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ORIGINAL REPORT

Southwest Oncology Group S0802: A Randomized, Phase II Trial of Weekly Topotecan With and Without Ziv-Aflibercept in Patients With Platinum-Treated Small-Cell Lung Cancer

Jeffrey W. Allen, James Moon, Mary Redman, Shirish M. Gadgeel, Karen Kelly, Philip C. Mack, Hanna M. Saba, Mohamed K. Mohamed, Mohammad Jahanzeb, and David R. Gandara

Jeffrey W. Allen, University of Tennessee Health Science Center, Memphis, TN; James Moon, Mary Redman, Southwest Oncology Group Statistical Center, Seattle, WA; Shirish M. Gadgeel, Karmanos Cancer Institute, Wayne State University, Detroit, MI; Karen Kelly, Phillip C. Mack, David R. Gandara, University of California Davis Cancer Center, Sacramento, CA; Hanna M. Saba, Central Illinois CCOP/Cancer Care Specialists of Central Illinois, Effingham, IL; Mohamed K. Mohamed, Moses Cone Health System, Greensboro, NC; and Mohammad Jahanzeb, University of Miami, Miami, FL.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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Corresponding author: Jeffrey Allen, MD, 2504 Harrison St, Suite C, Eureka, CA 95501; e-mail: Jeffrey.allen@stjoe.org.

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ABSTRACT

Purpose
Development of new therapies for previously treated small-cell lung cancer (SCLC) is a major unmet need. Here, we describe a randomized, phase II trial of weekly topotecan with or without ziv-aflibercept (VEGF-trap) in this clinical setting.

Patients and Methods
Patients with previously treated SCLC (one line of platinum-based chemotherapy), performance status of 0 to 1, adequate organ function, treated brain metastases, and no recent vascular events or bleeding diatheses were eligible. Eligible patients were stratified as platinum-sensitive or platinum-refractory and randomly assigned to receive weekly topotecan 4 mg/m^2 intravenously (IV) with or without ziv-aflibercept 6 mg/kg IV every 21 days. Progression-free survival (PFS) at 3 months was the primary end point.

Results
In 189 randomly assigned patients, treatment arms were well balanced with regard to clinical characteristics. The 3-month PFS was significantly improved with the addition of ziv-aflibercept in patients who had platinum-refractory disease (27% *v* 10%; $P = .02$) but not in patients with platinum-sensitive disease (24% *v* 15%; $P = .22$). Although response rate was low, disease control rate was higher with combination therapy than with topotecan alone in patients who had platinum-sensitive disease (37% *v* 18%; $P = .05$) and in those who had platinum-refractory disease (25% *v* 15%; $P = .14$). Overall survival (OS) was not significantly improved in either strata. Grades 3 to 5 toxicities were more common with the addition of ziv-aflibercept.

Conclusion
Ziv-aflibercept improved the 3-month PFS in patients who had platinum-refractory SCLC, but its addition increased toxicity. OS was similar with combined ziv-aflibercept and topotecan compared with topotecan in both strata.

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INTRODUCTION

Although the incidence of small-cell lung cancer (SCLC) is decreasing in the United States, perhaps because of the changing smoking patterns, there have been no significant changes in its outcome in more than 3 decades.[1] The majority of patients with SCLC present with extensive stage disease and are treated palliatively with platinum-based chemotherapy. Although response rates (RRs) are high with first-line chemotherapy, relapse is nearly universal, and response to second-line chemotherapy is limited and partially dependent on the duration of unmaintained remission after first-line platinum-based therapy. Patients who have a durable response to first-line chemotherapy have historically fared much better than those patients who either do not respond (ie, refractory disease) or those who have only a transient response (< 60 to 90 days).[2] Topotecan, a camptothecin analog, is the only US Food and Drug Administration–approved agent for second-line therapy of SCLC, but activity is limited primarily to the platinum-sensitive population, and topotecan produces significant myelosuppression when given in its standard schedule (ie, daily for five days).[3-5] Weekly topotecan is an alternative dosing schedule that is associated with less toxicity and similar disease control rates (DCRs).[6,7] Many additional drugs have utility in the second-line setting and are included in guidelines (eg, paclitaxel,[8,9] docetaxel,[10] irinotecan,[11] temozolomide,[12] gemcitabine,[13,14] vinorelbine,[15] and ifosfamide[16]), but their therapeutic

contributions are modest at best. There clearly is a need to identify novel therapies that are effective in this setting.

The vascular endothelial growth factor (VEGF) family of cytokines are glycoproteins that modulate growth, differentiation, vascular permeability, and lymph node development through interaction with cellular receptors, chiefly the vascular endothelial growth factor receptor (VEGFR) family.[17-19] In SCLC, a high level of circulating VEGF is associated with poor survival and a lower likelihood of response to treatment.[20,21] Ziv-aflibercept (VEGF-trap) is a novel human fusion protein composed of high-affinity binding domains from the extracellular domain of VEGFR1 and VEGFR2 fused to the Fc fragment of human immunoglobulin G1. Ziv-aflibercept binds circulating VEGF-A, VEGF-B, and placental growth factor (all ligands for VEGFR) with high affinity, essentially removing these ligands from the circulation.[22] In preclinical models, ziv-aflibercept has shown activity in a variety of malignancies. Ziv-aflibercept has been approved by the US Food and Drug Administration (as Zaltrap, sanofi-aventis, Paris, France; Regeneron, Tarrytown, NY) in combination with irinotecan, fluorouracil, and folinic acid (FOLFIRI) for the treatment of adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.[23]

We sought to evaluate the efficacy of topotecan with or without ziv-aflibercept in patients who had relapsed or refractory extensive stage SCLC after one line of platinum-based chemotherapy (ClinicalTrials.gov Identifier: NCT00828139). On the basis of prior Southwest Oncology Group (SWOG) trials in this setting, we chose 3-month progression-free survival (PFS) as the primary end point and hypothesized that the addition of ziv-aflibercept to topotecan would result in improvement from 20% to 40%. We also sought to evaluate the overall survival (OS), RR, disease control rate (DCR), and the toxicity and safety of the ziv-aflibercept and topotecan combination. Patients were stratified as either platinum sensitive or refractory.

PATIENTS AND METHODS

Patient Population

Patients were required to have histologically or cytologically confirmed SCLC with documented progression after one line of platinum-based chemotherapy. They were stratified according to response and treatment-free interval as either platinum sensitive (ie, complete response or partial response and $>$ 90 day treatment-free interval for extensive stage or $\geq$ 180 days for limited stage) or platinum refractory (ie, no response and/or treatment-free interval $\leq$ 90 days for extensive stage and $<$ 180 days for limited stage), as described previously.[24]

Patients were required to have a neutrophil count $\geq$ 1,500/μL, a platelet count $\geq$ 100,000/μL, adequate renal function (ie, serum creatinine $\leq$ 1.5 times the institutional upper limit of normal or a measured creatinine clearance $\geq$ 60 mL/min). Patients were excluded if they had recent vascular events (ie, myocardial infarction, cerebrovascular accident, transient ischemic attacks, uncontrolled hypertension, or worsening angina within the previous 6 months). Those who had bleeding diatheses, including hemoptysis (ie, $>$ 0.5 teaspoon within the previous 3 months), gastrointestinal bleeding, or peptic ulcer disease within 3 months before study entry were similarly excluded. Patients on chronic anticoagulation were eligible, as were patients with brain metastases, provided the metastases were treated and stable for more than 3 months before study entry. CNS imaging was required before study entry.

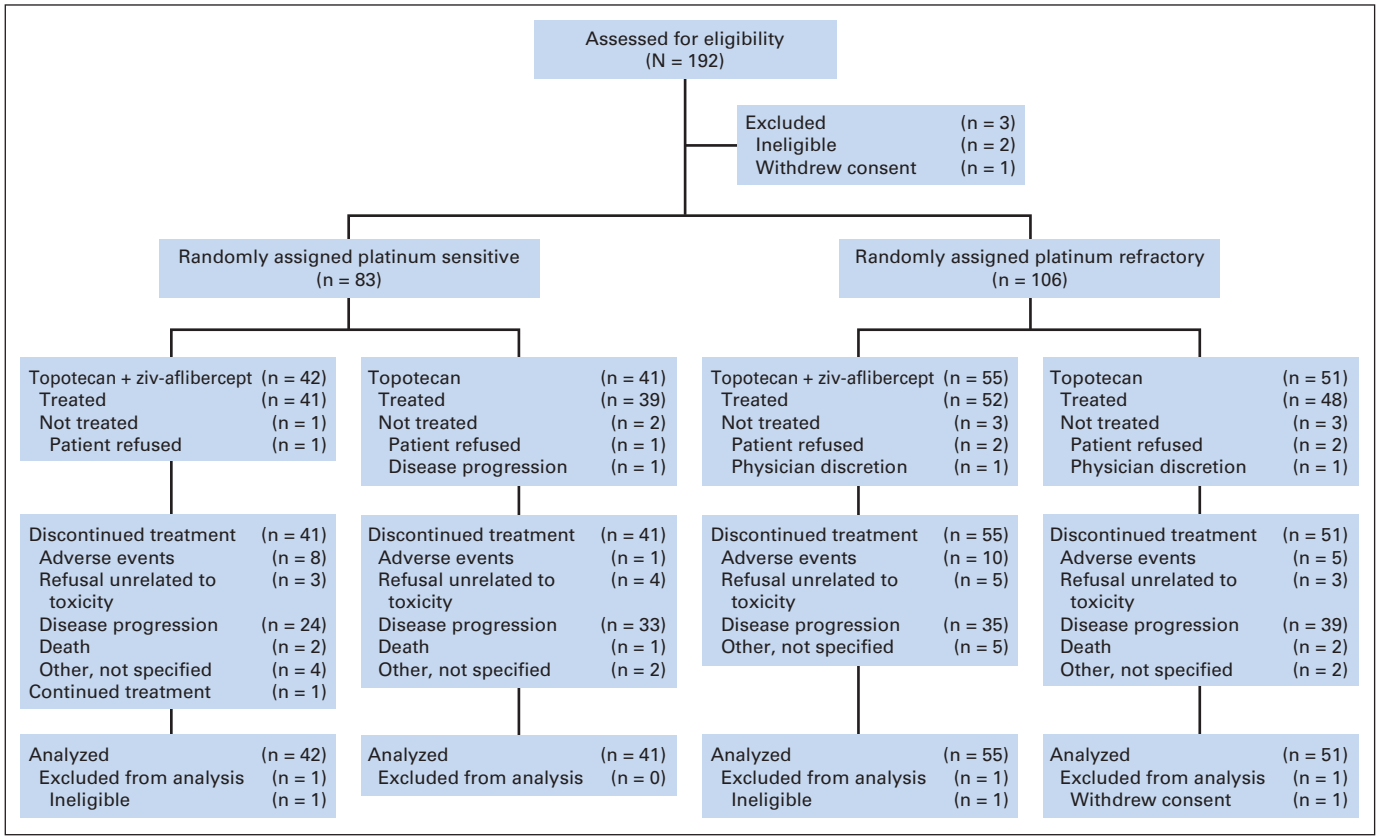

Fig 1. CONSORT diagram.

Table 1. Baseline Characteristics

Characteristic	Treatment Strata							
	Platinum Sensitive (n = 83)				Platinum Refractory (n = 106)			
	Arm A: Ziv-Aflibercept + Topotecan (n = 42)		Arm B: Topotecan (n = 41)		Arm A: Ziv-Aflibercept + Topotecan (n = 55)		Arm B: Topotecan (n = 51)	
	No.	%	No.	%	No.	%	No.	%
Median age, years	63.4		60.1		60.9		63.6	
Sex								
M	17	40	13	32	26	47	34	67
F	25	60	28	68	29	53	17	33
Ethnicity								
White	36	86	40	98	49	89	43	84
Black	4	10	1	2	3	5	4	8
Pacific Islander	1	2	0	0	0	0	0	0
Asian	0	0	0	0	0	0	1	2
Native American	0	0	0	0	2	4	1	2
Unknown/other	1	2	0	0	1	2	2	4
Metastatic disease site								
Single lesion, single organ	4	10	9	22	4	7	4	8
Multiple lesions, single organ	11	26	9	22	9	16	11	22
Multiple lesions, multiple organs	25	60	22	54	41	75	34	67
None	2	5	1	2	1	2	2	4
Performance status								
0	14	33	17	41	12	22	19	37
1	28	67	24	59	43	78	32	63
Stage								
Extensive	27	64	23	56	39	71	42	82
Limited	15	36	18	44	16	29	9	18

National Cancer Institute Common Terminology Criteria for Adverse Events, version 3, was used for toxicity reporting. All patients provided a signed informed consent in accordance with institutional and federal guidelines.

Treatment Regimens

Patients were randomly assigned in a 1:1 fashion after stratification to receive topotecan 4 mg/m^2 intravenously (IV) over 30 minutes on days 1, 8, and 15 and ziv-aflibercept 6 mg/kg IV over 30 minutes on day 1 (arm A) or topotecan alone on the same schedule (arm B). Treatment cycles were 21 days in length. Patients on both arms omitted day-15 topotecan starting with cycle 5. Response evaluations were required every 6 weeks throughout study treatment. Patients were required to have recovery from hematologic toxicities (ie, absolute neutrophil count $\geq$ 1,500/μL, hemoglobin $\geq$ 9 g/dL, and platelet count $\geq$ 100,000/μL) before initiating a new treatment cycle. Patients with grade 3 or 4 nonhematologic toxicities were required to have recovery to grade 1 or better before initiating a new treatment cycle. Patients receiving ziv-aflibercept who experienced grade 2 or higher hypertension were required to have a systolic blood

Table 2. Study Treatment

Treatment Characteristic	Treatment Strata			
	Platinum Sensitive (n = 83)		Platinum Refractory (n = 106)	
	Arm A: Ziv-Aflibercept + Topotecan (n = 42)	Arm B: Topotecan (n = 41)	Arm A: Ziv-Aflibercept + Topotecan (n = 55)	Arm B: Topotecan (n = 51)
No. of cycles administered				
Median	2	2	2	2
Range	1-13	1-10	1-11*	1-6
Reason for discontinuation				
Adverse events	8	1	10	5
Refusal unrelated to adverse events	3	4	5	3
Progression/relapse	24	33	35	39
Death	2	1	0	2
Other (not specified)	4	1	5	2
Major protocol deviations	1	2	3	3

*Maximum No. of cycles of ziv-aflibercept was 9.

pressure ≤ 150 mmHg and a diastolic blood pressure ≤ 90 mmHg before initiating a new treatment cycle. Patients experiencing toxicity that required discontinuation of ziv-aflibercept could remain on study and receive topotecan alone. Dose reduction to 3 mg/kg was allowed for ziv-aflibercept, whereas topotecan reductions to 3 mg/m^2 and to 2 mg/m^2 were allowed and specified in the protocol. Patients removed from study for reasons other than progressive disease were monitored for subsequent disease progression.

Statistical Considerations

The primary end point of the study was 3-month PFS, defined as the duration from the date of random assignment to the date of first documentation of progressive disease, symptomatic deterioration, or death as a result of any cause. Secondary end points included OS, RR, DCR, and safety and toxicity.

Accrual proceeded separately in each stratum. For each stratum, the study was designed to detect an improvement in 3-month PFS from 20% to 40% (corresponding to a 1.75 hazard ratio) with a type I error rate of 10% and 90% power. On the basis of this hypothesis, 86 patients were needed in each stratum. With this design and 1 year of follow-up, there would be 80% power to detect an improvement in OS from a median of 7 months to 11.6 months (hazard ratio [HR], 1.65) in the platinum-sensitive stratum and from 5 months to 8 months (HR, 1.6) in the platinum-refractory stratum by using a one-sided test with $\alpha = 10\%$. The design included one interim analysis for futility that was conducted when 50% of the expected events (approximately 42 events in both strata combined) had occurred. The study was monitored by the SWOG Data and Safety Monitoring Committee.

The primary outcome of 3-month PFS was analyzed with Fisher's exact test after complete information was available on all patients. In addition, PFS and OS estimates were calculated with the method of Kaplan-Meier[25] and compared with a log-rank test. Confidence intervals for the median were constructed with the method of Brookmeyer and Crowley.[26]

The RR was defined as the number of confirmed and unconfirmed complete responses and partial responses in the subset of patients who had measurable disease per RECIST 1.0. The DCR was defined as the number of patients who had a best response of stable disease or better in the subset of patients who had measurable disease. RRs, DCRs, and toxicity rates were compared with Fisher's exact test.

RESULTS

Patient Population

A total of 192 patients were registered to the study between July 2009 and March 2012 (Fig 1). One patient each was deemed ineligible

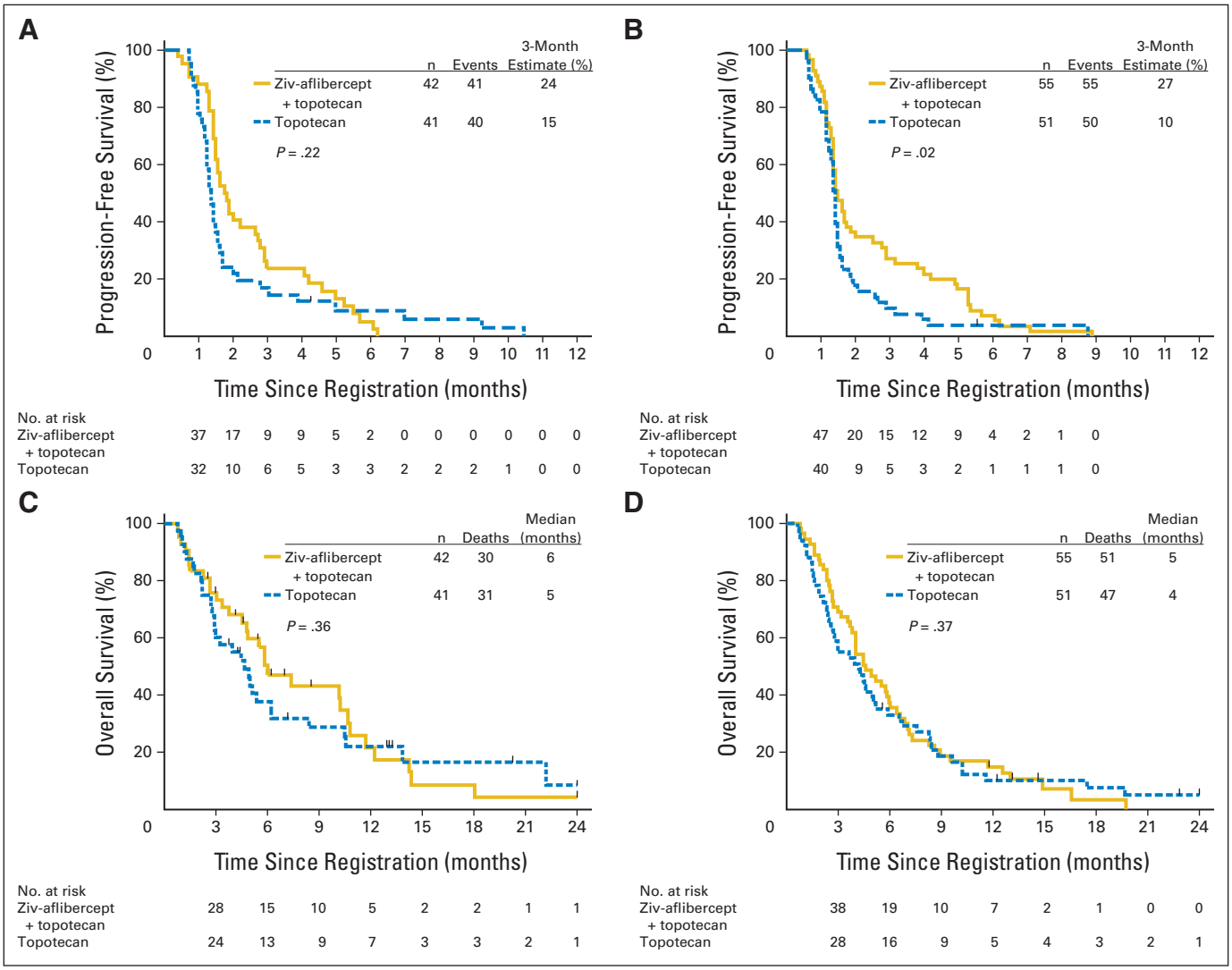

Fig 2. Comparison of treatment arms within subgroups: progression-free survival for patients with (A) platinum-sensitive disease and (B) platinum-refractory disease; overall survival for patients with (C) platinum-sensitive disease and (D) platinum-refractory disease.

Table 3. Response Data

	Treatment Strata							
	Platinum Sensitive (n = 80)				Platinum Refractory (n = 99)			
	Arm A: Ziv-Aflibercept + Topotecan (n = 41)		Arm B: Topotecan (n = 39)		Arm A: Ziv-Aflibercept + Topotecan (n = 51)		Arm B: Topotecan (n = 48)	
Response	No.	%	No.	%	No.	%	No.	%
CR	0	0	0	0	0	0	0	0
PR*	1	2	0	0	1	2	0	0
SD	14	34	7	18	12	24	7	15
DCR†	15	37	7	18	13	25	7	15
Progressive disease	18	44	29	74	29	57	33	69
Symptomatic deterioration	3	7	1	3	2	4	3	6
Early death	0	0	0	0	0	0	1	2
Assessment inadequate	5	12	2	5	7	14	4	8

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate.
*Both partial responses were unconfirmed.
†DCR = CR + PR + SD.

in the platinum-sensitive (inadequate renal function) and platinum-refractory (inadequate hematologic function) strata. One additional patient withdrew consent to participate in the trial before starting treatment, was lost to follow-up, and was not evaluable for any end points. Table 1 describes patient characteristics, which were well balanced for each stratum.

Study Treatment

The most common reason for treatment discontinuation was progressive disease (Table 2). Nine patients did not receive protocol treatment and were classified as major protocol deviations; three were in the platinum-sensitive stratum, and six were in the platinum-refractory stratum. These nine patients were included in the analyses of efficacy end points per intent to treat, but they were not evaluable for adverse events.

Survival

For the platinum-sensitive stratum, the estimated 3-month PFS was 24% (90% CI, 14% to 37%) in arm A compared with 15% (90% CI, 7% to 27%) in arm B ($P = .22$). The median PFS was 1.8 months (90% CI, 1.5 to 2.2 months) for arm A compared with 1.3 months (90% CI, 1.2 to 1.4 months) for arm B. The HR for PFS in arm A versus arm was 1.32 (90% CI, 0.91 to 1.92). The median OS estimates were 6.0 months (90% CI, 4.8 to 10.2 months) for arm A and 4.6 months (90% CI, 2.9 to 5.3 months) for arm B ($P = .36$). For the platinum-refractory stratum, the 3-month PFS was 27% (90% CI, 18% to 39%) for arm A compared with 10% (90% CI, 4% to 20%) for arm B ($P = .02$). The estimated median PFS was 1.4 months for arm A (90% CI, 1.3 to 1.7) and 1.4 months (90% CI, 1.3 to 1.4) for arm B. The HR for PFS in arm A versus arm B was 1.51 (90% CI, 1.08 to 2.10). The median OS estimates were 4.6 months (90% CI, 4.0 to 5.8 months) for arm A and 4.2 months (90% CI, 2.7 to 5.0 months) for arm B ($P = .37$; Figs 2A through 2D).

In an analysis of both strata combined, the HR for PFS in arm A versus arm B was 1.40 (90% CI, 1.10 to 1.78; $P = .02$). The 3-month PFS estimates were 26% (90% CI, 19% to 33%) for arm A and 12% (90% CI, 7% to 18%) for arm B ($P = .01$). The median PFS estimates were 1.6 months (95% CI, 1.4 to 1.8 months) and 1.3 months (90% CI, 1.3 to 1.4 months) for arm A and arm B, respectively. The HR for death in arm A versus arm B was 1.07 (90% CI, 0.82 to 1.39; $P = .34$). The median OS estimates were 5.4 months (90% CI, 4.5 to 5.9 months) and 4.4 months (90% CI, 2.9 to 4.9 months) for arm A and arm B, respectively.

Response

Patients with measurable disease at baseline (n = 80 with platinum-sensitive disease; n = 99, platinum-refractory disease) were included in the analysis of RRs and DCRs. Patients without response determination because of inadequate assessments were included as nonresponders. In the platinum-sensitive stratum, there was one unconfirmed partial response on arm A (overall response rate [ORR], 2%; 90% CI, 0% to 11%) compared with none on arm B (ORR, 0%; 90% CI, 0% to 7%; $P = .51$). The DCR was 37% (90% CI, 24% to 51%) for arm A compared with 18% (90% CI, 9% to 31%) for arm B ($P = .05$). In the platinum-refractory stratum, there was one unconfirmed partial response on arm A (ORR, 2%; 90% CI, 0% to 9%) compared with none on arm B (ORR, 0%; 90% CI, 0% to 6%; $P = .52$). The DCR was 25% (90% CI, 16% to 37%) for arm A compared with 15% (90% CI, 7% to 27%) for arm B ($P = .14$; Table 3).

In an analysis of both strata combined, the ORRs were 2% (90% CI, 0% to 7%) for arm A and 0% (90% CI, 0% to 3%) for arm B ($P = .50$). The DCRs were 30% (90% CI, 23% to 39%) and 16% (90% CI, 10% to 24%) for arm A and arm B, respectively ($P = .03$).

Safety

A summary of the main treatment-related toxicities of grade 3 or greater is shown in Table 4. There was one grade 5 event on arm A (pulmonary hemorrhage) and three on arm B (n = 2, infection; n = 1, renal failure). Grade 4 neutropenia was seen in 3.2% of patients in arm A and 5.7% in arm B. Grade 3 or higher nonhematologic adverse events were more common in arm A than arm B ($P < .001$). Overall, the rate of treatment discontinuation as a result of toxicity was higher in arm A than in arm B (18% *v* 6%). The

Table 4. Treatment-Related Adverse Events for Which at Least One Patient Experienced a Grade 3 or Higher Event

	No. of Grade ≥ 3 Events by Treatment Arm					
	Arm A: Ziv-Aflibercept + Topotecan (n = 93)			Arm B: Topotecan (n = 87)		
Adverse event	3	4	5	3	4	5
Hematologic						
Hemoglobin	8	1	0	6	0	0
Hemolysis	1	0	0	1	0	0
Leukocytes	15	2	0	18	3	0
Lymphopenia	4	1	0	12	0	0
Neutrophils	27	3	0	17	5	0
Platelets	20	10	0	14	3	0
Maximum grade any hematologic adverse event	38	14	0	37	8	0
Nonhematologic						
Cardiac, general	2	1	0	0	0	0
Coagulation	1	0	0	0	0	0
Constitutional symptoms	14	1	0	3	0	0
Gastrointestinal	9	1	0	2	1	0
Hemorrhage/bleeding	5	0	1	0	0	0
Infection	3	1	0	1	1	2
Metabolic/laboratory	9	2	0	5	0	0
Musculoskeletal/soft tissue	3	0	0	1	0	0
Neurology	4	1	0	2	0	0
Pain	6	0	0	0	0	0
Pulmonary/upper respiratory	8	0	0	2	1	0
Renal/genitourinary	0	0	0	1	0	1
Syndromes	0	1	0	0	0	0
Vascular	1	1	0	0	0	0
Maximum grade any nonhematologic adverse event	32	7	1	7	2	3
Maximum grade any adverse event	45	19	1	37	10	3

difference between arms was significant in the platinum-sensitive stratum (19% *v* 2%; $P = .045$) but not in the platinum-refractory stratum (18% *v* 10%; $P = .22$).

Fatigue was more commonly reported with arm A (n = 14, grade 3; n = 1, grade 4) compared with arm B (n = 3, grade 3). Typical VEGF-related adverse events—such as thrombosis (n = 1, grade 3; n = 1, grade 4), hypertension (n = 3, grade 3), proteinuria (n = 1, grade 3), and hemorrhages (n = 5, grade 3; n = 1, grade 5)—were reported but were all seen at fairly low rates.

DISCUSSION

Despite a substantial rationale for study of antiangiogenic therapy in SCLC, S0802 is one of only a few trials, to our knowledge, to evaluate this class of targeted therapies, and the only one, to our knowledge, to investigate ziv-aflibercept in this patient population. Although the addition of ziv-aflibercept to topotecan significantly improved the primary end point of 3-month PFS in patients with SCLC who had platinum-refractory disease (27% *v* 10%; $P = .02$) and numerically in those who had platinum-sensitive disease (24% *v* 15%; $P = .22$), the median PFS and OS were similar across both strata and the ORR was low, with a 2% RR observed in the combination arm in both strata. The DCR was higher with the addition of ziv-aflibercept in both strata (37% *v* 18% [$P = .05$] in platinum-sensitive disease and 25% *v* 15% [$P = .14$] for platinum-refractory disease), which suggests evidence of biologic activity.

There were more grades 3 to 5 toxicities seen in the combination arm than with topotecan alone, and treatment discontinuation because of toxicity was more likely in the combination arm, particularly in patients who had platinum-sensitive disease compared with those who had platinum-refractory disease. The addition of ziv-aflibercept increased fatigue compared with topotecan alone. A similar phenomenon was seen with the addition of ziv-aflibercept to FOLFIRI in patients with metastatic colorectal carcinoma[23] and with single-agent ziv-aflibercept in patients with non–small-cell lung cancer.[27] Other notable toxicities, including dehydration (n = 6), hyponatremia (n = 6), and dyspnea (n = 7), were increased in the combination arm but likely could be managed, given their frequency in this disease setting.

The fact that antiangiogenic agents can result in antitumor efficacy in the absence of a robust RECIST RR is well demonstrated by the phase III SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol) trial of sorafenib versus placebo in hepatocellular cancer, in which sorafenib resulted in improved PFS and OS despite a RR of only 2.3%.[28] Of interest, the results of S0802 mimic those of a phase II trial of single-agent ziv-aflibercept in previously treated patients with non–small-cell lung cancer, in which the RR was also only 2%, yet PFS, OS at 6 months, and OS at 12 months were consistent with antitumor activity of a cytostatic nature.[27]

Bevacizumab, a monoclonal antibody to VEGF in common use as an adjunct to chemotherapy in several malignancies, has undergone limited study in SCLC in both the first- and second-line settings. In the first-line setting, nonrandomized studies of chemotherapy plus bevacizumab have shown favorable results compared with historical controls.[29-31] However, in a randomized, phase II study, the addition of bevacizumab to chemotherapy increased PFS without increasing OS.[32] In the second-line setting, a single-arm, phase II study of bevacizumab and paclitaxel in patients with chemotherapy-sensitive disease demonstrated an ORR of 18.1%, a DCR of 40%, and a median OS of 30 weeks,[33] whereas a similar study in patients with chemotherapy-resistant disease demonstrated an ORR of 20%, a DCR of 36.7%, and a median OS of 6.3 months.[34]

Considering the initial high RRs of SCLC to DNA-damaging chemotherapy regimens, it is disappointing that the first-line therapy of SCLC has remained essentially unchanged for the past 20 years. After initial response, almost all patients with extensive-stage disease experience relapse within 6 to 8 months, and second-line therapies are of marginal benefit, particularly in the subgroup defined as platinum refractory. Interestingly, in S0802, patients who had platinum-refractory disease appeared to derive a greater benefit from the addition of ziv-aflibercept than those who had platinum-sensitive disease and were less likely to discontinue treatment because of toxicity. Although these results may simply reflect greater activity of topotecan alone in platinum-sensitive disease or the relatively small patient sample size in S0802, preclinical data suggest that VEGF expression and VEGF levels are increased in patients who have poor response and poor survival in SCLC,[20,21] thus suggesting a biologic explanation for our clinical findings. We elected to use 3-month PFS as our primary end point rather than a more traditional phase II end point, such as RR, on the basis of analysis of the SWOG database in previously

treated SCLC that suggested consistency of this end point. Use of 3-month PFS instead of RR also was used to identify patients who may benefit from antiangiogenic treatment in the absence of objective response. In support of this rationale, published second-line studies with chemotherapy plus bevacizumab in SCLC have shown high rates of stable disease, an uncommon finding in previously treated patients with SCLC.[33,34]

There are several limitations to our study. At the time that the study was conceived, there were significant concerns regarding the safety of anti-VEGF therapies in SCLC. As a compromise, a chemotherapy partner (weekly topotecan) was selected largely on the basis of its favorable toxicity profile. It could be argued that topotecan has modest activity in previously treated SCLC, regardless of schedule, and that its activity is evident primarily in the platinum-sensitive subgroup. Nevertheless, in a recent phase III trial in colorectal cancer, ziv-aflibercept demonstrated benefit when added to topoisomerase I inhibitor–based therapy, albeit in combination with irinotecan.[23] In summary, although clinical efficacy was modest at best, S0802 met its primary end point of improved 3-month PFS, which suggests biologic activity of this antiangiogenic agent in combination with weekly topotecan in a subset of patients who have platinum-refractory disease. Toxicities were more pronounced with the addition of ziv-aflibercept, and additional studies to define the optimal dose and schedule of ziv-aflibercept in combination with chemotherapy in SCLC are warranted. Efforts to define predictive biomarkers of ziv-aflibercept activity clearly are needed to help enrich study populations to those patients most likely to experience clinical benefit from the addition of ziv-aflibercept.

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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AUTHOR CONTRIBUTIONS

Conception and design: Jeffrey W. Allen, James Moon, Mary Redman, Karen Kelly, Philip C. Mack, Mohammad Jahanzeb, David R. Gandara
Provision of study materials or patients: Shirish M. Gadgeel, Mohamed K. Mohamed, David R. Gandara
Collection and assembly of data: James Moon, Mary Redman, Hanna M. Saba, Mohamed K. Mohamed
Data analysis and interpretation: Jeffrey W. Allen, James Moon, Mary Redman, Shirish M. Gadgeel, Philip C. Mack, Mohammad Jahanzeb, David R. Gandara
Manuscript writing: All authors
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GLOSSARY TERMS

RECIST (Response Evaluation Criteria in Solid Tumors): a model proposed by the Response Evaluation Criteria Group by which a combined assessment of all existing lesions, characterized by target lesions (to be measured) and nontarget lesions, is used to extrapolate an overall response to treatment.

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.

