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ORIGINAL REPORT

Phase II Study of Vandetanib or Placebo in Small-Cell Lung Cancer Patients After Complete or Partial Response to Induction Chemotherapy With or Without Radiation Therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20

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ABSTRACT

Purpose
This double-blind randomized phase II trial examined whether vandetanib, an inhibitor of vascular endothelial and epidermal growth factor receptors, could prolong progression-free survival in responding patients with small-cell lung cancer.

Patients and Methods
Eligible patients with complete response (CR) or partial response (PR) to combination chemotherapy (± thoracic or prophylactic cranial radiation) received oral vandetanib 300 mg/d or matched placebo. With 100 patients and 77 events, the study had 80% power to detect an improvement in median progression-free survival from 4 to 6.5 months (one-sided, 10%-level test).

Results
Between May 2003 and March 2006, 107 patients were accrued; 46 had limited disease and 61 extensive disease. There were fewer patients with a performance status of 0 (n = 11 *v* 20), and fewer had CR to initial therapy (n = 4 *v* 8) in the vandetanib arm. Vandetanib patients had more toxicity and required more dose modifications for gastrointestinal toxicity and rash. Asymptomatic Corrected QT interval (QT_C) prolongation was observed in eight vandetanib patients. Median progression-free survival for vandetanib and placebo was 2.7 and 2.8 months, respectively (hazard ratio [HR], 1.01; 80% CI, 0.75 to 1.36; one-sided $P = .51$). Overall survival for vandetanib was 10.6 versus 11.9 months for placebo (HR, 1.43; 80% CI, 1.00 to 2.05; one-sided $P = 0.9$). In planned subgroup analyses, a significant interaction was noted ($P = .01$): limited-stage vandetanib patients had longer overall survival (HR, 0.45; one-sided $P = .07$) and extensive-stage vandetanib patients shorter survival compared with placebo (HR, 2.27; one-sided $P = .996$).

Conclusion
Vandetanib failed to demonstrate efficacy as maintenance therapy for small-cell lung cancer.

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INTRODUCTION

Lung cancer is the most common cause of cancer-related mortality in North America, and accounts for more deaths than breast, colon, and prostate cancers combined.[1,2] Although small-cell lung cancer (SCLC) accounts for only 15% to 20% of all lung cancer cases, 60% of lung cancer patients have extrathoracic metastases at the time of diagnosis, and few of these patients survive more than 1 year after diagnosis despite response rates exceeding 60% from treatment with a platinum drug in combination with etoposide.[3,4] Trials of three- and four-drug regimens, dose intensification, or incorporating third-generation cytotoxic agents (gemcitabine, taxanes, vinorelbine, irinotecan, and topotecan) have failed to improve outcomes.[5] The Surveillance, Epidemiology, and End Results (SEER) database has demonstrated only marginal gains in 2- and 5-year survival rates for SCLC during the last 30 years.[6]

Advances in the understanding of molecular carcinogenesis have led to the development of targeted agents for several tumor types, including c-kit receptor inhibitors for GI stromal tumors[7] and the epidermal growth factor receptor (EGFR)

antagonists[8] and vascular endothelial growth factor (VEGF) inhibitors for non–small-cell lung cancer (NSCLC).

Almost three decades have passed since Folkman[8a] first proposed the hypothesis that angiogenesis is critical for tumor growth. Evidence that angiogenesis plays an important role specifically in lung cancer has emerged more recently, although the majority of data relates to NSCLC.[9] With respect to SCLC, Lucchi et al[10] reported that high microvessel density predicted poorer outcome in univariate analyses in patients undergoing surgical resection followed by adjuvant chemotherapy. Only expression of VEGF was significant on multivariate analysis. Increased serum basic fibroblast growth factor levels also predict a poor outcome in SCLC, whereas increased interleukin-2 has been shown to confer a favorable prognosis. High expression levels of the matrix metalloproteinases MMP-3, -11, and -14 have been shown to be independent negative prognostic indicators.[11,12] Thus, there is considerable rationale for evaluating angiogenesis inhibitors in SCLC.

Although data from early trials of agents purported to have some antiangiogenesis activity such as interferon and matrix metalloproteinase inhibitors (MMPIs) have been disappointing,[13] recent reports of thalidomide in untreated extensive-stage SCLC are encouraging.[14] Vandetanib (ZD6474; Zactima; AstraZeneca, Wilmington, DE) is an orally bioavailable inhibitor of VEGF receptor-2 (VEGFR, KDR) and, to a lesser extent, EGFR.[15]

We report here the results of the National Cancer Institute of Canada–Clinical Trials Group (NCIC-CTG) BR.20 trial of vandetanib as maintenance therapy in patients with SCLC who have responded to chemotherapy.

PATIENTS AND METHODS

Patients

Patients 16 years of age or older were eligible if they had histologic or cytologic proof of SCLC (small-cell or variant; mixed histology was not permitted) and had received at least four cycles of combination chemotherapy, achieving complete response (CR) or partial response (PR). The choice of platinum-based chemotherapy regimen and any radiation were left to the discretion of the investigator.

Patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; life expectancy of at least 12 weeks; and adequate hematology and biochemistry. They were ineligible if they had brain metastases that were untreated, or treated with persistent symptoms; necrosis; or hemorrhage; or if they required increasing doses of steroids. Other ineligible patients included those with other invasive malignancies within the preceding 5 years (excluding nonmelanomatous skin lesions); those receiving medications known to prolong corrected QT interval (QT_C) or inhibit/induce cytochrome P450 3A4 (cyp3A4); patients who had significant cardiovascular conditions, bleeding diatheses, recent major surgery or bleeding, and severe infections or medical conditions; and pregnant or nursing women. The protocol was approved by an Ethics Review Board at each institution; all patients provided written informed consent.

Evaluations

Before random assignment, all patients underwent complete history and physical examinations, routine hematology and biochemistry, toxicity evaluation, left ventricular ejection fraction, ECG, and quality-of-life (QoL) assessment; where applicable, a pregnancy test was performed within 72 hours of random assignment. Samples for pharmacokinetics (PK) and tissue banking (consenting patients) were also collected. Imaging studies including computed tomography (CT) chest and abdomen and bone scans (and any additional radiology performed before initiation of induction therapy that had been abnormal) had to be performed within 42 days before random assignment.

QoL assessment, physical examination, and biochemistry were repeated every 4 weeks during protocol therapy; hematology, ECG, and PK were performed every 1 to 2 weeks for the first 8 weeks and then every 4 weeks. Toxicity was evaluated using National Cancer Institute Common Toxicity Criteria version 2.0. Response was assessed, using Response Evaluation Criteria in Solid Tumors[16] criteria at 4 weeks and then every 8 weeks thereafter until progression.

Treatment

Random assignment had to take place within 42 days of the last dose of chemotherapy, unless radiation was administered subsequently (random assignment required within 21 or fewer days of completion) and could not occur before recovery from toxicity. Patients were randomly assigned to receive vandetanib 300 mg/d orally or matched placebo. Doses were modified for toxicity (held for grade 3 or worse toxicity; resumed at reduced dose when grade 2 or better) or evidence of QT_C prolongation (held if single $\geq$ 550- or 100-ms increase compared with baseline; or confirmed $\geq$ 500-ms increase or 60- to 99-ms increase from baseline; dose reduced after recovery to $\leq$ 460 ms). Patients continued treatment until disease progression or unacceptable toxicity, or for a maximum of 2 years. Treatment was double blinded, and patients were unblinded only if essential for the management of toxicity.

QoL

The European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (QLQ-C30)[17] and lung cancer module (QLQ-LC13)[18] were completed before random assignment, at 4 weeks, and then every 8 weeks until disease progression. The EORTC QLQ-C30 is a self-administered cancer-specific questionnaire with multidimensional scale. It consists of five functional domains: physical, role, emotional, cognitive, and social; three symptom domains: fatigue, nausea and vomiting, and pain; six single-symptom items: dyspnea, sleep, appetite, constipation, and diarrhea; and a global assessment domain. The QLQ-LC13 lung cancer module assesses cough hemoptysis, dyspnea, sore mouth, dysphagia, peripheral neuropathy, alopecia, site-specific pain, and pain medication. For each functional domain and symptom item, a linear transformation is applied to standardize the raw score to the range from 0 to 100. All analyses were exploratory and included all randomly assigned patients who had at least one follow-up evaluation for QoL in addition to the baseline evaluation. No formal adjustment on *P* values was made for multiple tests.

Statistical Considerations

The primary end point of the study was progression-free survival (PFS). Secondary end points included overall survival (OS), toxicity, and QoL. The sample size was calculated on the basis of an estimated PFS of 4 months for placebo patients, assuming equal accrual of extensive- and limited-disease patients. To have an 80% chance of detecting a 2.5-month delay in median PFS in the treatment arm using a one-sided, 10%-level test, 77 events were required (an estimated 120 patients were needed). Because of the slower than expected accrual rate, the sample size was modified in March 2005 to 100 patients. No interim analysis was planned or conducted.

Random assignment was by a Web-based program that dynamically minimizes the chance of an imbalance in the two treatment arms within the following stratification factors: center, thoracic radiotherapy (early [before day 1 of cycle 4] *v* late *v* none), extent of disease at diagnosis (extensive *v* limited disease), and response to prior therapy (CR *v* PR).

Analysis of pretreatment characteristics, response rate, and all efficacy analyses included all randomly assigned patients, as assigned, irrespective of eligibility. Safety and drug exposure analyses were performed on all patients who received at least one dose of study medication (vandetanib/placebo), on the basis of the actual drug they received. Patients who completed a baseline evaluation and at least one evaluation during the trial were included in the QoL analyses. For efficacy analyses, all comparisons between treatment arms were carried out using a one-sided test at an α level of 10% or two-sided of 20% level unless otherwise specified. No formal adjustments were made for the multiplicity of inferences for multiple clinical end points. ECOG PS (0 *v* 1+2), sex (male *v* female), age ($<$ 60 *v* $\geq$ 60 years) and race (white *v* other), in addition to the described stratification factors, were used in adjusted analyses. PFS was calculated from the date of random assignment until the date of progressive

disease (PD) or death resulting from any cause occurred. For patients without documented PD, PFS was censored on the date salvage therapy began; or on the date of the last disease assessment. The log-rank test stratified by the stratification factors at random assignment was used to compare the difference in the PFS between the two treatment arms. Overall survival was calculated in months from the date of random assignment to the date of death, or excluded at the last day the patient was known alive on or before the data cutoff date.

Data management and statistical analyses were performed at National Cancer Institute of Canada–Clinical Trials Group central office in Kingston, Ontario, Canada.

RESULTS

The study was activated in May 2003 and closed to accrual in April 2006; the date of data cutoff was June 30, 2006. Median follow-up was 13.5 months.

Patient Characteristics

Among 107 randomly assigned patients, four were found ineligible (prior cardiac condition, progression before random assignment [n = 2], and untreated brain metastases). All 107 patients were included in the efficacy analyses, whereas 105 were included in the toxicity and exposure analyses (two patients did not receive study drug). Patient characteristics are summarized in Table 1. Vandetanib patients were less likely to have ECOG PS of 0, be age 60 years or older, have had late radiotherapy, and have had CR to prior therapy, but were more likely to have liver metastases. All patients had received chemotherapy, usually platinum and etoposide based. Two thirds of patients underwent prior radiation treatment. Seventy-three percent of patients had comorbid conditions such as cardiovascular and endocrine disease (data not shown).

Drug Administration

One patient in each arm did not receive any study treatment. The median duration of treatment for vandetanib patients was 7 weeks (range, 2 to 105 weeks) and for placebo was 12 weeks (range, 2 to 101 weeks). Although vandetanib patients were significantly more likely to have dose modifications for toxicity (GI, rash, and QT_C prolongation; $P = .002$); the majority of vandetanib patients (79%) received at least 80% of the planned dose.

Toxicity

Hospitalization rates were similar between the two arms. Hematologic effects were generally comparable between the two treatment

Table 1. Patient Characteristics

Characteristic	Vandetanib (n = 53)		Placebo (n = 54)		Total (N = 107)	
	No.	%	No.	%	No.	%
Sex						
Female	26	49.1	23	42.6	49	45.8
Male	27	50.9	31	57.4	58	54.2
ECOG PS						
0	11	20.8	20	37.0	31	29.0
1	37	69.8	29	53.7	66	61.7
2	5	9.4	5	9.3	10	9.3
Race/ethnicity						
Asian			2	3.7	2	1.9
Black	1	1.9			1	0.9
White	52	98.1	51	94.4	103	96.3
Other			1	1.9	1	0.9
Age, years						
Median	56.9		62.4		58.5	
< 60	34	64.2	22	40.7	56	52.3
≥ 60	19	35.8	32	59.3	51	47.7
Thoracic radiotherapy						
Late	3	5.7	8	14.8	11	10.3
Early	24	45.3	19	35.2	43	40.2
None	26	49.1	27	50.0	53	49.5
Extent of disease						
Extensive	30	56.6	31	57.4	61	57.0
Limited	23	43.4	23	42.6	46	43.0
Response to prior therapy						
CR	4	7.5	8	14.8	12	11.2
PR	49	92.5	46	85.2	95	88.8
Prior radiotherapy	35	66.0	36	66.7	71	66.4
Disease sites						
Bone	11	20.8	10	18.5	21	19.6
Brain	1	1.9	3	5.6	4	3.7
Liver	13	24.5	7	13.0	20	18.7
Lung	33	62.3	38	70.4	71	66.4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response.

arms, with 6% grade 3 or 4 neutropenia. Two patients receiving placebo underwent blood transfusion as supportive care. Biochemistry effects were mild; vandetanib patients were slightly more likely to have mild alkaline phosphatase and ALT rises.

Vandetanib patients tended to have more severe toxicity (grade 3, 4, and 5, 26 of 53 *v* nine of 52; $P = .1$), more QT_C prolongation (eight of 52 *v* zero of 53; $P = .003$), hypertension (21% *v* 9%), diarrhea (41 of 52 *v* 21 of 53; $P < .001$) and rash (37 of 52 *v* 26 of 53; $P < .001$), but were slightly less likely to have thromboembolism (2% *v* 6%) or hemoptysis and pneumonitis (4% *v* 8% each) compared with placebo patients (Table 2). There were no drug-related deaths reported.

PFS

At the time of the analysis, 83 patients had documented PD or had died; vandetanib patients were slightly less likely to have received chemotherapy (28% *v* 32%) and radiation (34% *v* 43%) after progression. As seen in Figure 1, there was no evidence of an advantage in PFS for vandetanib (vandetanib, 2.7 months [80% CI, 1.1 to 4.5 months]; placebo, 2.8 months [80% CI, 1.9 to 5.6 months]; hazard ratio [HR], 1.01; 80% CI, 0.75 to 1.36; one-sided $P = .51$). These results were supported by the stratified Cox regression model, performed adjusting for preselected factors: sex (male *v* female), age (< 60 *v* ≥ 60 years), and ECOG PS (0 *v* 1+); none were statistically significantly associated with PFS (data not shown). Proportional hazards models were used with interaction term to test whether treatment effects were homogeneous across the levels of each factor; the treatment effect was relatively better among female patients, younger patients (< 60 years), those with limited disease, and those with early radiotherapy (Table 3), although numbers in each group were small.

OS

A total of 59 deaths had occurred at the time of the analysis (Fig 2). There was no evidence of an advantage in OS for vandetanib (one-sided $P = .9$; vandetanib *v* placebo, 10.6 *v* 11.9 months; HR, 1.43; 80% CI, 1.00 to 2.05). The results from the unstratified log-rank test supported the conclusion (one-sided $P = .73$; estimated HR, 1.17; 80% CI, 0.70 to 1.96). Proportional hazards models were used with interaction term to test whether treatment effects were homogeneous across the levels of each factor; significant interactions were noted for extent of disease ($P = .01$) and timing of radiotherapy ($P < .001$; Table 4).

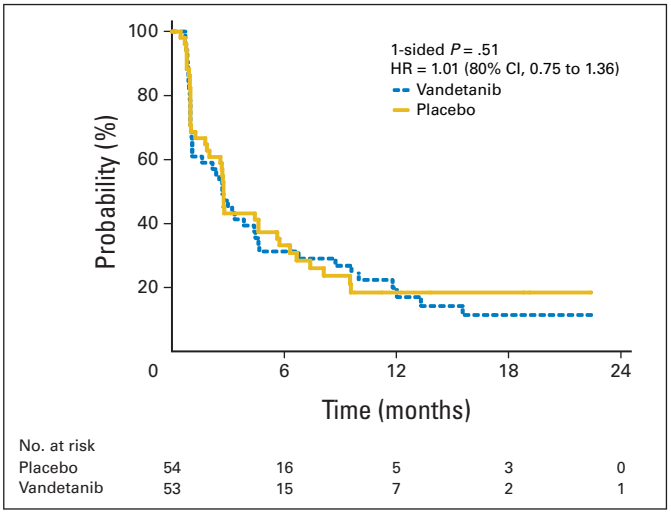

Fig 1. Progression-free survival. HR, hazard ratio.

QoL

The QoL analysis is based on responses from 98 of the 107 enrolled patients. Baseline QoL assessments were completed by more than 94%, but treatment compliance varied, ranging from 50% to 100%. However, no significant differences in compliance were seen between those on the vandetanib and placebo arms.

Vandetanib patients had worse QoL at baseline in terms of role functioning ($P = .09$), cough ($P = .04$), hemoptysis ($P = .08$), pain elsewhere ($P = .03$), and financial difficulties ($P = .02$), but other domains were comparable. During the trial, the QoL was comparable in all five functional domains between vandetanib and placebo patients. Vandetanib patients had better QoL symptom items in hemoptysis ($P = .13$) and pain elsewhere ($P = .12$), but inferior to placebo patients in diarrhea ($P = .01$) and sore mouth ($P = .05$).

Table 2. Reported Adverse Events Irrespective of Causality

Adverse Event	%			
	Vandetanib (n = 52)		Placebo (n = 53)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Neutropenia	23	6	17	6
Alkaline phosphatase	38	4	26	0
Bilirubin	7	4	2	0
ALT	48	10	15	4
Hypertension	21	2	9	2
Prolonged QT_C	15	0	0	0
Fatigue	79	14	85	9
Diarrhea	79	17	40	2
Nausea	56	2	55	0
Hemoptysis	4	0	8	0
Pneumonitis	4	2	8	0
Rash	71	4	49	4

Abbreviation: QT_C, corrected QT interval.

DISCUSSION

SCLC offers a unique opportunity to evaluate an angiogenesis inhibitor as maintenance therapy because a high proportion of patients respond to chemotherapy, yet most relapse shortly after discontinuing treatment, and the median survival, even for limited-stage patients, is less than 2 years. For three decades, trials of new chemotherapy regimens and drugs have failed to substantially[5] improve survival, and a platinum-based doublet, usually in combination with etoposide, remains the globally accepted standard of care.[4] To improve outcomes, numerous strategies have been tried, including dose intensification, bone marrow transplantation, maintenance therapy with both chemotherapy and other agents, and, more recently, trials of molecularly targeted agents[19,20] To date, none of these approaches has had a significant effect on survival, and several trials have shown considerable toxicity from the added therapy, sometimes accompanied by a statistically significant and clinically meaningful[13] negative impact on quality of life.

BR.20 is the first randomized controlled trial of a VEGF receptor tyrosine kinase inhibitor to be reported in SCLC. Disappointingly,

Table 3. PFS by Subsets

Subset	Vandetanib No.	Vandetanib Median PFS	Vandetanib 80% CI	Placebo No.	Placebo Median PFS	Placebo 80% CI	HR	80% CI	Interaction *P*
Thoracic Radiotherapy									.05
Early	24	9.99	6.77 to 12.0	19	5.13	2.76 to 8.11	0.7	0.4 to 1.1	
Late	3	1.08	0.99 to 4.40	86.8	6.67	2.79 to 7.39	6.8	2.1 to 22	
No radiation	26	1.03	0.99 to 1.61	27	1.00	0.99 to 2.00	1.3	0.9 to 1.9	
Extent of disease									.219
Limited	23	9.99	4.67 to 12.0	23	6.67	4.63 to 8.11	0.8	0.5 to 1.3	
Extensive	30	1.08	0.99 to 1.61	31	1.94	0.99 to 2.73	1.4	1.0 to 2.0	
Previous response									.386
CR	4	3.84	2.99 to ∞	8	NR	6.67 to ∞	3.2	0.9 to 12	
PR	49	2.69	1.08 to 3.35	46	2.69	1.87 to 2.76	0.9	0.7 to 1.2	
Sex									.154
Male	27	1.61	1.02 to 2.69	31	2.76	2.69 to 4.63	1.5	1.0 to 2.1	
Female	26	3.84	2.99 to 9.59	23	2.66	1.25 to 5.62	0.7	0.5 to 1.1	
Age group, years									.146
< 60	34	3.22	2.69 to 4.47	22	2.66	1.77 to 4.44	0.8	0.5 to 1.3	
≥ 60	19	1.05	0.99 to 2.37	32	2.76	2.69 to 5.75	1.5	1.0 to 2.3	
Race									.189
White	52	2.79	2.17 to 3.84	51	2.76	2.66 to 4.44	1.0	0.8 to 1.3	
Other	1	0.99	0 to ∞	3	NR	2.00 to ∞	5.6	0.0 to ∞	

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CR, complete response; NR, not reached; PR, partial response.

the study failed to show a benefit for adjuvant or maintenance treatment with vandetanib after achievement of maximal benefit with chemotherapy and radiation. However, significant interaction was seen with stage, with limited-stage patients showing a trend toward a benefit in overall survival, although at .07, the *P* value did not quite reach significance. Another interesting observation was the trend toward greater treatment effect in women for PFS, although, again, the difference was not significant. A similar trend was seen in a trial of vandetanib in NSCLC.[21] In contrast, however, in ECOC 4599, women with advanced NSCLC did not appear to derive an overall survival benefit from the addition of bevacizumab to paclitaxel/carboplatin, although they did have higher response rates and longer PFS.[9]

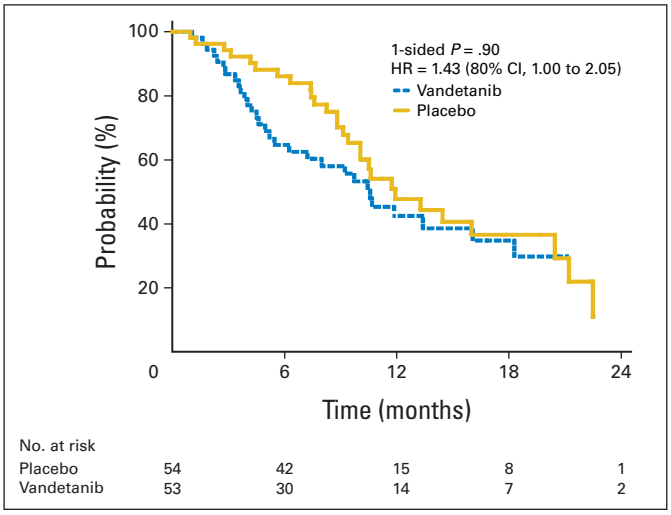

Fig 2. Overall survival. HR, hazard ratio.

Vandetanib targets both the EGF and the VEGF receptors, although it is thought that, at lower doses such as 100 mg, its activity is mainly directed against VEGFR. In NSCLC, it has been evaluated at doses of 300 and 100 mg/d with no evidence of greater activity at the higher dose. It is possible that if the 100-mg dose had been used in BR.20, the antiangiogenic effect of the drug might have been the same, yet vandetanib might have been better tolerated, thereby leading to fewer dose reductions and discontinuations.

Other studies of novel maintenance therapy have, for the most part, also had negative results in SCLC. In the National Cancer Institute of Canada–Clinical Trials Group and EORTC BR.12 trial of maintenance marimastat, there was no survival benefit for patients treated with MMPIs compared with placebo.[13] Furthermore, significant musculoskeletal toxicity required discontinuation of therapy in almost 20% of patients, and caused significant worsening of their QoL.

The interferons are a family of naturally occurring cytokines that have immunomodulatory, antiviral, and antiangiogenic properties. Four randomized trials have evaluated interferons as adjuvant therapy after response to chemotherapy in SCLC.[22-25] Overall, there was no increase in overall survival in the interferon-treated patients in any of the trials. In fact, in two of the trials, interferon treatment was associated with poorer survival, although a trend toward superior long-term survival was reported in two studies for patients with limited-stage disease who had achieved complete remission. This is of interest in view of the trend toward improved survival in limited-stage patients in our trial.

In contrast to the aforementioned studies, the results from a French Intergroup randomized phase III placebo-controlled trial of thalidomide provide some reason for optimism.[14] In patients with previously untreated extensive stage SCLC a statistically significant survival benefit was demonstrated in favor of thalidomide treatment. In this study, thalidomide was administered concurrently with

Table 4. OS by Subset

Subset	Vandetanib No.	Vandetanib Median OS	Vandetanib 80% CI	Placebo No.	Placebo Median OS	Placebo 80% CI	HR	80% CI	Interaction *P*
Thoracic radiotherapy									< .001
Early	24	NR	16.0 to ∞	19	16.0	11.9 to 21.2	0.4	0.2 to 0.8	
Late	3	2.40	1.84 to ∞	8	13.2	13.2 to ∞	2.5	0.0 to ∞.	
No radiation	26	4.96	4.24 to 7.23	27	10.0	8.80 to 10.6	2.3	1.5 to 3.6	
Extent of disease									.010
Limited	23	NR	0 to ∞	23	21.2	11.9 to 22.5	0.5	0.2 to 0.9	
Extensive	30	5.19	4.50 to 7.23	31	10.0	8.80 to 11.7	2.3	1.5 to 3.4	
Previous response									.444
CR	4	NR	3.84 to ∞	8	NR	0 to ∞	3.3	0.7 to 16	
PR	49	10.5	7.23 to 13.4	46	10.6	10.0 to 13.2	1.1	0.8 to 1.5	
Sex									.577
Male	27	9.72	4.96 to 11.8	31	10.6	9.40 to 13.2	1.5	1.0 to 2.4	
Female	26	16.0	9.23 to ∞	23	16.0	11.9 to 20.4	1.1	0.6 to 1.9	
Age group, years									.330
< 60	34	10.5	9.23 to 18.3	22	14.4	10.5 to 20.4	1.0	0.6 to 1.7	
≥ 60	19	7.23	3.55 to 13.4	32	10.6	10.0 to 21.2	1.7	1.0 to 2.7	
Race									.033
White	52	10.5	7.98 to 13.4	51	11.9	10.5 to 16.0	1.1	0.8 to 1.6	
Other	1	1.61	0 to ∞	3	NR	3.12 to ∞	5.6	0.0 to ∞	

Abbreviations: OS, overall survival; HR, hazard ratio; CR, complete response; NR, not reached; PR, partial response.

chemotherapy from cycle 2 to 4 in responding patients, and thereafter as maintenance therapy. We elected to administer vandetanib as single-agent maintenance therapy after completion of all first-line treatment. In view of the results of the French thalidomide trial, we question whether our results might have been better if vandetanib treatment had been administered concurrently with chemotherapy from the start of treatment. However, in limited-stage disease, where we saw our greatest treatment effect, phase I dose escalation trials would have to be performed to confirm the safety of triple therapy with chemotherapy, concurrent radiotherapy, and this angiogenesis inhibitor. The results of similar trials of thalidomide in both SCLC and NSCLC performed by the London Lung Cancer Group and those of bevacizumab and the tyrosine kinase inhibitors sorafenib and sunitinib in SCLC are awaited with great interest to determine the future role of angiogenesis inhibitors in the treatment of SCLC.

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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REFERENCES

1. Jemal A, Siegel R, Ward E, et al: Cancer Statistics, 2007. CA Cancer J Clin 57:43-66, 2007

2. National Cancer Institute of Canada. Canadian Cancer Statistics, 11-15, 2000

3. Schottenfeld D: Etiology and epidemiology of lung cancer, in Pass H, Mitchell J, Johnson D, et al (eds): Lung Cancer Principles and Practice (ed 2). Philadelphia, PA, Lippincott Williams & Wilkins, 2000

4. Ettinger D, Johnson B: Update: NCCN small cell and non-small cell lung cancer Clinical Practice Guidelines. J Natl Compr Cancer Net 3:S17-S21 (2005)

5. DeVore RF, Johnson DH: Chemotherapy for small cell lung cancer, in Pass H, Mitchell J, Johnson D, et al (eds): Lung Cancer Principles and Practice (ed 2). Philadelphia, PA, Lippincott Williams & Wilkins, 2000, pp 923-939

6. Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: Analysis of the Surveillance, Epidemiologic, and End Results database. J Clin Oncol 24:4539-4544, 2006

7. Logroño R, Jones DV, Faruqi S, et al: Recent advances in cell biology, diagnosis, and therapy of gastrointestinal stromal tumor (GIST). Cancer Biol Ther 3:251-258, 2004

8. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005

8a. Folkman J: Tumor angiogenesis: Therapeutic implications. N Engl J Med 285:1182-1186, 1971

9. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 355:2542-2550, 2006

10. Lucchi M, Mussi A, Fontanini G, et al: Small cell lung carcinoma (SCLC): The angiogenic phenomenon. Eur J Cardiothorac Surg 21:1105-1110, 2002

11. Michael M, Babic B, Khokha R, et al: Expression and prognostic significance of metalloproteinases and their tissue inhibitors in patients with small-cell lung cancer. J Clin Oncol 17:1802-1808, 1999

12. Ruotsalainen T, Joensuu H, Mattson K, et al: High pretreatment serum concentration of basic fibroblast growth factor is a predictor of poor prognosis in small cell lung cancer. Cancer Epidemiol Biomarkers Prev 11:1492-1495, 2002

13. Shepherd FA, Giaccone G, Seymour L, et al: Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: A trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer. J Clin Oncol 20:4434-4439, 2002

14. Pujol JL, Breton JL, Gervais R, et al: A prospective randomized phase III, double-blind, placebo-controlled study of thalidomide in extended-disease (ED) SCLC patients after response to chemotherapy (CT): An intergroup study FNCLCC Cleo04 - IFCT 00-01. J Clin Oncol 24:378s, 2006 (suppl; abstr 7057)

15. Kovacs MJ, Reece DE, Marcellus D, et al: A phase II study of ZD6474 (Zactima), a selective inhibitor of VEGFR and EGFR tyrosine kinase in patients with relapsed multiple myeloma: NCIC CTG IND.145. Invest New Drugs 24:529-535, 2006

16. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors (RECIST guidelines). J Natl Cancer Inst 92:205-216, 2000

17. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993

18. Bergman B, Aaronson NK, Ahmedzai S, et al: The EORTC QLQ-LC13: A modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 30A:635-642, 1994

19. Krug LM, Crapanzano JP, Azzoli CG, et al: Imatinib mesylate lacks activity in small cell lung carcinoma expressing c-kit protein: A phase II clinical trial. Cancer 103:2128-2131, 2005

20. Moore AM, Einhorn LH, Estes D, et al: Gefitinib in patients with chemo-sensitive and chemo-refractory relapsed small cell cancers: A Hoosier Oncology Group phase II trial. Lung Cancer 52:93-97, 2006

21. Heymach JV, Johnson BE, Prager D, et al. A phase II trial of ZD6474 plus docetaxel in patients with previously treated non-small cell lung cancer. J Clin Oncol 24:368s, 2006 (suppl; abstr 7016)

22. Mattson K, Niiranen A, Pyrhonen S, et al: Natural interferon alfa as maintenance therapy for small cell lung cancer. Eur J Cancer 28A:1387-1391, 1992

23. Lebeau B, Salmoniere PDL, Ozenne G, et al: Alpha Interferon as maintenance therapy for small cell lung cancer (SCLC). Proc Am Soc Clin Oncol 18:475a, 1999 (abstr 1832)

24. Kelly K, Crowley JJ, Bunn PA, et al: Role of recombinant interferon alfa-2a maintenance in patients with limited-stage small-cell lung cancer responding to concurrent chemoradiation: A Southwest Oncology Group study. J Clin Oncol 13:2924-2930, 1995

25. Jett JR, Maksymiuk AW, Su JQ, et al: Phase III trial of recombinant interferon gamma in complete responders with small-cell lung cancer. J Clin Oncol 12:2321-2326, 1994

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