active secondary malignancies, CNS metastases, active infection, or psychiatric illness that would have affected compliance were excluded, as were pregnant or breastfeeding women. Recent or current use of oral and/or parenteral anticoagulants, aspirin ($>$ 325 mg/d), nonsteroidal anti-inflammatory agents, dipyramidole, ticlopidine, clopidogrel, or cilostazol was not allowed. Patients with a history of hypertension had to be well controlled (BP $\leq$ 150/85) on a stable regimen. Prior radiation therapy was permitted, but additional sites of evaluable disease were required. Written informed consent was required. This study was approved by the institutional review boards of all participating centers and was conducted in accordance with the United States Food and Drug Administration Good Clinical Practice Requirements.

Study Design

Eligible patients were treated with cisplatin 60 mg/m^2 intravenously (IV) over 30 to 60 minutes on day 1, which was followed by etoposide 120 mg/m^2 IV over 60 minutes on days 1 through 3 every 3 weeks for up to four cycles. Bevacizumab 15 mg/kg was administered over 90 minutes by IV infusion after completion of chemotherapy. If the first infusion was tolerated, subsequent infusions were shortened to 30 to 60 minutes. Chemotherapy dose reductions were permitted for febrile neutropenia, thrombocytopenic bleeding, creatinine greater than 2.0 and less than 3.0 mg/dL with creatinine clearance greater than 60 mL/min, and cisplatin-related neurotoxicity. Bevacizumab was administered regardless of delays in administration of chemotherapy. Bevacizumab administration was delayed for proteinuria greater than 200 mg/24 hours, BP greater than 150/110 or symptomatic BP elevation, platelets less than 75,000 μL, grade 1 nonpulmonary hemorrhage, grades 3 or 4 hepatic toxicity (ie, AST $>$ 5$\times$ the upper limit of normal [ULN] or bilirubin $>$ 3$\times$ the ULN). Bevacizumab dose was based on the patient's weight at screening; if this weight changed by more than 10%, the dose was recalculated. After planned chemotherapy, patients who did not experience progression were allowed to continue on bevacizumab at the same dose and schedule for a total of 1 year. All patients received standard supportive care, as appropriate. Patients were observed for survival information every 3 months for 3 years.

Study Parameters

Baseline evaluations included physical exam, assessment of ECOG PS, standard hematology, chemistry, electrolytes, urinalysis, and international normalized ratio/activated partial thromboplastin time. These were repeated before each cycle of chemotherapy and at each follow-up visit thereafter. A pretreatment pregnancy test was performed in women of childbearing potential. Baseline tumor assessments, with prospective identification of sentinel lesions to be observed during the course of the study, included computed tomography scans of head, chest, and abdomen as well as bone scans when clinically indicated. Tumor status was assessed after cycles 2 and 4 and then every two cycles for patients receiving bevacizumab alone and every 3 months for patients off study treatment according to standard ECOG tumor response criteria. Responses were independently determined by the treating physician and an independent review facility.

Laboratory Correlates

Plasma samples were collected from patients before cycle 1 and after completion of cycle 2 (before cycle 3; termed hereafter as week-7 samples). Pretreatment samples were analyzed for levels of ICAM, VCAM, E-Selectin, bFGF, and VEGF by using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis MN). Some factors were measured at week 7. A total of 3 mL of peripheral blood was drawn into a citrated Vacutainer tube and was mixed immediately by inverting the tube 10 to 15 times. Samples then were centrifuged within 30 minutes of collection for 10 minutes at 4°C at 3000 $\times$ *g*. Plasma was removed and was transferred to cryogenic storage tubes. Samples were stored immediately at $-$70°C. They were shipped on dry ice to University Hospitals Case Medical Center (Cleveland, OH) for analysis. Samples were run in duplicate, and the average was recorded. The lower limits of detection for VCAM, ICAM, E-selectin, VEGF, and bFGF were 0.6 ng/mL, 0.35 ng/mL, 0.1 ng/mL, 6.4 pg/mL, and 1.0 pg/mL, respectively.

Statistical Considerations

The primary end point of this study was the proportion of patients alive at 6 months without disease progression (ie, progression-free survival [PFS]). On the basis of the median PFS time of the observation arm of ECOG 7593,[12] this study was designed to have 93% power and a type I error rate of 8% to detect an improvement in the median PFS from 2.3 to 3.8 months, which translates to an improvement in the 6-month PFS from 16% to 33%. This study employed a two-stage design; in the first stage, 27 patients were accrued, and it was assumed that 25 of them would be eligible. If 20% of patients were alive and free from progression at 6 months, the treatment would be considered promising, and the study would continue with stage 2. If at least 14 patients (23%) among the 60 eligible patients were alive and free from progression at 6 months, this treatment would be considered sufficiently promising to be considered for additional evaluation, potentially within the context of a phase III trial. Efficacy analyses were based on an intent-to-treat analysis. Secondary end points were best objective response, OS, and toxicity. This study was continuously monitored for life-threatening or fatal hemoptysis. PFS was defined as the interval in months from the date of registration on the study to the date of documented disease progression or death without progression. Patients without documented progression or death reported were censored at the time of the last documented disease evaluation. OS was defined as the time in months from date of registration to the date of death as a result of

any cause, and patients who were alive at the time of analysis were censored at their last follow-up dates.

Inference on the 6-month PFS rate was made by calculating the *P* value and the 95% CI for this proportion, which was conditional on the stopping criteria for the modified two-stage design. Specifically, the method of Atkinson and Brown[13] was used to calculate the 95% CI. It was assumed that the outcomes were ordered on the basis of the number of responses observed, so an exact binomial calculation of observing a result as, or more extreme than, what was observed was used to calculate the *P* value. The Kaplan-Meier[14] curves were used to estimate event-time distributions and medians, and the Greenwood formula[15] was used to estimate the standard errors (SEs) of the estimates. Fisher's exact test was used to test for associations between categoric variables. Log-rank tests were used to test for differences in event-time distributions, and Cox proportional hazards models were fitted to obtain estimates of hazard ratios (HRs) in univariate and multivariate models. All *P* values are two sided, and CIs were at the 95% level. No adjustments were made for multiple comparisons.

The primary objective of the correlative studies was to determine if pretreatment levels of VEGF predict response to therapy. Patients were divided into two groups on the basis of pretreatment VEGF level by using the median value as cutoff and by assuming a 25% overall response (ie, complete response and partial response) for patients with VEGF levels greater than the median. A Fisher's exact test with a one-sided, 2.5% type I error rate would have 80% power to detect a 40% increase in response. This study had 80% power to detect a difference in median PFS from 3.0 months in the high-VEGF group to 6.6 months in the low-VEGF group, with a one-sided, 2.5%-level, log-rank test. Other objectives related to changes in the levels of markers (ie, VCAM, E-selectin, bFGF) between pretreatment and week 7 evaluations included response, PFS, and OS. The analyses done were similar to those listed earlier in this section. HRs reflect results that used the low-level group as the reference group.

RESULTS

From June 2004 to August 2006, 65 patients were enrolled. Two patients were excluded from analysis; one had questionable pathology, and one never started therapy. Table 1 lists the baseline characteristics of eligible patients. The median age of patients was 65 years (range, 45 to 83 years). Men accounted for 42.9% of patients; 9.5% had an ECOG PS of 2. The median number of cycles administered was six (range, one to 18).

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Patients (N = 63) No.	%
Age, years		
Median	65	
Range	45-83	
Sex		
Male	27	42.9
Female	36	57.1
Ethnicity		
White	60	95.2
Nonwhite	3	4.8
Performance status		
0	20	31.8
1	37	58.7
2	6	9.5
Weight loss in previous 6 months, %		
< 5	41	66.1
5 to < 10	14	22.6
10 to < 20	5	8.1
≥ 20	2	3.2
Unknown	1	

Efficacy Results

The median follow-up at the time of analysis was 27.5 months. After the planned suspension, 10 patients were alive and free from progression at 6 months among the 31 patients accrued, and the study was reopened to accrual. Nineteen patients (30%) were alive and free from progression at 6 months among all 63 eligible patients. The median PFS was 4.7 months (95% CI, 4.3 to 5.5 months), and the 6-month PFS was 30.2% (95% exact CI adjusted for the modified design, 18.8% to 41.5%; $P = .004$; Fig 1A). The median OS was 10.9 months (95% CI, 7.9 to 12.2 months; Fig 1B), and the 1-year OS was 38.1% (95% CI, 26% to 50.1%). The overall response rate was 63.5%; one patient had a complete response, and 39 patients had partial responses. An additional 10 patients (15.9%) had stable disease (Table 2). There was no difference in PFS between men and women (5.0 months *v* 4.6 months, respectively; $P = .96$). The PFS was 4.7 months for white patients, compared with 2.4 months for nonwhite patients ($P = .17$). Among PS, weight loss in previous 6 months, sex, and presence of pleural effusion at baseline, the only predictor of PFS or OS was PS. Patients who had a PS greater than 0 had an increased risk of progression or death compared with patients who had a PS of 0 (PFS: HR, 2.09; 95% CI, 1.17 to 3.70; OS: HR, 1.96; 95% CI, 1.09 to 3.50).

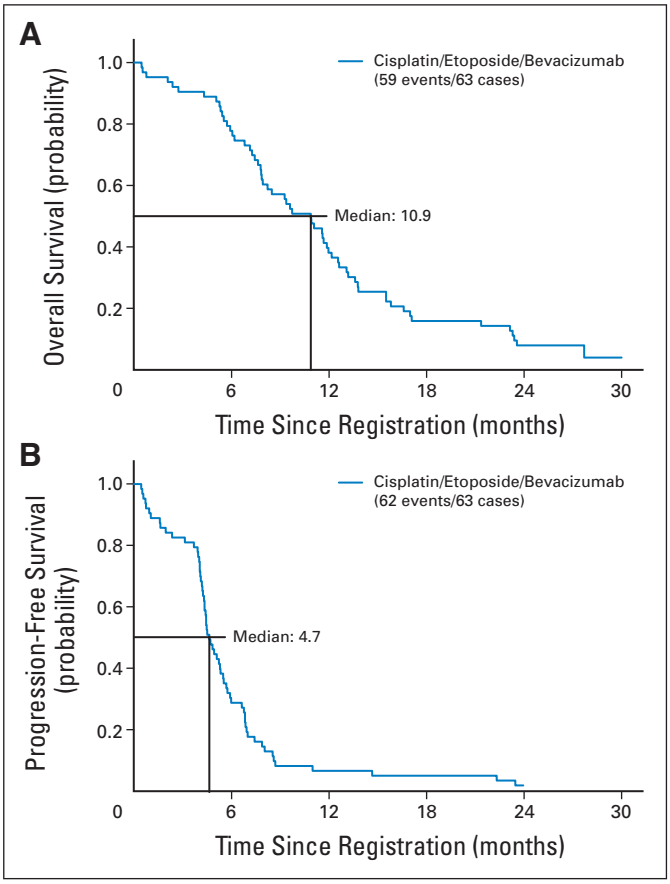

Fig 1. (A) Overall survival and (B) progression-free survival for cisplatin, etoposide, and bevacizumab.

Table 2. Best Objective Response Summary

Response	Patients (N = 63) No.	%
Complete	1	1.6
Partial	39	61.9
No change/stable disease	10	15.9
Progressive disease	8	12.7
Unevaluable	5	7.9

Safety and Toxicity

Toxicity data for 64 patients are presented in Table 3. Sixteen patients (25%) experienced a grade 3 adverse event (AE), and 31 patients (48.4%) experienced a grade 4 AE. The most common hematologic AEs were leukopenia, neutropenia, and thrombocytopenia. Febrile neutropenia occurred in five patients (7.8%). The most common nonhematologic AEs were fatigue and weakness. AEs thought to be related to the addition of bevacizumab included grade 3 hypertension in five patients (7.8%), epistaxis in six patients (9.4%), grade 3 pulmonary hemorrhage in one patient, and grade 3 abdominal hemorrhage in one patient. Thirteen patients (20.3%) experienced grades 1 or 2 hemorrhage, the majority of which were due to epistaxis. There were two possible grade 4, bevacizumab-associated AEs: one patient with cardiac ischemia, and another with thromboembolism. Two patients died as a result of an AE; one death was the result of multiorgan failure, and another death was the result of a lung infection with grades 3 to 4 neutropenia.

Table 3. Toxicity

Toxicity	% of Patients by Toxicity Grade Grade 3	Grade 4
Hematologic		
Anemia	3.1	1.6
Leukocytes	20.3	9.4
Lymphopenia	0	1.6
Neutropenia	12.5	45.3
Thrombocytopenia	9.4	4.7
Febrile neutropenia	4.7	3.1
Nonhematologic		
Sinus bradycardia	1.6	0
Hypotension	0	1.6
LV diastolic dysfunction	1.6	0
Fatigue/weakness	14.1	0
Anorexia	1.6	0
Dehydration	4.7	0
Diarrhea	6.3	0
Mucositis	1.6	0
Nausea/vomiting	6.3	0
Infection	1.6	0
Hypocalcemia	1.6	1.6
Hyponatremia	9.4	1.6
Hypokalemia	1.6	0
Ataxia/walking	3.1	0
Dizziness	1.6	0
Dyspnea	0	1.6
Musculoskeletal	7.8	0
Bevacizumab associated		
Hypertension	7.8	0
Cardiac ischemia	0	1.6
Pulmonary hemorrhage	1.6	0
Abdominal hemorrhage	1.6	0
Epistaxis	9.4	0
Thrombosis/embolism	0	1.6

NOTE. Total number of patients = 64. Two grade 5 toxicities occurred: one patient experienced multiorgan failure, and one patient experienced lung infection and grade 3 to 4 neutropenia.
Abbreviation: LV, left ventricle.

Correlative Studies

Thirty-two patients had their baseline samples submitted for inclusion in the correlative study, of which 31 were analyzable. Nineteen (61.3%) of these 31 patients submitted a second sample at week 7. Baseline VEGF levels did not correlate with response to chemotherapy ($P = .43$). No association between response rate and any biomarker level was seen. Patients who had high baseline VCAM levels had a higher risk of progression (HR, 2.11; 95% CI, 0.99 to 4.49; $P = .05$) and death (HR, 2.69; 95% CI, 1.22 to 5.92; $P = .01$; Table 4) compared with those who had low levels. Patients with high bFGF showed a trend toward higher risk of death (HR, 2.06; 95% CI, 0.96 to 4.42; $P = .06$); patients with low ICAM levels also showed this trend (HR, 0.48; 95% CI, 0.22 to 1.02; $P = .06$). Baseline VCAM, ICAM, and bFGF levels were statistically significant ($P < .05$) in multivariate COX models after analysis was adjusted for sex, PS, and weight loss. No significant associations were found between outcome and change in levels from baseline.

DISCUSSION

This phase II study was designed to evaluate the safety and efficacy of bevacizumab in combination with PE in patients with ED-SCLC. Our data suggest that the addition of bevacizumab to PE results in improved PFS and OS compared with patients treated with PE alone on other clinical studies.[4-6] Two other trials have combined bevacizumab with chemotherapy in patients with ED-SCLC. CALGB (Cancer and Leukemia Group B) 30306 enrolled 72 patients from the same population and employed bevacizumab (15 mg/kg on day 1), cisplatin (30 mg/m^2 on days 1 and 8), and irinotecan (85 mg/m^2 on days 1 and 8) every 21 days for up to six cycles. Grades 3 to 4 toxicities were similar to those observed in our study, except that there was a higher incidence of nausea/vomiting, diarrhea, and dehydration in the CALGB study. One patient died as a result of CNS hemorrhage secondary to a stroke. The authors reported a higher response rate and PFS of 75% and 7.1 months, respectively, and an OS of 11.7 months.[16] They, too, found no relationship between plasma VEGF levels and response rate, OS, or PFS.[16] A second trial of 23 (of 50 planned) patients with ED-SCLC combined carboplatin (AUC 4 on day 1), irinotecan (60 mg/m^2 on days 1, 8, and 15), and bevacizumab (10 mg/kg every 2 weeks) and reported a 78% response rate. Survival data are pending.[17]

In non–small-cell lung cancer, patients with squamous cell histology were at increased risk of bleeding.[18] As squamous cell carcinoma is usually a centrally located tumor, it has been postulated that

Table 4. Correlative Markers With HR Comparing Baseline High to Low Levels

Marker	Marker Level					Statistical Analysis			
	Baseline		Week 7			PFS		OS	
	Median	Range	Median	Range	% Change From Baseline	HR	*P*	HR	*P*
VEGF, pg/mL	52	−6.4-161.0	610	261-844	525.7	0.95	.9	1.65	.19
VCAM, ng/mL	626	313-1,559	740	567-2,076	152	2.11	.05	2.69	.01
E-selectin, ng/mL	32	11-107	21	15-68	−6.6	0.91	.79	0.88	.75
bFGF, pg/mL	5.01	1.65-27.5	13.7	4.2-127	4.63	1.48	.28	2.06	.06
ICAM, ng/mL	291	143-471	279	149-552	−28	0.75	.44	0.48	.06

Abbreviations: HR, hazard ratio; PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor; VCAM, vascular cell adhesion molecule; bFGF, basic fibroblast growth factor; ICAM, intercellular cell adhesion molecule.

the hemoptysis was related to the location of the tumor. However, Sandler et al[19] found that tumor location was not a risk factor for bleeding. In our study, the incidence of pulmonary hemorrhage was 4.6%, and SCLC histology did not appear to be a risk factor for hemorrhage after treatment with bevacizumab. The incidence of grades 3 to 4 neutropenia of 57.8% was higher than seen in prior studies of patients with SCLC treated with chemotherapy with[16] or without bevacizumab[4-6] or in bevacizumab-treated patients in ECOG 4599.[7] However the incidence of febrile neutropenia was less than 10% and was similar to CALGB 30306.[16]

Similar to the two prior studies that combined bevacizumab in patients with NSCLC[7,11] and colorectal cancer,[20] there was no correlation between baseline VEGF levels and survival in patients treated on this study. In this study, the median baseline VEGF level was higher compared with that seen in NSCLC.[7] Similar to a prior study by Shin et al[21] we found patients who had high ICAM levels had a nonsignificant trend towards improved OS compared with patients who had low levels. This is in contrast to ECOG 4599, which found that, regardless of therapy, patients with low ICAM levels had a significantly better survival.[7,11] This difference most likely reflects the biology of the disease. In addition, baseline ICAM levels in this study were higher than those in ECOG 4599, which indicates a potentially higher angiogenic load in these patients, as soluble ICAM levels have been shown to be reflective of the ICAM expression on endothelial cells.[22] This is the first study to report an inverse correlation between baseline VCAM and survival in SCLC. A previous group showed little staining when using the immunohistochemistry methodology for VCAM in endothelial cells of SCLC specimens.[23] Although patients with increased levels of baseline VCAM had higher risks of death and progression, we could not tell whether this was a prognostic or predictive marker, because this was a single-arm study.

Although cross-study comparisons are difficult to make, our data suggest that the addition of bevacizumab to PE in patients with ED-SCLC results in a similar response rate and improved PFS and OS relative to this chemotherapy regimen without bevacizumab.[4-6] This regimen appears well tolerated, as it had minimal increase in toxicities compared with chemotherapy alone. To additionally investigate this regimen, an industry-sponsored, randomized, phase II trial of platinum-based chemotherapy with or without bevacizumab is currently is underway.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(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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