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Clinical Trial Results

Randomized Phase II Trial of Parsatuzumab (Anti-EGFL7) or Placebo in Combination with Carboplatin, Paclitaxel, and Bevacizumab for First-Line Nonsquamous Non-Small Cell Lung Cancer

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01366131
- **Sponsor(s)**: Genentech, Inc.
- **Principal Investigator**: Martin Reck
- **IRB Approved**: Yes

Lessons Learned

- The lack of efficacy associated with anti-EGFL7 combined with standard bevacizumab and chemotherapy in this phase II trial in non-small cell lung carcinoma is consistent with the lack of benefit observed in colorectal carcinoma, highlighting the challenge of enhancing the efficacy of VEGF inhibition in unselected populations.
- Future efforts with agents like anti-EGFL7 should be guided by advances in pharmacodynamic and predictive biomarker development for antiangiogenic agents.

Abstract

Background. Epidermal growth factor-like domain 7 (EGFL7) is an extracellular matrix-associated protein that is upregulated during angiogenesis and supports endothelial cell survival. This phase II trial evaluated the efficacy of the anti-EGFL7 antibody, parsatuzumab, in combination with bevacizumab plus platinum-based therapy for advanced or recurrent nonsquamous non-small cell lung cancer (NS-NSCLC).

Methods. Patients ($n = 104$) were randomized to either placebo or parsatuzumab (600 mg) in combination with bevacizumab (15 mg/kg) and carboplatin/paclitaxel, administered on day 1 of each 21-day cycle. Carboplatin and paclitaxel were administered for up to six cycles. Bevacizumab and parsatuzumab/placebo were administered for a maximum of 24 months.

Results. The progression-free survival (PFS) hazard ratio (HR) was 1.7 (95% confidence interval [CI], 1.0–2.8; $p = .047$). The median PFS was 6.7 months for the parsatuzumab arm versus 8.1 months for the placebo arm. The hazard ratio for overall survival (OS) was 1.1 (95% CI, 0.5–2.2; $p = .847$). The objective response rate (ORR) was 29% in the parsatuzumab arm and 56% in the placebo arm. Overall safety and tolerability were consistent with the established toxicity profile of bevacizumab.

Conclusion. There was no evidence of efficacy for the addition of parsatuzumab to the combination of bevacizumab and chemotherapy for first-line NS-NSCLC. ***The Oncologist*** 2018;23:654–e58

Discussion

EGFL7 is a tumor-enriched, vascular-restricted extracellular matrix protein that promotes endothelial cell adhesion and survival [1]. In murine tumor models, the combination of an anti-EGFL7 antibody and anti-VEGF enhanced the antiangiogenesis and survival prolongation associated with anti-VEGF monotherapy [2]. Parsatuzumab (MEGF0444A) is a humanized anti-EGFL7 IgG1 monoclonal antibody that selectively blocks the interaction between EGFL7 and endothelial cells. Based on the safety profile and evidence of pharmacodynamic modulation observed in a phase Ib trial of parsatuzumab in combination with bevacizumab with or without paclitaxel [2, 3], parsatuzumab was advanced to two phase II trials, one in colorectal cancer (CRC) [4] and another the current study in NS-NSCLC, respectively.

The primary objective of this study was to evaluate the efficacy of parsatuzumab in combination with standard

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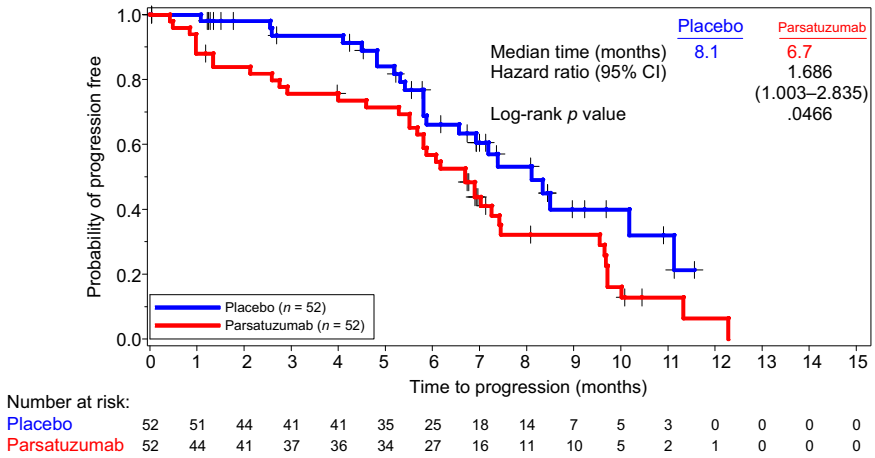

Figure 1. Kaplan-Meier estimates of progression-free survival. Note: + = censored value.

Abbreviations: CI, confidence interval; parsatuzumab, paclitaxel + carboplatin + bevacizumab + MEGF0444A; placebo, paclitaxel + carboplatin + bevacizumab.

carboplatin, paclitaxel, and bevacizumab in patients with advanced or recurrent NS-NSCLC, as measured by PFS. At the primary analysis, the PFS HR was 1.7 (95% CI, 1.0–2.8; $p = .047$), with median PFS of 6.7 months for the parsatuzumab arm versus 8.1 months for the control arm. Likewise, secondary outcome measures showed no evidence of benefit: the ORR was 29% in the parsatuzumab arm and 56% in the placebo arm, and the immature HR for OS was 1.1 (95% CI, 0.5–2.2; $p = .847$). These results reinforce the overall lack of efficacy observed with parsatuzumab in a phase II trial in combination with chemotherapy consisting of folinic acid, 5-FU, and oxaliplatin, known as modified FOLFOX6 or mFOLFOX6, plus bevacizumab in CRC (HR for PFS and OS, 1.17 and 0.97, respectively) [4].

Although the overall rate of adverse events (AEs) and serious adverse events (SAEs) was similar in the two study arms, a numerical imbalance in grade ≥3 bleeding AEs was observed (four events, including two fatal events, in the parsatuzumab arm versus no events in the placebo arm). Nevertheless, fatal hemorrhage is an established safety signal for bevacizumab in this population, and there was no apparent exacerbation of any other bevacizumab-related AEs in patients receiving parsatuzumab. Thus, given that the CRC trial [4] did not demonstrate an increased risk of bleeding associated with parsatuzumab, it appears unlikely that the numerical imbalance observed in this trial is reflective of a significant difference in toxicity.

The experience with parsatuzumab illustrates the challenge of improving outcomes with standard bevacizumab and chemotherapy regimens through enhanced antiangiogenesis in unselected populations. Unfortunately, robust predictive biomarkers for bevacizumab in NSCLC patients remain elusive despite intensive efforts. Because archival tissue submission was optional for this small trial, retrospective interrogation of biomarker-based subgroups was of limited utility. New mechanistic insights and biomarker hypotheses are likely required to guide future development of antiangiogenic combinations.

Trial Information	
Disease	Lung cancer—NSCLC
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Randomized
Primary Endpoint	Progression-free survival
Secondary Endpoint	Safety

Additional Details of Endpoints or Study DesignPatients

Patients with histologically or cytologically documented inoperable (stage IV) or recurrent nonsquamous NSCLC and measurable disease as defined by RECIST, version 1.1, who had not been previously treated for stage IV or recurrent NSCLC were eligible for participation in this study. Other inclusion criteria included an age of at least 18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and adequate hematologic, hepatic, and renal function (including urine dipstick for proteinuria <2+ or measured urinary excretion of no more than 1 g of protein per 24 hours). Exclusion criteria included any prior systemic therapy for NSCLC (patients with disease progression >12 months after completion of adjuvant chemotherapy or radiotherapy were not excluded), malignancies other than NSCLC within 5 years, radiotherapy to thorax with curative intent within 28 days before initiation of study treatment, clinically detectable third-space fluid collections, clinically suspected or confirmed central nervous system metastases or carcinomatous meningitis, and contraindications to the use of bevacizumab (such as history of grade ≥2 hemoptysis within 3 months, evidence of tumor invading major blood vessels on imaging, inadequately controlled hypertension, New York Heart Association class II or greater congestive heart coagulopathy, current use of antiplatelet agents or full-dose anticoagulants, major surgical procedure within 28 days, or history of gastrointestinal perforation). In Germany, patients with tumors that harbor an activating mutation in the epidermal growth factor receptor gene were also excluded based on a Health Authority request.

Study Design
This was a phase II, multicenter, randomized, double-blind, placebo-controlled trial conducted at 27 clinical study sites in the U.S., France, Germany, Hungary, Czech Republic, Poland, and Australia. Eligible patients were randomly assigned 1:1 to receive paclitaxel (200 mg/m^2), carboplatin (area under curve [AUC] of 6 mg • min/ml (Calvert formula), bevacizumab 15 mg/kg, and placebo or paclitaxel/carboplatin/bevacizumab (as above) and parsatuzumab 400 mg intravenous (IV) on day 1 of each 21-day cycle. Randomization was stratified by ECOG performance status (0 vs. 1), number of gender (male vs. female), and prior adjuvant chemotherapy (yes vs. no). Chemotherapy was continued until disease progression or unacceptable toxicity or for a maximum of six cycles, and bevacizumab and parsatuzumab/placebo were continued until disease progression or unacceptable toxicity for a maximum of 24 months. Patients who otherwise qualified for continued treatment but experienced unacceptable toxicity attributed to a specific component of the assigned regimen could selectively discontinue one or more agents, with the stipulation that bevacizumab and parsatuzumab/placebo should be held or given together according to standard bevacizumab hold and discontinuation criteria. Crossover at the time of disease progression was not permitted.

Assessments
Tumor assessments were performed at baseline and every two cycles (6 weeks) after study treatment initiation. Tumor response was assessed by the investigator according to RECIST version 1.1. Responses required confirmation at least 4 weeks after they were first noted. All patients were followed for survival and subsequent anticancer therapy approximately every 3 months until death, loss to follow-up, or study termination. Safety was assessed on the basis of reports of adverse events, laboratory test results, and vital signs. Adverse events were categorized according to the Common Toxicity Criteria of the National Cancer Institute, version 4.0. All adverse events and SAEs, regardless of attribution, were collected until 90 days following the last administration of study treatment or initiation of other anticancer therapy, whichever occurred first. After this period, investigators were instructed to report only SAEs felt to be related to prior study treatment. All deaths occurring within 90 days following the last administration of study treatment, regardless of cause, were reported as SAEs. Protocol-specified adverse events of special interest included any grade 3 bleeding event; symptomatic congestive heart failure; bleeding events associated with thrombocytopenia that require a blood transfusion; grade 2 pulmonary hemorrhage; grade 2 intracranial hemorrhage or spinal cord hemorrhage; wound dehiscence requiring medical or surgical intervention; and any of the following adverse events of any grade: arterial thromboembolic event, gastrointestinal perforation, tracheoesophageal fistula, and reversible posterior leukoencephalopathy syndrome. Immunogenicity and pharmacokinetics were assessed as previously described [4]. Submission or archival tumor tissue was optional, and 49 of 104 patients submitted tissue that was adequate for gene expression analysis, which was performed as previously described [4].

Statistical Analysis
Efficacy analyses included all randomly assigned patients and were based on the treatment arm to which patients were allocated. The primary efficacy outcome measure was PFS (defined as the time from randomization to the first occurrence of progression based on RECIST version 1.1 or death from any cause on study) as determined by the investigator. Death on study was defined as death from any cause within 30 days of the last study treatment. Data for patients without disease progression or death on study were censored at the time of the last tumor assessment (or, if no tumor assessments were performed after the baseline visit, at the time of randomization plus 1 day). Secondary efficacy outcome measures included objective response (confirmed partial response plus complete response), duration of response, and overall survival. Safety analyses included all patients who received any amount of study treatment (carboplatin, paclitaxel, bevacizumab, or parsatuzumab/placebo). The study was intended to enroll approximately 100 patients, and the primary analysis was to be performed after approximately 60 investigator-assessed PFS events. The final data cutoff (February 1, 2013) reflected 62 PFS events.

The emphasis of the efficacy analyses was on estimation of the magnitude of the treatment effect rather than hypothesis testing. Based on the sample size of 60 events observed in the two treatment arms combined, the 95% confidence interval around the estimated HR will be (0.60 $\times$ HR, 1.66 $\times$ HR) using Schoenfeld's approximation [5]. Thus, the 95% confidence interval around an encouraging hazard ratio of 0.7 would be (0.42, 1.16). This trial is hypothesis-generating and is only able to detect a relatively large benefit of combination therapy with paclitaxel, carboplatin, bevacizumab, and MEGF0444A. For example, with 60 events in the two treatment arms combined, there is 80% power to detect an HR = 0.48 at a one-sided significance level of 0.025.

Changes in Study Conduct or Planned Analyses
The protocol was amended on September 17, 2012, to include new data from ad hoc unblinded safety analyses of Study MEF4984g (this study) and Study MEF4982g [4] that were triggered by the report of two fatal hemorrhage events in this study. Study conduct modifications resulting from these analyses were (a) any grade $\geq$3 bleeding AE was to be reported in an expedited fashion as a protocol-defined AE of special interest; (b) concomitant use of nonsteroidal anti-inflammatory drugs while receiving study treatment was discouraged; and (c) if concomitant administration of full-dose anticoagulation was required on study, parsatuzumab/placebo was to be permanently discontinued. After the protocol-specified primary analysis, the sponsor decided to terminate the study given the clear lack of benefit associated with parsatuzumab in patients with NSCLC. Accordingly, analyses intended to support certain secondary and exploratory objectives were not performed: Descriptive statistics, plots, and pharmacokinetic parameters were not derived. Global Health Status/Quality of Life data were not analyzed.

Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information for Phase II Control

Drug 1	
Generic/Working Name	Placebo
Drug Type	Other
Drug Class	Other
Dose	600 mg per flat dose
Route	IV
Drug 2	
Generic/Working Name	Bevacizumab
Company Name	Genentech/Roche
Drug Type	Antibody

Drug Class	Angiogenesis—antivascular
Dose	15 mg/kg
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of 24 months (34 cycles)
Drug 3	
Generic/Working Name	Paclitaxel
Drug Type	Small molecule
Drug Class	Microtubule-targeting agent
Dose	200 mg/m^2
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of six cycles.
Drug 4	
Generic/Working Name	Carboplatin
Drug Type	Small molecule
Drug Class	Platinum compound
Dose	AUC of 6 mg • min/ml (Calvert formula)
Route	IV
Schedule of Administration	Dose: AUC of 6 mg • min/ml (Calvert formula); schedule of administration: every 21 days until disease progression or unacceptable toxicity for a maximum of six cycles

Drug Information for Phase II Experimental	
Drug 1	
Generic/Working Name	Parsatuzumab (MEGF0444A)
Company Name	Genentech/Roche
Drug Type	Antibody
Drug Class	Angiogenesis—antivascular
Dose	600 mg per flat dose
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of 24 months (34 cycles)
Drug 2	
Generic/Working Name	Bevacizumab
Company Name	Genentech/Roche
Drug Type	Antibody
Drug Class	Angiogenesis—antivascular
Dose	15 mg/kg
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of 24 months (34 cycles)
Drug 3	
Generic/Working Name	Paclitaxel
Company Name	EBEWE Pharma
Drug Type	Small molecule
Drug Class	Microtubule-targeting agent
Dose	200 mg/m^2
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of six cycles
Drug 4	
Generic/Working Name	Carboplatin

Company Name	EBEWE Pharma
Drug Type	Small molecule
Drug Class	Platinum compound
Dose	6 mg per
Route	IV
Schedule of Administration	Every 21 days until disease progression or unacceptable toxicity for a maximum of six cycles

Patient Characteristics for Phase II Both Arms	
Number of Patients, Male	67
Number of Patients, Female	37
Stage	Locally advanced or inoperable: 5
	Metastatic: 98
Age	Median (range): 63.5 (37–82)
Number of prior systemic therapies	Median (range): No prior therapies: *n* = 100 (96.2%); Patients with prior therapies: *n* = 4 (3.8%)
Performance Status: ECOG	0 — 51 (49.0%)
	1 — 53 (51.0%)
	2 —
	3 —
	Unknown —

Primary Assessment Method for Phase II Control	
Title	Total patient population
Number of Patients Enrolled	52
Number of Patients Evaluable for Toxicity	51
Number of Patients Evaluated for Efficacy	52
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 29 (56%)
(Median) Duration Assessments PFS	8.1 months, CI: 5.88–11.14
(Median) Duration Assessments Duration of Treatment	5.3 months

Primary Assessment Method for Phase II Experimental	
Title	Total patient population
Number of Patients Enrolled	52
Number of Patients Evaluable for Toxicity	52
Number of Patients Evaluated for Efficacy	52
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (1.9%)
Response Assessment PR	*n* = 14 (26.9%)
(Median) Duration Assessments PFS	6.7 months, CI: 5.68–7.43
(Median) Duration Assessments Duration of Treatment	5.4 months

Phase II Control Adverse Events

	All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Blood and lymphatic system disorders—Neutropenia	50%	2%	6%	22%	20%	0%	50%
Nausea	50%	22%	20%	8%	0%	0%	50%

Alopecia	57%	6%	37%	0%	0%	0%	43%
Blood and lymphatic system disorders—Thrombocytopenia	60%	12%	14%	10%	4%	0%	40%
Fatigue	64%	12%	18%	6%	0%	0%	36%
General disorders and administration site conditions—Asthenia	64%	16%	14%	6%	0%	0%	36%
Blood and lymphatic system disorders—Anemia	66%	2%	22%	10%	0%	0%	34%
Constipation	66%	16%	18%	0%	0%	0%	34%
Anorexia	66%	18%	16%	0%	0%	0%	34%
Diarrhea	68%	16%	12%	4%	0%	0%	32%
Nervous system disorders—Neuropathy peripheral	68%	14%	16%	2%	0%	0%	32%
Dyspnea	72%	8%	16%	4%	0%	0%	28%
Arthralgia	74%	12%	10%	4%	0%	0%	26%
Hypertension	74%	0%	8%	18%	0%	0%	26%
Insomnia	76%	10%	14%	0%	0%	0%	24%
Epistaxis	76%	22%	2%	0%	0%	0%	24%
Vomiting	78%	14%	2%	4%	2%	0%	22%
Myalgia	78%	14%	8%	0%	0%	0%	22%
Dysgeusia	78%	14%	8%	0%	0%	0%	22%

Adverse events regardless of relationship to study drug in >10 safety-evaluable patients, placebo arm ($n = 51$).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Phase II Experimental Adverse Events

	All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Fatigue	52%	17%	25%	6%	0%	0%	48%
Alopecia	56%	17%	27%	0%	0%	0%	44%
Blood and lymphatic system disorders—Neutropenia	57%	4%	12%	15%	10%	2%	43%
Diarrhea	60%	23%	15%	2%	0%	0%	40%
Anorexia	62%	17%	19%	2%	0%	0%	38%
Nausea	66%	15%	17%	2%	0%	0%	34%
Constipation	65%	25%	10%	0%	0%	0%	35%
General disorders and administration site conditions—Asthenia	67%	10%	23%	0%	0%	0%	33%
Blood and lymphatic system disorders—Anemia	69%	8%	17%	6%	0%	0%	31%
Nervous system disorders—Neuropathy peripheral	71%	17%	10%	2%	0%	0%	29%
Blood and lymphatic system disorders—Thrombocytopenia	74%	4%	10%	12%	0%	0%	26%
Dyspnea	75%	10%	13%	2%	0%	0%	25%
Epistaxis	75%	21%	4%	0%	0%	0%	25%
Arthralgia	77%	8%	13%	2%	0%	0%	23%
Cough	79%	15%	6%	0%	0%	0%	21%
Vomiting	81%	13%	4%	2%	0%	0%	19%

Adverse events regardless of relationship to study drug in >10 safety-evaluable patients, experimental arm ($n = 52$).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Adverse Events				
Adverse event	**Placebo, *n* = 51, *n* (%)**		**MEGF0444A, *n* = 52, *n* (%)**	
Any AEs	51 (100)		51 (98)	
Grade ≥3 AEs	46 (90)		43 (83)	
SAEs	30 (59)		29 (56)	
AEs leading to d/c of parsatuzumab/placebo	17 (33)		18 (35)	
AEs leading to d/c of bevacizumab	13 (26)		18 (35)	
AEs leading to d/c of carboplatin	16 (31)		16 (31)	
AEs leading to d/c of paclitaxel	19 (37)		18 (35)	
AEs leading to death	8 (16)		15 (29)	
Grade 5 disease progression	4 (7.8)		7 (13)	
Other grade 5 AEs	4 (7.8)		8 (15)	
	Total	**Grade ≥3**	**Total**	**Grade ≥3**
AEs of special interest, *n* (%)	28 (55)	11 (22)	26 (50)	9 (17)
Hemorrhage	18 (35)	0 (0)	18 (35)	4 (7.7)
Arterial thromboembolic events	2 (3.9)	1 (2.0)	2 (3.8)	2 (3.8)
Congestive heart failure	2 (3.9)	1 (2.0)	0 (0)	0 (0)
Hypertension	14 (28)	10 (20)	11 (21)	4 (7.7)
Wound healing	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal perforation	0 (0)	0 (0)	0 (0)	0 (0)
Other bevacizumab-associated AEs, *n* (%)				
Proteinuria	3 (5.9)	1 (2.0)	6 (11.5)	3 (5.8)
Neutropenia	31 (61)	26 (51)	26 (50)	18 (35)

Abbreviations: AEs, adverse events; d/c, discontinuation; MEGF0444A, parsatuzumab; SAEs, serious adverse events.

Serious Adverse Events Regardless of Relationship to Study Drug in >2 Safety-Evaluable Patients Overall			
Preferred term	**Placebo arm, *n* = 51, *n* (%)**	**Experimental arm, *n* = 52, *n* (%)**	**Total, *n* = 103, *n* (%)**
Malignant neoplasm progression	4 (7.8)	5 (9.6)	9 (8.7)
Febrile neutropenia	2 (3.9)	3 (5.8)	5 (4.9)
Pulmonary embolism	4 (7.8)	1 (1.9)	5 (4.9)
Anemia	1 (2.0)	3 (5.8)	4 (3.9)
Diarrhea	2 (3.9)	1 (1.9)	3 (2.9)
General physical health deterioration	2 (3.9)	1 (1.9)	3 (2.9)
Nausea	2 (3.9)	1 (1.9)	3 (2.9)
Neutropenia	1 (2.0)	2 (3.8)	3 (2.9)
Pneumonia	1 (2.0)	2 (3.8)	3 (2.9)

Adverse Events Comments

Serious adverse events, regardless of attribution to study drug, were reported for 29 patients (55.8%) in the experimental arm and 30 patients (58.8%) in the placebo arm. All deaths that occurred during the protocol-specified adverse event reporting period (90 days following last administration of study treatment), regardless of attribution, were to be reported as serious adverse events, including death due to disease progression.

As of March 12, 2014, 42 deaths (24 patients in the parsatuzumab arm and 18 patients in the placebo arm) were reported. In the parsatuzumab arm, 15 deaths occurred during the adverse event reporting period (90 days following last administration of study treatment), of which 7 were attributed to disease progression and 8 were attributed to other adverse events. Of these adverse events, fatal events of gastric ulcer hemorrhage and pulmonary hemorrhage were assessed as related to parsatuzumab and bevacizumab. In addition, an autopsy was performed in association with an event of fatal pneumonia that was assessed as unrelated to study treatment. The immediate cause of death was identified as aspiration of blood caused by intratumoral bleeding. The investigator made no change to the AE term of pneumonia or to the attribution following the autopsy. In the placebo arm, eight deaths occurred during the adverse event reporting period, of which four were attributed to disease progression and four were attributed to other adverse events. None of these events were attributed to study treatment.

Overall, 41 patients (78.8%) in the parsatuzumab arm and 46 patients (90.2%) in the placebo arm experienced a grade 3/4/5 adverse event. Four grade ≥3 bleeding adverse events were reported: grade 5 gastric ulcer hemorrhage (as above), grade 5 pulmonary hemorrhage (as above), grade 4 hemoptysis, and grade 3 hematuria. All four events occurred in the parsatuzumab arm. The hemoptysis event occurred approximately 4 months after discontinuation of parsatuzumab and was attributed to bevacizumab and concomitant warfarin. The other three bleeding events were considered related to parsatuzumab/placebo.

With the exception of the numerical imbalance in grade ≥3 hemorrhage events described above, there was no apparent exacerbation of AEs of special interest in the parsatuzumab arm.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Company stopped development
Investigator's Assessment	Inactive because results did not meet primary endpoint

VEGF-mediated tumor angiogenesis is a validated anticancer target. Bevacizumab, a monoclonal antibody against VEGF-A, has demonstrated clinical benefit in several cancers, including non-small cell lung cancer (NSCLC) [6]. In the phase III Eastern Cooperative Oncology Group (ECOG) 4599 study, the addition of bevacizumab (15 mg/kg) to carboplatin and paclitaxel was associated with a prolongation of progression-free survival (PFS; hazard ratio [HR] = 0.66) and overall survival (OS; HR = 0.79) [7]. These results were supported by AVAil, another phase III study in first-line NSCLC, which demonstrated improvement of PFS with the addition of bevacizumab to cisplatin and gemcitabine (HR for 7.5 mg/kg dose = 0.75, HR for 15 mg/kg dose = 0.82) [8]. Strategies to enhance the clinical utility of antiangiogenic therapy include preventing vascular recovery after treatment with a VEGF inhibitor [9, 10].

Epidermal growth factor-like domain 7 (EGFL7) is a vascular-restricted extracellular matrix protein that is upregulated during angiogenesis and promotes endothelial cell adhesion and survival under stress [1, 11–16]. EGFL7 is deposited in perivascular tracks that persist after vessel regression; vessel regrowth after antiangiogenic therapy may occur along these EGFL7-containing extracellular matrix tracks [11, 17–21].

Parsatuzumab (MEGF0444A) is a humanized IgG1 monoclonal anti-EGFL7 antibody therapy that selectively blocks the interaction between EGFL7 and endothelial cells (Genentech unpublished data, [17]). Blocking EGFL7 function in tumors could inhibit vascular growth and regrowth after vessel damage induced by antiangiogenic therapy, thereby further reducing tumor perfusion. In murine tumor models, anti-EGFL7 given in combination with anti-VEGF further decreased tumor vascular density ([17] and unpublished data) and resulted in significantly prolonged OS compared with anti-VEGF alone [2]. Safety, tolerability, and evidence of pharmacodynamic modulation in a phase Ib trial of parsatuzumab in combination with bevacizumab with or without paclitaxel [3] led to the conduct of two concurrent phase II trials of parsatuzumab in combination with bevacizumab and chemotherapy in patients with NSCLC (this study) and colorectal cancer (CRC) [4].

In this study, 104 patients (Table 1) with previously untreated stage IV or recurrent NSCLC were randomized to receive parsatuzumab or placebo in combination with bevacizumab, carboplatin, and paclitaxel until disease progression or unacceptable toxicity (Fig. 2). The protocol-specified primary analysis was performed after 62 PFS events, with all patients followed for a minimum of 6.5 months. The PFS hazard ratio was 1.7 (95% confidence interval, 1.0–2.8; $p = .047$), with median PFS of 6.7 months for the parsatuzumab arm versus 8.1 months for the placebo arm (Fig. 1). Objective responses also favored the placebo arm (objective response rate [ORR] 29% in the parsatuzumab arm vs. 56% in the placebo arm).

Of note, the performance of the placebo arm compares favorably with the phase III historical benchmarks provided by ECOG 4599 (carboplatin/paclitaxel/bevacizumab, median PFS 6.2 months, ORR 35%) [7] and POINTBREAK (carboplatin/pemetrexed/bevacizumab, median PFS 5.6 months, ORR 33%) [22]. In contrast, the parsatuzumab arm outcomes were consistent with these benchmarks. Whether these efficacy data reflect (a) imbalanced randomization with respect to unrecognized prognostic or predictive factors, or (b) detriment associated with parsatuzumab, cannot be definitively determined based on the small sample size. However, sensitivity analyses that utilize a broader definition of PFS events (e.g., including all death events, clinical progression events, and/or early censoring events) consistently attenuate the PFS difference between the arms (data on file). Moreover, an updated median OS, after an additional 3.5 months of follow-up and nine more events, showed a median OS of 12.6 months in both arms (hazard ratio 1.23, data on file). Finally, the phase II study of parsatuzumab added to chemotherapy consisting of folinic acid, 5-FU, and oxaliplatin, known as modified FOLFOX6 or mFOLFOX6, and bevacizumab in first-line CRC showed a PFS hazard ratio of 1.17 and an OS hazard ratio of 0.97 [4], reinforcing the apparent lack of efficacy rather than harm associated with the addition of parsatuzumab.

Limited exploration of predictive biomarkers suggested a trend toward PFS benefit associated with parsatuzumab in patients with low tumor EGFL7 expression (defined as less than or equal to the median, HR 0.72), consistent with findings in the phase Ib study of parsatuzumab/bevacizumab (data on file). However, caveats include the limited sampling of archival tumor (provided by 49 of 104 patients) and the lack of corroboration of tumor EGFL7 as a predictive marker in the phase II trial of parsatuzumab in CRC [4]. No PFS benefit associated with parsatuzumab was observed in subgroups defined by the stratification factors (ECOG, prior adjuvant therapy, sex) or by plasma VEGF levels.

The overall safety and tolerability profile was similar in the two arms, as reflected by similar proportions of patients experiencing adverse events (AEs; 98% in the parsatuzumab arm, 100% in the placebo arm; Adverse Events table), grade ≥3 AEs (83% in the parsatuzumab arm, 90% in the placebo arm), serious adverse events (56% in the parsatuzumab arm, 59% in the placebo arm; Serious Adverse Events table), and AEs leading to

parsatuzumab/placebo discontinuation (35% in the parsatuzumab arm, 33% in the placebo arm). However, a numerical imbalance in grade $\geq$3 bleeding AEs was observed, with four events in the parsatuzumab arm (grade 5 gastric ulcer hemorrhage, grade 5 pulmonary hemorrhage, grade 4 hemoptysis, and grade 3 hematuria) and no events in the placebo arm. The hemotypsis event occurred approximately 4 months after discontinuation of parsatuzumab and was attributed to bevacizumab and concurrent warfarin. The other three bleeding events were considered related to parsatuzumab. There was no apparent exacerbation of any other bevacizumab-related adverse events in patients receiving parsatuzumab. Given that fatal hemorrhage is an established risk of bevacizumab-based therapy in NSCLC patients [23], and given that the phase II trial in CRC did not suggest any trend toward increased risk of bleeding associated with parsatuzumab [4], it seems less likely that the numerical imbalance between the arms reflects a true safety signal. Nevertheless, based on this limited data set, the possibility of an increased risk of bleeding associated with parsatuzumab cannot be excluded.

In conclusion, despite promising preclinical biology supporting the evaluation of anti-EGFL7 to enhance the antiangiogenic effect of VEGF inhibition, the addition of parsatuzumab to bevacizumab plus standard chemotherapy regimens demonstrated no evidence of efficacy in an unselected population of patients with advanced NSCLC. Unfortunately, robust predictive biomarkers for bevacizumab in NSCLC patients remain elusive despite intensive efforts [24]. As therapy for NSCLC becomes increasingly stratified, with evolving diagnostic strategies to guide the optimal use of immunotherapy as well as targeted agents, it is likely that such predictive biomarkers will be more important than ever for the successful development of antiangiogenic therapies.

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FIGURES AND TABLES

Table 1. Baseline patient and disease characteristics

Characteristic	Placebo ($n = 52$)	MEGF0444A ($n = 52$)	All patients ($n = 104$)
Age in years, median (range)	63.5 (37–82)	64.5 (44–76)	63.5 (37–82)
Sex, *n* (%)			
Male	34 (65.4)	33 (63.5)	67 (64.4)
Female	18 (34.6)	19 (36.5)	37 (35.6)
Ethnicity, *n* (%)			
Hispanic or Latino	2 (3.8)	1 (1.9)	3 (2.9)
Not Hispanic or Latino	47 (90.4)	47 (90.4)	94 (90.4)
Not reported	2 (3.8)	4 (7.7)	6 (5.8)
Unknown	1 (1.9)	0 (0.0)	1 (1.0)
Race, *n* (%)			
Asian	1 (1.9)	(0.0)	1 (1.0)
Black	1 (1.9)	1 (1.9)	2 (1.9)
White	48 (92.3)	47 (90.4)	95 (91.3)
Other race	2 (3.8)	4 (7.7)	6 (5.8)
ECOG performance status, *n* (%)			
0	28 (53.8)	23 (44.2)	51 (49.0)
1	24 (46.2)	29 (55.8)	53 (51.0)
Adjuvant therapy, *n* (%)			
Yes	4 (7.7)	0 (0.0)	4 (3.8)
No	48 (92.3)	52 (100.0)	100 (96.2)
Time from primary diagnosis in months, median (range)	0.9 (0–72)	0.9 (0–68)	0.9 (0–72)
Histology, *n* (%)			
Adenocarcinoma	49 (94.2)	52 (100.0)	101 (97.1)
Large cell	2 (3.8)	0 (0.0)	2 (1.9)
Other	1 (1.9)	0 (0.0)	1 (1.0)
Initial staging, tumor site, *n* (%)			
T1	16 (30.8)	7 (14.0)	23 (22.5)
T2	18 (34.6)	18 (36.0)	36 (35.3)
T3	9 (17.3)	8 (16.0)	17 (16.7)
T4	9 (17.3)	17 (34.0)	26 (25.5)
Initial staging, lymph nodes, *n* (%)			
N0	13 (25.0)	11 (21.6)	24 (23.3)
N1	7 (13.5)	9 (17.6)	16 (15.5)
N2	20 (38.5)	16 (31.4)	36 (35.0)
N3	7 (13.5)	10 (19.6)	17 (16.5)
NX	5 (9.6)	5 (9.8)	10 (9.7)
Initial staging, metastatic, *n* (%)			
M0	7 (13.5)	4 (7.7)	11 (10.6)
M1	43 (82.7)	47 (90.4)	90 (86.5)
MX	2 (3.8)	1 (1.9)	3 (2.9)
Current disease status, *n* (%)			
Locally advanced or inoperable	2 (3.8)	3 (5.9)	5 (4.9)
Metastatic	50 (96.2)	48 (94.1)	98 (95.1)
Time from locally advanced or inoperable or metastatic diagnosis in months, median (range)	0.6 (0–18)	0.7 (0–32)	0.7 (0–32)

(continued)

Table 1. (continued)

Characteristic	Placebo ($n = 52$)	MEGF0444A ($n = 52$)	All patients ($n = 104$)
Number of sites of metastatic disease, *n* (%)			
0	1 (1.9)	1 (1.9)	2 (1.9)
1	10 (19.2)	8 (15.4)	18 (17.3)
2	15 (28.8)	18 (34.6)	33 (31.7)
3	16 (30.8)	12 (23.1)	28 (26.9)
4	8 (15.4)	9 (17.3)	17 (16.3)
5	1 (1.9)	3 (5.8)	4 (3.8)
6+	1 (1.9)	1 (1.9)	2 (1.9)
Prior systemic therapy, *n* (%)			
No	48 (92.3)	52 (100.0)	100 (96.2)
Yes	4 (7.7)	0 (0.0)	4 (3.8)
Prior surgery, *n* (%)			
No	28 (53.8)	28 (53.8)	56 (53.8)
Yes	24 (46.2)	24 (46.2)	48 (46.2)
Prior radiotherapy, *n* (%)			
No	46 (88.5)	43 (82.7)	89 (85.6)
Yes	6 (11.5)	9 (17.3)	15 (14.4)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

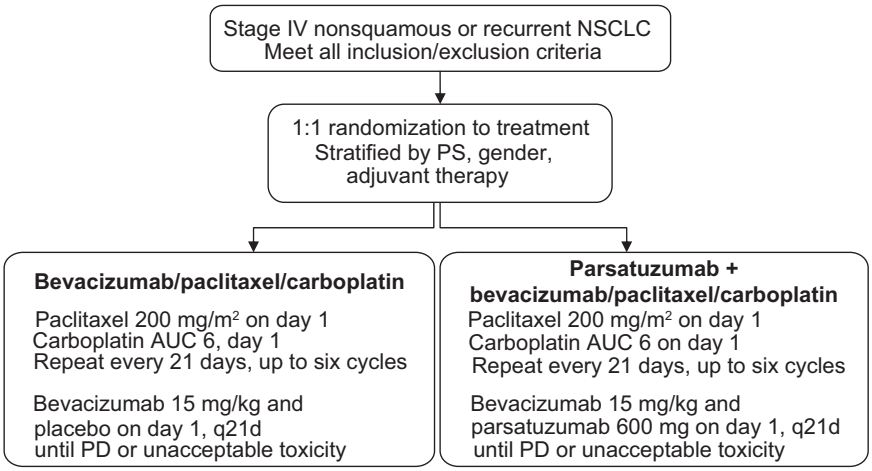

Figure 2. Study scheme.

Abbreviations: AUC 6, area under curve of 6 mg • min/ml (Calvert formula); NSCLC, non-small cell lung cancer; PD, progressive disease; PS, performance status; q21d, every 21 days.