Original Article

Vismodegib or Cixutumumab in Combination With Standard Chemotherapy for Patients With Extensive-Stage Small Cell Lung Cancer: A Trial of the ECOG-ACRIN Cancer Research Group (E1508)

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BACKGROUND: Preclinical targeting of the hedgehog pathway by vismodegib and of insulin-like growth factor 1 receptor by cixutumumab enhances the efficacy of chemotherapy and also demonstrates activity against the tumor cell fraction responsible for disease recurrence in small cell lung cancer. **METHODS:** Patients with newly diagnosed extensive-stage small cell lung cancer (SCLC-ED) were randomized to receive four 21-day cycles of cisplatin and etoposide alone (cisplatin at 75 mg/m^2 on day 1 and etoposide at 100 mg/m^2 on days 1-3; arm A) or in combination with either vismodegib (150 mg/d by mouth; arm B) or cixutumumab (6 mg/kg/wk intravenously on day 1; arm C). The primary endpoint was progression-free survival (PFS). Circulating tumor cells (CTCs) were isolated/enumerated with the Veridex CellSearch platform at the baseline. **RESULTS:** One hundred fifty-two eligible patients were treated. Patient demographics and disease characteristics were well balanced between the 3 arms except for the higher rate with a performance status of 0 in arm B ($P = .03$). The median PFS times in arms A, B, and C were 4.4, 4.4, and 4.6 months, respectively; the median overall survival (OS) times were 8.8, 9.8, and 10.1 months, respectively; and the response rates were 48%, 56%, and 50%, respectively. None of the comparisons of these outcomes were statistically significant. The median OS was 10.5 months for those with low CTC counts ($\leq$100/7.5 mL) at baseline and 7.2 months for those with high CTC counts (hazard ratio, 1.74; $P = .006$). **CONCLUSIONS:** There was no significant improvement in PFS or OS with the addition of either vismodegib or cixutumumab to chemotherapy in patients with SCLC-ED. A low baseline CTC count was associated with a favorable prognosis. ***Cancer* 2016;122:2371-8**. © *2016 American Cancer Society*.

KEYWORDS: circulating tumor cell (CTC), cixutumumab, small cell lung cancer, extensive disease, vismodegib.

INTRODUCTION

Small cell lung cancer (SCLC) accounts for 12% of all cases of lung cancer in the United States.[1] SCLC is characterized by its rapid doubling time and the early development of metastatic disease, and for decades, combination chemotherapy, consisting of a platinum agent and the topoisomerase II inhibitor etoposide, has been the mainstay of systemic treatment for this disease. Approximately two-thirds of all SCLC cases have extensive-stage small cell lung cancer (SCLC-ED). Response rates to first-line chemotherapy range from 60% to 70% in patients with SCLC-ED; however, despite the impressive efficacy, most patients rapidly develop resistant disease, and their overall prognosis and outcome are poor. For patients with SCLC-ED, the median survival is 9 to 11 months, and only 5% of patients are alive 2 years after their diagnosis.[2] Despite multiple efforts to combine chemotherapeutic and targeted agents with the standard first-line therapy, the results have

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This study was presented in part at the 2013 Annual Meeting of the American Society of Clinical Oncology; May 31-June 4, 2013; Chicago, IL.

DOI: 10.1002/cncr.30062, **Received:** February 23, 2016; **Revised:** March 30, 2016; **Accepted:** April 1, 2016, **Published online** May 10, 2016 in Wiley Online Library (wileyonlinelibrary.com)

been dismal.[2] There is a critical need to incorporate mechanistically based novel compounds targeting tumor cells or signaling pathways that are altered in SCLC.

Hedgehog Signaling and SCLC

The hedgehog signaling pathway is a critical regulator of proliferation and differentiation during embryonic development. This pathway has been shown to be essential in early lung formation and development through epithelial-mesenchymal interactions.[3,4] There are 3 known ligands of this pathway in humans: Sonic hedgehog, Indian hedgehog, and Desert hedgehog. The signaling cascade is initiated by hedgehog binding to patched 1 receptor (Ptch-1), a transmembrane protein. In the absence of a hedgehog ligand, Ptch-1 constitutively inhibits the transmembrane protein smoothened (Smo) and renders the pathway inactive. However, the binding of a hedgehog ligand to Ptch-1 relieves the inhibition of Smo, which then activates a protein complex and downstream transcription of hedgehog targets in the nucleus, including Gli-1 and Ptch-1; this leads to the upregulation of target genes important for cellular proliferation and clonogenicity. Hedgehog signaling may play a significant role in the development and proliferation of SCLC. Both Sonic hedgehog and Gli-1 are expressed and upregulated in SCLC in comparison with normal airway epithelium.[5] Preclinical models suggest that hedgehog pathway inhibition may delay or prevent the recurrence of residual disease after chemotherapy.[6] Vismodegib (GDC-0449) is a selective hedgehog pathway inhibitor that blocks hedgehog signaling by binding to SMO and inhibiting the activation of downstream hedgehog target genes.[7] We hypothesized that by targeting tumor progenitor cells, vismodegib may inhibit the clonogenic growth of SCLC; this might translate into improved progression-free survival (PFS) when it is added to the standard regimen of cisplatin and etoposide (CE).

Insulin-Like Growth Factor 1 Receptor (IGF-1R) and SCLC

IGF-1R, a member of the insulin receptor subclass of receptor tyrosine kinase, is activated by the ligands insulin-like growth factor 1 (IGF-1) and IGF-2 and triggers mitogenic and antiapoptotic signaling pathways contributing to cellular transformation and malignant growth.[8] IGF-1R is autophosphorylated upon ligand binding and activates the phosphoinositide 3-kinase–AKT pathway, which is strongly implicated in the development and growth of cancer cells as well as resistance to chemotherapy. Signaling through phosphoinositide 3-kinase also can activate the Raf/mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway to promote metastasis.[8,9] Current data suggest that IGF-1 and IGF-2 drive tumor cell proliferation and survival through multiple oncogenic pathways. IGF-1, the IGF-1R ligand, has been shown to be expressed in human lung cancer, with a tendency of increased production by highly metastatic cells leading to proliferation, survival, and chemoresistance.[9,10] Targeted inhibition of IGF-1R with cixutumumab thus represents an attractive approach to enhance chemotherapeutic efficacy,[11] and this has led to its incorporation into the current study.

Circulating Tumor Cell (CTC) Counts in SCLC

Recent data suggest that CTCs can be detected in nearly all patients[12] with metastatic lung cancer and may have relevance as a source of tumor tissue that can serve as a prognostic indicator for SCLC-ED as an exploratory measure. We sought to enumerate the CTCs in all enrolled subjects.

MATERIALS AND METHODS

Patient Selection

This was a multicenter, open-label Eastern Cooperative Oncology Group (ECOG)–American College of Radiology Imaging Network (ACRIN) study for patients with histologically or cytologically confirmed SCLC-ED. The salient eligibility criteria were as follows: age $\geq$ 18 years, ECOG performance status of 0 or 1, acceptable organ and marrow function, treated and stable brain metastasis, adequate contraception in women of child-bearing potential (not breastfeeding and not pregnant) and in men, no prior chemotherapy or biologic therapy for SCLC (prior radiotherapy was permitted if it had been completed 14 days before study initiation), no history of allergic reactions to agents biologically similar to vismodegib or cixutumumab, and absence of uncontrolled intercurrent cardiac or psychiatric illness or diabetes mellitus. The study was performed after the protocol was approved by the institutional review boards of the participating institutions, and it was registered at ClinicalTrials.gov (NCT00887159).

Study Design and Treatment

The treatment schema for this trial is displayed in Figure 1. Each cycle was 3 weeks (21 days) in length. Patients were randomized equally to 1 of 3 treatment arms. Arm A was given CE; for this regimen, premedications for etoposide were given, and then etoposide was administered (100 mg/m^2) via an intravenous infusion over a 60- to 120-minute period. Then, prehydration for cisplatin was

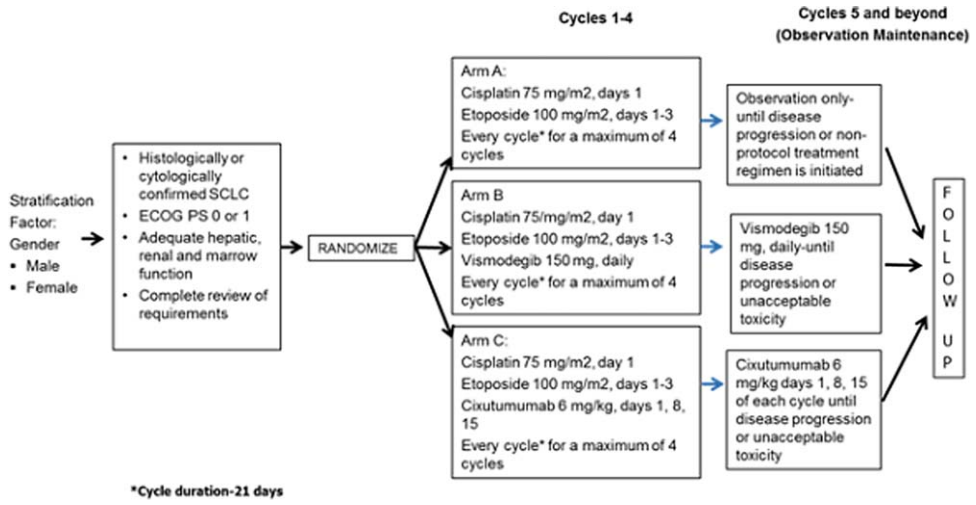

Figure 1. Schema for the E1508 trial. ECOG indicates Eastern Cooperative Oncology Group; PS, performance status; SCLC, small cell lung cancer.

given, and this was followed by intravenous cisplatin (75 mg/m^2) over a 60- to 120-minute period with postcisplatin hydration. Days 2 and 3 included etoposide premedications and etoposide only (intravenously over a 60- to 120-minute period). Four cycles of cisplatin (day 1 of four 21-day cycles) and etoposide (days 1-3 of four 21-day cycles) were administered. Patients in arm A were observed after the completion of 4 cycles of chemotherapy and were seen in follow-up (including imaging) on the same schedule as those randomized to arms B and C. Patients randomized to arm B received CE plus vismodegib dosed as a 150-mg tablet. CE was given at the same dose, on the same schedule, and for the same duration used in arm A. On days 1 to 3, oral vismodegib was given on an empty stomach after premedication and before the administration of etoposide. Vismodegib was taken daily throughout the first 4 cycles and was continued daily after 4 cycles of chemotherapy until disease progression or unacceptable toxicity. Patients randomized to arm C received CE plus cixutumumab (6 mg/kg), which was given intravenously after premedication for etoposide (on day 1) over the course of 1 hour. Cixutumumab was also given on days 8 and 15 in each treatment cycle. After 4 cycles of chemotherapy, cixutumumab was administered weekly until disease progression or unacceptable toxicity.

A maximum of 2 dose reductions was allowed. Patients discontinued all protocol treatment if a third dose reduction was required. A dose reduction for all adverse events was permanent for all subsequent cycles. CE was dose-reduced according to the package insert. If a patient discontinued cixutumumab for a related toxicity such as an infusional reaction or grade 3 symptomatic/grade 4 hyperglycemia, the dose levels were 5 and 3 mg/kg/wk. There were no specific dose modifications for vismodegib.

Computed tomography scans were performed every 2 cycles for an assessment of response. During the maintenance and follow-up phase, the scans were performed every 6 weeks. PFS determination was based on an investigator's review of radiographic images.

Statistical Considerations

The primary endpoint of this phase 2 randomized study was PFS, which was defined as the time from randomization to death from any cause or documented disease progression per the Response Evaluation Criteria in Solid Tumors (version 1.0), whichever occurred first, and patients were censored at the date on which they were last known to be alive and progression-free. Secondary endpoints included overall survival (OS), which was defined as the time from randomization to death from any cause with censoring at the last follow-up date, the overall response rate per the Response Evaluation Criteria in Solid Tumors, and toxicity via the Common Terminology Criteria for Adverse Events (version 4.0). The goal was to select the regimen with superior anticancer activity for further evaluation in a phase 3 study. A total of 162 patients (54 per arm) were needed for 2 primary comparisons involving each of the experimental arms (B and C) and the control arm (A). With an overall 1-sided, 0.10-level log-rank test, there was 90% power to detect a 42% reduction in the PFS hazard ratio (HR) of 0.139 to 0.082,

TABLE 1. Demographics and Disease Characteristics

Variable	Category	Arm A: Cisplatin and Etoposide	Arm B: Cisplatin, Etoposide, and Vismodegib	Arm C: Cisplatin, Etoposide, and Cixutumumab	Total
Total patients, No.		48	52	52	152
Sex, No. (%)	Female	25 (52)	26 (50)	25 (48)	76 (50)
	Male	23 (48)	26 (50)	27 (52)	76 (50)
Age, y	Median	61	64	64	63
	Range	38–77	52–87	45–83	38–87
Race, No. (%)	White	41 (85)	49 (94)	46 (88)	136 (89)
	Black	6 (12)	0 (0)	2 (4)	8 (5)
	Asian	0 (0)	2 (4)	1 (2)	3 (2)
	Unknown	1 (2)	1 (2)	3 (6)	5 (3)
Performance status, No. (%)	0	11 (23)	26 (50)	18 (35)	55 (36)
	1	37 (77)	26 (50)	34 (65)	97 (64)
Central nervous system metastases, No. (%)	No	43 (90)	49 (94)	46 (88)	138 (91)
	Yes	4 (8)	2 (40)	5 (10)	11 (7)
	Unknown	1 (2)	1 (2)	1 (2)	3 (2)
Pleural effusion, No. (%)	No	36 (75)	41 (79)	39 (75)	116 (76)
	Yes	12 (25)	11 (21)	13 (25)	36 (24)
Prior radiotherapy, No. (%)	No	44 (92)	49 (94)	45 (87)	138 (91)
	Yes	4 (8)	3 (6)	7 (13)	14 (9)

and this corresponded to a 70% improvement in the median PFS of 5 to 8.5 months in each arm. Kaplan-Meier curves were used to estimate event-time distributions, and they were compared with log-rank tests. Cox proportional hazards models, stratified by sex, were used to estimate HRs and test for significance for PFS. Categorical data were compared with Fisher's exact test. All *P* values are 2-sided unless specified otherwise, and confidence intervals (CIs) are at the 95% level. No adjustments were made for multiple comparisons.

RESULTS

The study was activated on July 16, 2009. The trial was suspended to accrual on March 5, 2010 after it had accrued 32 patients for a protocol-specified analysis of toxicity because this was the first time that either cixutumumab or vismodegib was being combined with cisplatin and etoposide. Toxicity was assessed after each patient had completed 2 cycles of therapy, and safety issues were reviewed; this led to subsequent reactivation on May 24, 2010. Accrual was completed on August 12, 2011 after 168 patients had been enrolled. Six patients were ineligible: 1 had no evidence of SCLC on a histological examination, and 5 had baseline scans that were not within 28 days of registration. Ten patients never started the assigned therapy: 3 had medical reasons (patient and/or physician decision), 1 had a low creatinine clearance, 1 progressed before starting treatment, 3 refused treatment, 1 had adverse events before starting treatment, and 1 was ineligible. Thus, 152 patients were included in the primary analysis (48 in arm A, 52 in arm B, and 52 in arm C). This analysis reports on data received as of October 10, 2014.

Patient Demographics and Disease Characteristics

Patient demographics and disease characteristics at the time of registration for this trial are summarized by treatment arm in Table 1. The variables appear to be well balanced by treatment arm with the exception of performance status ($P = .03$) and race ($P = .05$).

Adverse Events

On March 5, 2010, the E1508 trial was suspended per protocol so that a safety analysis could be conducted for the first 10 patients registered into each arm of this 3-arm trial. At the time of suspension, 32 patients had been accrued to the trial. It was decided that there were no concerning trends in toxicity observed. The plan for the safety analysis was to reactivate the trial, to continue to review the Adverse Event Expedited Reporting System data monthly, and to review the toxicity incidence table every 6 months for the data monitoring committee. Another review of the nonhematologic grade 4 and 5 events took place per protocol in January 2011 (without suspension of accrual) after 25 patients had registered into each arm; it was deemed safe to continue accrual because no concerning toxicity issues were observed.

Postbaseline treatment-related grade 3 and 4 adverse events are displayed in Table 2. The most common treatment-related grade 3 to 5 adverse event was neutropenia: 50% in arm A, 53% in arm B, and 59% in

TABLE 2. Incidence of Postbaseline Treatment-Related Grade 3 and 4 Adverse Events

Adverse Event	Arm A: Cisplatin and Etoposide (n = 53), %		Arm B: Cisplatin, Etoposide, and Vismodegib (n = 53), %		Arm C: Cisplatin, Etoposide, and Cixutumumab (n = 52), %	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Anemia	23	2	11	—	13	—
Febrile neutropenia	13	2	8	4	4	—
Fatigue	25	—	11	—	23	—
Fever	2	—	—	—	—	—
Diarrhea	—	—	6	—	12	—
Mucositis, oral	2	—	—	—	8	—
Nausea	11	—	11	—	21	—
Vomiting	9	—	6	—	13	—
Lung infection	4	—	6	—	2	—
Sepsis	—	—	—	—	—	4
Alanine aminotransferase increase	2	—	—	—	—	—
Creatinine increase	—	—	2	—	2	2
Neutropenia	8	42	13	40	15	44
Thrombocytopenia	11	11	2	4	12	13
Weight loss	—	—	6	—	6	—
Anorexia	8	—	4	—	12	—
Dehydration	13	—	4	—	13	—
Hyperglycemia	2	—	—	—	8	—
Hypokalemia	8	2	2	—	86	—
Hyponatremia	13	—	2	11	124	4
Hypophosphatemia	—	—	4	—	4	—
Tumor lysis syndrome	2	—	—	—	—	—
Generalized muscle weakness	4	—	2	—	4	—
Myalgia	—	—	2	—	—	—
Renal dysfunction	4	2	—	—	6	—
Hypertension	—	—	4	—	—	—
Thromboembolic event	2	2	2	—	—	—
Overall worst degree	28	53	28	53	25	65

The incidence for all patients who received treatment is reported.

TABLE 3. Response and Survival by Treatment Arm

Efficacy	Arm A: Cisplatin and Etoposide (n = 48)	Arm B: Cisplatin, Etoposide, and Vismodegib (n = 52)	Arm C: Cisplatin, Etoposide, and Cixutumumab (n = 52)
PFS (95% CI), mo	4.4 (3.6–5.5)	4.4 (4.1–5.4)	4.6 (4.4–5.5)
OS (95% CI), mo	8.8 (7.8–11.2)	9.8 (8.7–12.4)	10.1 (8.8–14)
Response rate (CR + PR), %	48	56	50
SD, %	17	13	27

Abbreviations: CI, confidence interval; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

arm C. However, the incidence of febrile neutropenia was higher in the control arm (15% in arm A) versus arms B (12%) and C (4%); this was not statistically significant. Hyperglycemia, a common toxicity in patients on IGF-1R inhibitors, was seen in only 8% (grade 3) with cixutumumab. The rate of grade 3 to 5 diarrhea was significantly increased in arm C (12%) versus arm A (0%; $P = .01$). Grade 4 platelet toxicity was observed in 11%, 4%, and 13% in arms A, B, and C, respectively. There were no bleeding events. Two patients had colonic perforation in arm C, and 2 patients had lethal cardiac events in arm A (control arm). Other notable and rare toxicities are listed in Table 2. There were 3 deaths in the study: 2 in arm A (1 related to infection and 1 due to myocardial infarction) and 1 in arm B (sepsis).

Efficacy

At the time of the analysis, 143 of the 152 eligible and treated patients had died, and a total of 148 patients had experienced a PFS event. The estimated median PFS was 4.4 months (95% CI, 3.6-5.5 months) for arm A, 4.4 months (95% CI, 4.1-5.4 months) for arm B, and 4.6

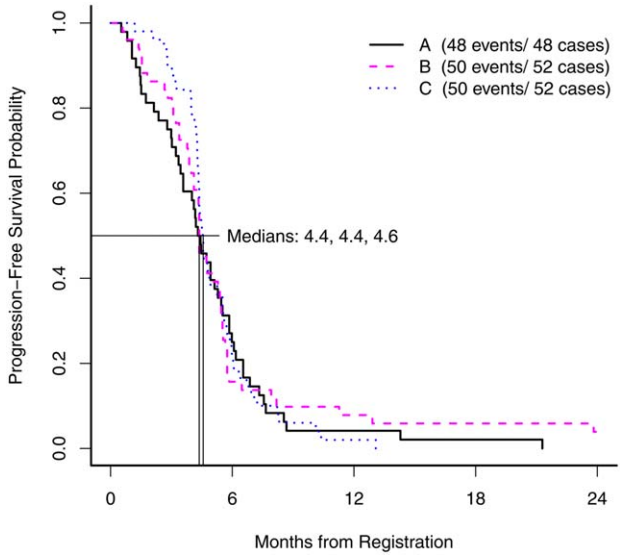

Figure 2. Progression-free survival by treatment.

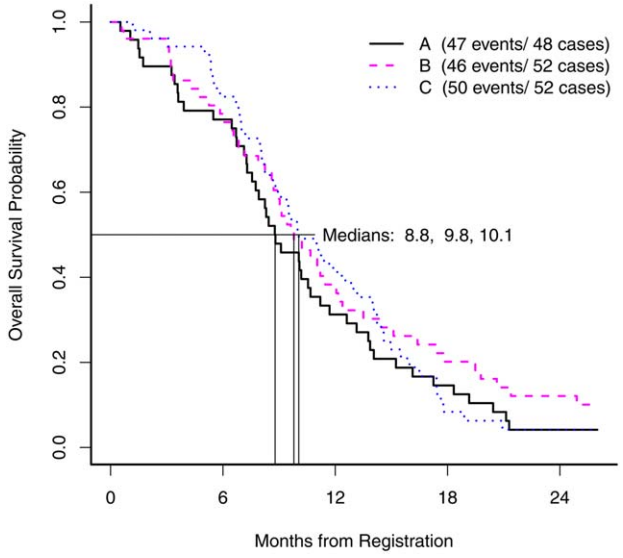

Figure 3. Overall survival by treatment.

months (95% CI, 4.4-5.5 months) for arm C. Figure 2 displays PFS by treatment arm for the primary analysis of all eligible and treated patients. The estimated median OS was 8.8 months (95% CI, 7.8-11.2 months) for arm A, 9.8 months (95% CI, 8.7-12.4 months) for arm B, and 10.1 months (95% CI, 8.8-14.0 months) for arm C. The median follow-up for all patients who remained alive was 35.8 months. Figure 3 displays OS by treatment arm for the primary analysis of all eligible and treated patients.

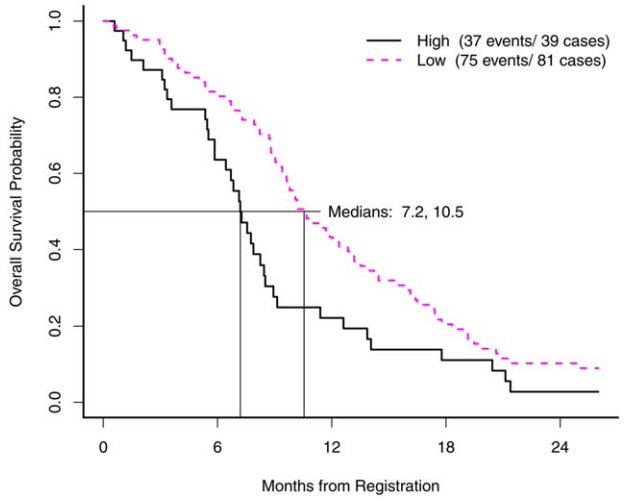

Figure 4. Overall survival by the circulating tumor cell group.

In the primary analysis set, there were 134 progressions (42 in arm A, 47 in arm B, and 45 in arm C) and 14 deaths without documented progression (6 in arm A, 3 in arm B, and 5 in arm C) for a total of 148 PFS events (48 in arm A, 50 in arm B, 50 in arm C). The combination of vismodegib with CE (arm B) did not appear to improve PFS in this patient population in comparison with CE alone (HR, 0.98; 95% CI, 0.65-1.47; 1-sided $P = .45$); the combination of cixutumumab with CE also did not appear to improve PFS in comparison with CE alone (HR, 0.99; 95% CI, 0.66-1.48; 1-sided $P = .48$). (Additional analyses via stratified log-rank tests resulted in similar P values.) We also note that the average daily dose of vismodegib during maintenance was 144.4 mg.

One complete response was reported in arm C; the numbers of complete and partial responses reported in arms A (n = 48), B (n = 52), and C (n = 52) were 23 (48%), 29 (56%), and 26 (50%), respectively.

Correlative Studies

CTCs were isolated and enumerated with the Veridex CellSearch platform. We defined a high CTC count as greater than 100 CTCs per 7.5 mL at the baseline. A total of 120 patients from the primary analysis set had baseline CTC results available for analysis, and 39 of them (32.5%) had high CTC counts. A high baseline CTC measurement conferred a worse outcome with respect to OS (Fig. 4). The median PFS was 4.5 months (95% CI, 4.4-5.3 months) among patients with low CTC counts and 4.1 months (95% CI, 3.3-5.4 months) among those with high CTC counts; the estimated PFS HR comparing

high and low groupings was 1.69 ($P = .01$; 95% CI, 1.13-2.52).

No other factors besides high CTCs were associated with PFS after adjustments for other factors in a multivariate Cox model (the explored variables were sex, performance status, treatment arm, age, pleural effusion, and weight loss in the prior 6 months). The median OS was 10.5 months (95% CI, 9.4-13.2 months) among patients with low CTC counts and 7.2 months (95% CI, 6.4-8.5 months) among those with high CTC counts; the estimated OS HR comparing high and low groupings was 1.76 ($P = .005$; 95% CI, 1.18-2.63). In a multivariate Cox model adjusted for ≥5% weight loss in the previous 6 months (vs <5% weight loss; HR, 1.75; $P = .006$), the adjusted OS HR comparing high and low CTC counts was 1.74 (95% CI, 1.17-2.61; $P = .006$). Tests for interactions between treatments and CTC groups were not significant. The test for an association with response was also not significant ($P = .17$).

DISCUSSION

Our study failed to detect an improvement in efficacy for the 2 experimental regimens with vismodegib and cixutumumab. There was no improvement in any of the efficacy parameters, including the response rate, PFS, and OS. Treatment tolerance was comparable between the treatment arms, so the lack of efficacy cannot be attributed to differences in the treatment delivery of the chemotherapy regimen with targeted therapy. These disappointing results can be added to the list of prior efforts that combined chemotherapy with a novel agent for SCLC.

IGF-1R inhibition, which was once thought to be a promising strategy for the treatment of cancer, has not been successful in improving survival for patients with lung cancer.[11] In non–small cell lung cancer, a randomized study of chemotherapy or targeted therapy with IGF-1R inhibitors failed to demonstrate an improvement in survival. A post hoc analysis of a randomized study observed favorable outcomes with IGF-1R inhibition in patients with elevated baseline IGF-1 levels.[13] This observation was not available at the time of the conception of our study, so we did not measure IGF-1 levels in our patients. Cixutumumab is no longer being developed as an anticancer agent after its failure against multiple tumor types.

Inhibition of the hedgehog pathway was considered particularly more relevant for SCLC because the recurrence of disease is attributable to the persistent stem cell population after combination chemotherapy. Preclinical studies had demonstrated hedgehog inhibition as a novel strategy for eradicating the stem cells.[14] Our study design included vismodegib during the concurrent phase and the maintenance phase. We cannot exclude the possibility that the administration of a hedgehog inhibitor strictly as maintenance therapy after maximal eradication of cancer cells might yield more favorable results. Thus, the combination of a platinum compound with etoposide remains the most effective treatment for this patient population.

SCLC remains a difficult disease to treat with no major improvements in survival in more than 2 decades. Recently, sequencing the genome of SCLC has demonstrated mutations in certain cell signaling pathways. It is well known that P53 mutations and retinoblastoma loss are observed in a high proportion of SCLC cases.[15] With this background, new classes of agents targeting mutated or aberrant pathways represent a logical approach to treating SCLC. Poly(adenosine diphosphate ribose) polymerase inhibitors are also promising because of their single-agent activity and preclinical synergy when they are given with platinum-containing regimens.[16] ECOG-ACRIN is conducting a randomized phase 2 study of chemotherapy with or without veliparib, a poly(adenosine diphosphate ribose) polymerase inhibitor, in patients with SCLC-ED. Immunotherapy also appears promising according to recent reports that demonstrated a response rate of approximately 30% with a combination of immune checkpoint inhibitors.[17,18] Further investigation of immune checkpoint inhibitors is currently underway for SCLC.

In summary, further evaluation of hedgehog inhibitors of IGF-1R inhibitors in combination with chemotherapy cannot be recommended for patients with SCLC. The utility of CTCs as a prognostic marker warrants further evaluation. If validated in subsequent studies, this could be an important stratification factor for clinical trials in SCLC.

FUNDING SUPPORT

This study was coordinated by the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group (Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD, group cochairs) and was supported in part by Public Health Service Grants CA180794, CA180820, CA180802, CA180791, CA189830, CA180790, CA189805, CA189863, CA180844, CA180864, and CA180870 from the National Cancer Institute (National Institutes of Health, Department of Health and Human Services). This article's content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute.

CONFLICT OF INTEREST DISCLOSURES

Charles M. Rudin reports acting as a consultant/advisor for AbbVie, AVEO, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Calithera, and Celgene and receiving research funding from Biomarin. Christine L. Hann reports funding from GlaxoSmithKline. Manish Monga is an employee of and has stock in Bristol-Myers Squibb. Suresh S. Ramalingam reports acting as a consultant for Eli Lilly and Genentech. Joan H. Schiller reports acting as a consultant/advisor for ARIAD, Boehringer Ingelheim, Agennix, Argole Systems, Clovis Oncology, Biodesix, AVEO, Eisai, Genentech/Roche, Synta, Dekkun Corporation, AbbVie, Eli Lilly, and Merck and receiving research funding from Synta, Astex Pharmaceuticals, EMD Serono, Merrimack, Endocyte, Genentech, Novartis, Clovis Oncology, and Johnson and Johnson.

AUTHOR CONTRIBUTIONS

Chandra P. Belani: Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of the manuscript. **Suzanne E. Dahlberg:** Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, and final approval of the manuscript. **Charles M. Rudin:** Conception and design, collection and assembly of data, data analysis, manuscript writing, and final approval of the manuscript. **Martin Flesher:** Collection and assembly of data, manuscript writing, and final approval of the manuscript. **Helen X. Chen:** Conception and design and final approval of the manuscript. **Naoko Takebe:** Conception and design, manuscript writing, and final approval of the manuscript. **Mario R. Velasco, Jr:** Collection and assembly of data, manuscript writing, and final approval of the manuscript. **William J. Tester:** Conception and design, manuscript writing, and final approval of the manuscript. **Keren Sturtz:** Collection and assembly of data, manuscript writing, and final approval of the manuscript. **Christine L. Hann:** Collection and assembly of data, manuscript writing, and final approval of the manuscript. **James C. Shanks:** Collection and assembly of data and final approval of the manuscript. **Manish Monga:** Collection and assembly of data, manuscript writing, and final approval of the manuscript. **Suresh S. Ramalingam:** Conception and design, manuscript writing, and final approval of the manuscript. **Joan H. Schiller:** Conception and design, data analysis and interpretation, manuscript writing, and final approval of the manuscript.

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