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A Multicenter, Phase 2 Study of Vascular Endothelial Growth Factor Trap (Aflibercept) in Platinum- and Erlotinib-Resistant Adenocarcinoma of the Lung

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Introduction: Aflibercept (vascular endothelial growth factor [VEGF] trap), a recombinant fusion protein, blocks the activity of VEGF-A and placental growth factor and has demonstrated activity in pretreated patients with lung cancer in a phase I trial. This study evaluated the efficacy and safety of intravenous aflibercept in patients with platinum- and erlotinib-resistant lung adenocarcinoma.

Methods: An open-label, single arm, multicenter trial was conducted, with the primary end point of response rate (modified RECIST). Additional endpoints included safety, duration of response, progression-free survival, and overall survival. Patients with platinum- and erlotinib-resistant lung adenocarcinoma were eligible. Aflibercept 4.0 mg/kg intravenous every 2 weeks was administered until progression of disease or intolerable toxicity.

Results: Ninety-eight patients were enrolled; 89 were evaluable for response. Median age was 60 years, 41% were men with Eastern Cooperative Oncology Group performance status 0/1/2 in 35/55/9% of patients. The overall response rate was 2.0%, (95% confidence interval, 0.2–7.2%). Median progression-free survival was 2.7 months, and overall was survival 6.2 months. Six- and 12-month survival rates were 54 and 29%, respectively. A median of four cycles was administered (range 1–22). Common grade 3/4 toxicities included dyspnea (21%), hypertension (23%), and proteinuria (10%). Two cases of grade 5 hemoptysis were reported, and one case each of tracheoesophageal fistula, decreased cardiac ejection fraction, cerebral ischemia, and reversible posterior leukoencephalopathy.

Conclusions: Aflibercept has minor single agent activity in heavily pretreated lung adenocarcinoma, and is well tolerated, with no unexpected toxicities. Further studies evaluating aflibercept in lung cancer, in combination with chemotherapy and other targeted therapies, are ongoing.

Key Words: VEGF inhibitor, Angiogenesis, Adenocarcinoma.

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Aflibercept (vascular endothelial growth factor [VEGF] trap) is a recombinant fusion protein, consisting of human VEGF receptor 1 extracellular domain 2 and receptor 2 extracellular domain 3, fused to the hinge region of the human IgG1 Fc domain. Potential advantages of aflibercept over other VEGF inhibitors include its high VEGF-A binding affinity (approximately 1000-fold greater than bevacizumab), the ability to bind VEGF-B, as well as placental growth factors 1 and 2, and a longer half-life.[1] It is currently unknown whether these advantages will translate into clinical superiority over other VEGF inhibitors, such as bevacizumab. In a phase 1 trial of aflibercept administered subcutaneously, one durable partial response was seen in a heavily pretreated patient with adenocarcinoma with bronchoalveolar features.[2] Toxicities seen in phase I trials of subcutaneously and intravenously administered aflibercept include hypertension and proteinuria, similar to other VEGF inhibitors.[1–3]

VEGF-mediated signaling is important in the development and progression of lung cancer and has been shown to be prognostic.[4–11] In two large randomized trials of first-line chemotherapy in advanced non-small cell lung cancer (NSCLC), bevacizumab in combination with chemotherapy has been shown to improve outcome over chemotherapy alone, including improved survival in one trial.[12,13] In addition, a recently reported trial of second-line erlotinib, an

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epidermal growth factor tyrosine kinase inhibitor (EGFR TKI), plus bevacizumab or placebo demonstrated that the erlotinib/bevacizumab combination yielded superior response rates, and better progression-free survival (PFS), although overall survival (OS) was not improved in this trial.[14] As such, inhibition of VEGF-mediated signaling in NSCLC is the first targeted therapy that reproducibly improves outcomes, i.e. response, PFS, and even OS, when added to cytotoxic chemotherapy.

In this study, we examined the efficacy and safety of aflibercept as a single agent in previously treated, platinum- and erlotinib-resistant adenocarcinoma of the lung.

MATERIALS AND METHODS

This was an open-label, single arm, multicenter phase 2 trial using a two-stage Simon design. All participating centers had Institutional Review Board approval to conduct the study. All patients provided written informed consent to participate.

Study Population

Patients were eligible to participate if they had advanced or metastatic adenocarcinoma of the lung (to decrease theoretical risk of pulmonary hemorrhage); received at least two previous therapies for advanced disease; were platinum- and erlotinib-resistant, defined as disease relapse or progression during or after treatment, or drug intolerance; measurable disease by RECIST[15]; age 18 or older; Eastern Cooperative Oncology Group performance status 0–2; no toxicities related to previous therapy for National Cancer Institute Common Toxicity Criteria version 3.0 $>$ grade 1; adequate organ and bone marrow function, including a urine protein:creatinine ratio less than or equal to 1.

Patients were excluded for squamous cell histology, previous VEGF, or VEGF receptor-2 inhibitor therapy except bevacizumab, uncontrolled hypertension, significant comorbidities including thromboembolic events within 6 months, a history of brain or meningeal metastases, spinal cord compression, clinically significant hemoptysis or underlying coagulopathy, active human immunodeficiency virus infection, pregnancy or breast-feeding, or inability to provide informed consent.

Study Treatment

Patients were treated with intravenous (IV) aflibercept at a dose of 4.0 mg/kg administered over 1 hour by infusion pump every 14 days.

Dose reduction was permitted for uncontrolled grade 3 hypertension, proteinuria, and any drug-related toxicity that met criteria of a serious adverse event, or resulted in more than 2 weeks delay in study treatment. The first dose reduction was to 3.0 mg/kg and the second to 2.0 mg/kg every 2 weeks. Patients requiring more than two dose reductions were removed from study.

Primary and Secondary Endpoints

The primary end point of the study was to determine the objective response rate of aflibercept 4.0 mg/kg IV every 2 weeks using modified RECIST. RECIST[15] was modified to subtract the longest cavitation diameters from the longest unidimensional measurements of the cavitated target lesions. All responses were to be confirmed in 4 to 6 weeks. Secondary objectives include assessment of the duration of response, PFS, OS, and safety.

Evaluations on Therapy

At baseline, patients were evaluated with history and physical examination, blood work including hematology and biochemistry, urinalysis for proteinuria, and computed tomography, or magnetic resonance imaging of the brain, chest, abdomen, and pelvis. These were repeated every 2 weeks except radiologic imaging which was repeated every 4 weeks or two cycles.

Statistical Considerations

A Simon two-stage design was used to test the null hypothesis that the true response rate was less than or equal to 5% versus the alternative hypothesis that the true response rate was more than or equal to 15%, with a one-sided alpha level of 0.05 and 90% power. If more than or equal to three objective responses were seen in the first 37 patients evaluated, an additional 47 evaluable patients were to be accrued. If fewer responses were seen, the trial was to be terminated unless data analysis suggested that further exploration was warranted. The null hypothesis would be rejected if more than or equal to eight responses were seen in the 84 evaluable patients.

Descriptive statistics were used to summarize safety and efficacy outcomes along with 95% confidence intervals (CI) where possible. The Kaplan-Meier method was used to estimate PFS and OS statistics. OS was calculated from the date of registration until the date of death or last date the patient was known to be alive. PFS was calculated from the date of registration until the first date of progression or death. Patients who were removed from treatment due to reasons other than progression or death were censored for these time-to-event analyses.

Exploratory analyses were performed to assess the association between hypertension on therapy (none, grade 1/2, and grade 3) and outcome (PFS and OS).

RESULTS

Ninty-eight patients from 35 institutions in Canada, France, and the United States were enrolled between February 2006 and August 2007. Two patients did not receive study drug, 89 were evaluable for efficacy, and 96 were included in the safety analysis. Patient characteristics including prior treatment details are listed in Table 1. Most patients were good performance status (91% Eastern Cooperative Oncology Group 0 or 1), and 69% had received at least three previous lines of therapy. Twenty patients had received previous bevacizumab. The median time from initial diagnosis for the cohort was 2.4 years (range 0.5–11.4 years), and the median time from last treatment or relapse until study entry was 1 month, with 91% of patients enrolling within 3 months. Based on observed responses and information about stable disease, the Independent Data Monitoring Committee recommended continued accrual into the second stage.

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Response Rates

The overall response rate by intent-to-treat analysis was 2.0%, (95% CI, 0.2–7.2%), using traditional and modified RECIST by investigator assessment, both partial responses. After accrual to stage 1, the data safety monitoring committee recommended that expansion to stage 2 was warranted, based on the rate and duration of stable disease observed in this heavily pretreated population. Sixty-seven percent of patients had stable disease at their first evaluation (30 days). A number of patients had prolonged disease stabilization and a waterfall plot reflecting the best percentage reduction from baseline using independent radiology assessment of modified RECIST measurements is shown in Figure 1.

TABLE 1. Patient Demographics

Characteristic	$N = 98$
Age (yr)	
Median (range)	60 (24–79)
Gender (%)	
Female/male	59/41
Performance status (%)	
0	35
1	55
2	9
Smoking status (%)	
Current smoker	11
Never smoker	21
Former smoker	67
Previous therapies (%)	
Platinum	99
Erlotinib or other EGFR inhibitor	97
Bevacizumab	20
Two previous lines	29
Three previous lines	31
≥4 previous lines	38
Other chemotherapy agents (%)	
Taxane	86
Gemcitabine	54
Pemetrexed	43
Vinorelbine	30
Etoposide	8
Previous surgery (%)	50
Previous radiation therapy (%)	49

PFS and OS

The median time to progression was 2.7 months (95% CI, 2.2–3.4 months), with 18% of patients progression free at 6 months (by investigator assessment using RECIST, shown in Figure 2). Median survival was 6.2 months (95% CI, 4.8–11.4 months) with 54% of patients alive at 6 months and 29% at 1 year (Figure 3). There was a trend for better OS in patients who developed grade 3 hypertension on aflibercept ($n = 22$) versus those who did not develop hypertension ($n = 60$).

Dose Delivery

The median number of cycles administered was four (range 1–22) with a median duration of exposure of 9 weeks (2–60 weeks). Median cumulative dose was 16 mg/kg (range 4–87) with a mean relative dose intensity of 93%, (standard deviation, 0.11). Twenty-three patients experienced one dose delay and 15 were delayed for more than one cycle. Only 11 patients required dose reduction.

Safety

The most common grades 3 and 4 toxicities seen included proteinuria, hypertension, and dyspnea. Other common toxicities included fatigue, headache, arthralgia, muscu-

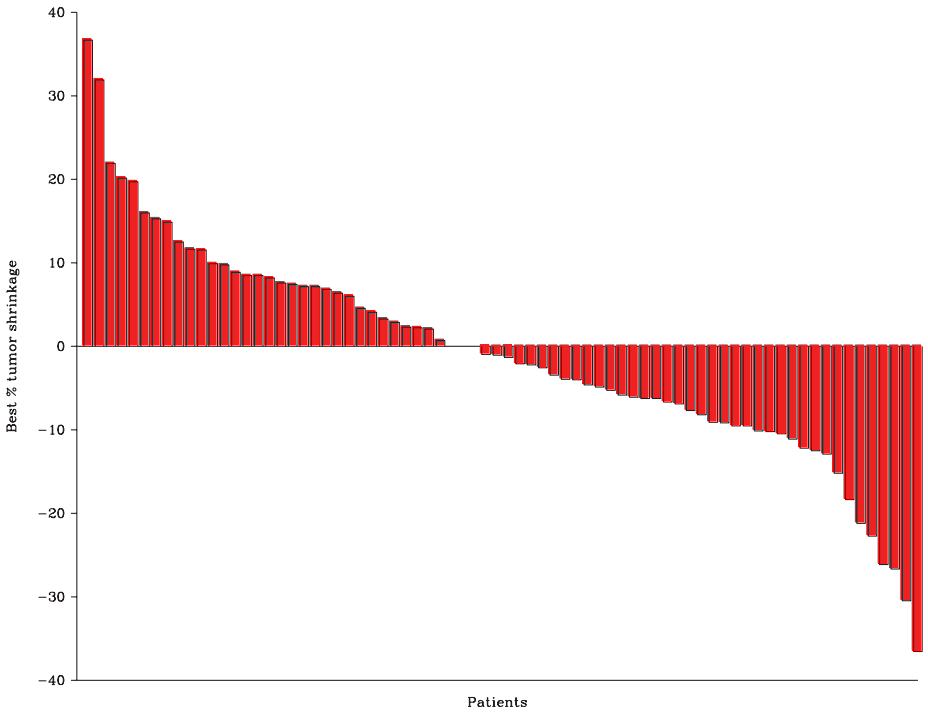

FIGURE 1. Tumor burden by waterfall plot. Best reduction as percent change from baseline using modified RECIST per independent radiology measurements.

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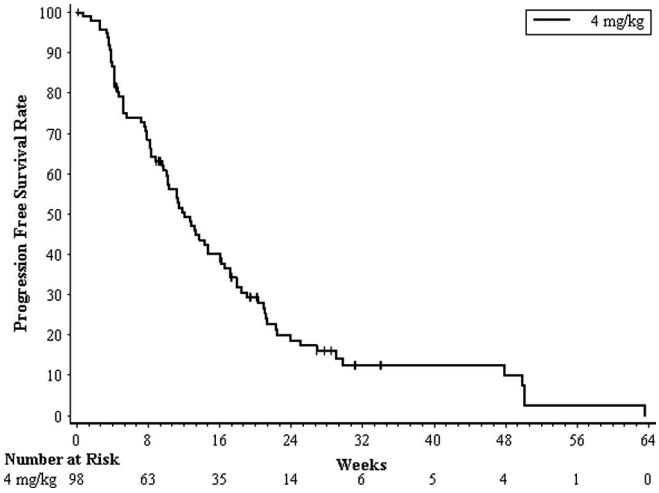

FIGURE 2. Progression-free survival ($N = 98$). Median progression-free survival 2.7 months; 6-month progression-free survival rate 18%.

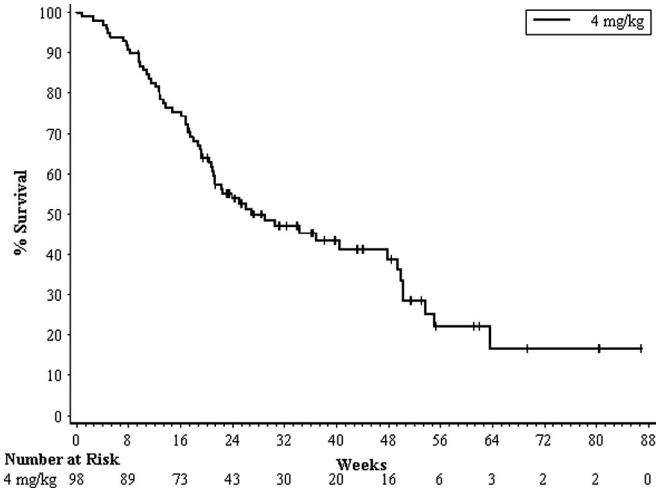

FIGURE 3. Overall survival ($N = 98$). Median survival 6.2 months; 6-month survival 54%; 12-month survival 29%.

loskeletal pain, dysphonia, epistaxis, and low-grade hemoptysis (Table 2). There were two treatment-related fatal adverse events on study, both grade 5 hemoptysis. A 64-year-old man developed nonmalignant bronchial ulcerative lesions seen on bronchoscopy after 20 cycles of aflibercept, and subsequent fatal hemoptysis 17 days postbronchoscopy, 30 days after his last treatment. A 61-year-old woman, previously treated with five lines of systemic therapy and radiotherapy, developed grade 5 hemoptysis at home on day 5 after cycle 8 of aflibercept. She had been evaluated with laryngoscopy the day before for increasing cough and hoarseness, with no abnormalities seen in the upper airway. Other serious adverse events deemed related to aflibercept included one case each of acquired tracheoesophageal fistula (cycle 2 and day 36), decreased left ventricular ejection fraction (35% after cycle 2), cerebral ischemia (cycle 4 and day 9), and reversible posterior leukoencephalopathy syndrome

TABLE 2. Treatment Emergent Adverse Events (≥10%) ($N = 96$)

Adverse Event	Any Grade (% Patients)	Grade ≥3 (%)
Fatigue	42	7
Hypertension	40	23
Dyspnea	40	21
Headache	39	4
Constipation	28	1
Dysphonia	28	0
Anorexia	25	3
Nausea	23	2
Cough	23	2
Epistaxis	21	1
Peripheral edema	21	1
Asthenia	17	3
Proteinuria	16	10
Vomiting	16	0
Arthralgia	15	0
Musculoskeletal pain	12	1
Diarrhea	12	2
Fever	12	0
Urinary tract infection	12	1
Hemoptysis	13	2[a]
CNS disorders[b]	2	2

[a] Both grade 5.
[b] One case of cerebral ischemia, one reversible posterior leukoencephalopathy.
CNS, central nervous system.

(cycle 1, day 14). The most common reason for study discontinuation was progressive disease (53%), followed by adverse events (20%). No patient stopped therapy for uncontrolled hypertension.

DISCUSSION

Aflibercept administered every 2 weeks at a dose of 4 mg/kg demonstrated minor single agent activity with evidence of disease stabilization in a heavily pretreated population of lung adenocarcinoma patients, who had received both platinum-based and EGFR inhibitor therapy. Aflibercept was well tolerated, with no unexpected toxicities. However, despite careful restrictions on eligibility to include only adenocarcinoma patients, and those without significant hemoptysis, the rate of fatal hemoptysis was 2%, consistent with what has been seen in other trials with bevacizumab and sunitinib.[12,13,16]

Although the overall response rate was disappointing, a substantial number of patients experienced at least some tumor regression, as shown in Figure 1. This is despite its use as a single agent in a heavily pretreated study population, with 70% of patients having received 3 or more lines of systemic therapy for advanced NSCLC. In addition, response is likely a suboptimal end point to measure activity of VEGF inhibitors, given the expectation that most of their effect as single agents would be cytostatic in nature. The frequency cavitation of tumor lesions on VEGF inhibitors rather than unidimensional tumor reduction also complicates the use of

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tumor response as a reliable marker of promising activity. However, in a review undertaken by the NCIC Clinical Trials Group of patients treated with VEGF inhibitors, use of modified
RECIST did not impact substantially on overall response rates determined using classic RECIST.[17] Alternate methods of measurement, such as volumetric computed tomography imaging[18] or functional imaging, may provide better endpoints to screen for activity with this class of agents, along with time to progression. The 6-month PFS rate of 18% and 6- and 12-month survival rates of 54% and 29%, respectively, are clearly promising in such a heavily pretreated population, although patient selection is a potential confounder.

Currently, there are also no data supporting single agent activity of bevacizumab in advanced NSCLC, despite the fact that bevacizumab has been shown to improve outcomes when added to first-line platinum-based chemotherapy.[12,13,19] In contrast, several VEGF tyrosine kinase inhibitors have demonstrated single agent activity in less heavily pretreated NSCLC patients, with response rates ranging from 7 to 10% with sunitinib, axitinib, vatalanib, and vandetanib and median time to progression from 2.4 to 5.8 months in phase II studies.[16,20–22] Sorafenib, another multitargeted tyrosine kinase inhibitor,[23,24] did not induce responses as a single agent in pretreated NSCLC nor has it been shown to add to first-line chemotherapy.[25] It remains unclear whether there may be potential differences in activity and tumor penetration between the small molecule VEGF tyrosine kinase inhibitors compared with larger molecules such as aflibercept and bevacizumab. Despite the low response rate in this study, PFS in this extensively pretreated patient sample was comparable to other VEGF inhibitor studies in advanced NSCLC.

Further questions remain regarding the incorporation of molecular markers to select patients who may benefit most from VEGF inhibitor therapy. At the present time, patient selection remains driven by perceived safety concerns. To decrease the risk of severe pulmonary hemorrhage, several trials of VEGF inhibitors have excluded patients with squamous cell histology, proximal lung tumors with central cavitation or those with significant hemoptysis at baseline, including the current trial.[12,13,18,26] Thus, to understand the potential activity of aflibercept in squamous cell histology, separate studies would need to be conducted in that population, recognizing the potential for incremental toxicity. There are several molecular markers of interest, but none has yet demonstrated ability to predict significant benefit from VEGF inhibitor therapy. These include baseline plasma VEGF levels, associated with greater response but not OS, and low ICAM-1 levels associated with better PFS in bevacizumab-treated patients in the E4599 randomized trial.[27] Hanrahan et al.[28] have demonstrated in studies of vandetanib that low baseline VEGF levels in advanced NSCLC may predict for better PFS with vandetanib versus gefitinib or docetaxel. Also treatment with VEGF inhibitors may lead to different patterns of cytokine and angiogenic factors than chemotherapy treatment, that may correlate with outcome and potentially be useful in the future as predictive markers of treatment resistance and/or benefit.[29,30]

Functional single nucleotide polymorphisms of VEGF are also of interest. Variant alleles of +936C>T and +405G>C single nucleotide polymorphisms have been associated with lower plasma VEGF levels and survival in patients with resected early stage NSCLC.[31] VEGF genotypes (VEGF-2578AA, VEGF-1154) may be associated with better survival in bevacizumab-treated patients as well as differential rates of hypertension, seen in the E2100 randomized trial of paclitaxel ± bevacizumab in advanced breast cancer.[32] The development of hypertension during VEGF inhibitor therapy has been associated with improved outcomes, including better survival.[33–36] This study also demonstrates a trend to better survival in those who developed grade 3 hypertension on treatment, although not statistically significant given the small numbers in the trial. These areas are worthy of further study, to help better define their potential role in predicting benefit and toxicity from VEGF inhibitor therapy.

Combinations of VEGF inhibitors with other targeted agents remain promising, including improved PFS in a study of second-line erlotinib plus bevacizumab compared with erlotinib alone.[14] Aflibercept is currently under development in other tumor types including colorectal, pancreas, prostate and ovarian cancers, where activity has been seen. In NSCLC, a phase III randomized trial, VITAL, that compares second-line docetaxel plus aflibercept or placebo, is ongoing. This trial may help to define the utility of aflibercept (and ongoing VEGF inhibition) in patients who have previously been treated with bevacizumab and first-line chemotherapy.

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