Title

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Journal

The Oncologist, 22(4)

ISSN

1083-7159

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Publication Date

2017-04-01

DOI

10.1634/theoncologist.2016-0133

Peer reviewed

The Oncologist®

Clinical Trial Results

Randomized Phase II Trial of Parsatuzumab (Anti-EGFL7) or Placebo in Combination with FOLFOX and Bevacizumab for First-Line Metastatic Colorectal Cancer

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01399684
- **Sponsor**: Genentech, Inc.
- **Principal Investigator**: Herbert Hurwitz
- **IRB Approved**: Yes

Lessons Learned

- These negative phase II results for parsatuzumab highlight the challenges of developing an agent intended to enhance the efficacy of vascular endothelial growth factor inhibition without the benefit of validated pharmacodynamic biomarkers or strong predictive biomarker hypotheses.
- Any further clinical development of anti-EGFL7 is likely to require new mechanistic insights and biomarker development for antiangiogenic agents.

Abstract

Background. EGFL7 (epidermal growth factor-like domain 7) is a tumor-enriched vascular extracellular matrix protein that supports endothelial cell survival. This phase II trial evaluated the efficacy of parsatuzumab (also known as MEGF0444A), a humanized anti-EGFL7 IgG_1 monoclonal antibody, in combination with modified FOLFOX6 (mFOLFOX6) (folinic acid, 5-fluorouracil, and oxaliplatin) bevacizumab in patients with previously untreated metastatic colorectal cancer (mCRC).

Methods. One-hundred twenty-seven patients were randomly assigned to parsatuzumab, 400 mg, or placebo, in combination with mFOLFOX6 plus bevacizumab, 5 mg/kg. Treatment cycles were repeated every 2 weeks until disease progression or unacceptable toxicity for a maximum of 24 months, with the exception of oxaliplatin, which was administered for up to 8 cycles.

Results. The progression-free survival (PFS) hazard ratio was 1.17 (95% confidence interval [CI], 0.71–1.93; $p = .548$). The median PFS was 12 months for the experimental arm versus 11.9 months for the control arm. The hazard ratio for overall survival was 0.97 (95% CI, 0.46–2.1; $p = .943$). The overall response rate was 59% in the parsatuzumab arm and 64% in the placebo arm. The adverse event profile was similar in both arms.

Conclusions. There was no evidence of efficacy for the addition of parsatuzumab to the combination of bevacizumab and chemotherapy for first-line mCRC. ***The Oncologist*** 2017;22:375–e30

Discussion

EGFL7 is a vascular-restricted extracellular matrix protein that promotes endothelial cell adhesion and survival [1–5]. Parsatuzumab, a humanized anti-EGFL7 IgG_1 monoclonal antibody, selectively blocks the interaction between EGFL7 and endothelial cells, thereby potentially inhibiting vascular regrowth and further reducing tumor perfusion after antiangiogenic therapy, such as vascular endothelial growth factor (VEGF) inhibition [6]. In several xenograft and genetically engineered murine tumor models, the addition of anti-EGFL7 enhanced the antiangiogenesis, tumor growth control, and survival associated with anti-VEGF monotherapy [7]. Favorable tolerability and evidence of pharmacodynamic modulation and antitumor activity were

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observed in a phase Ib trial that evaluated parsatuzumab in combination with bevacizumab and bevacizumab/paclitaxel [7, 8].

The current study was designed to evaluate the benefit of anti-EGFL7 when added to standard mFOLFOX6/bevacizumab in first-line metastatic colorectal cancer (mCRC); however, no improvement in progression-free survival (PFS) associated with parsatuzumab in comparison to placebo was observed (Figs. 1 and 2). Furthermore, no PFS benefit associated with parsatuzumab was detected in subgroups defined by Eastern Cooperative Oncology Group (ECOG) performance status, prior adjuvant therapy, number of metastatic sites at baseline, *KRAS* genotype, or tumor EGFL7 expression level. Of 127 patients in the intention-to-treat population, 115 had measurable EGFL7 and were stratified as above or below the median EGFL7 level. The adverse event profiles of the parsatuzumab and placebo arms were similar to each other and consistent with the established profile of mFOLFOX6/bevacizumab in mCRC patients. There was no evidence that the concomitant administration of parsatuzumab altered the duration or intensity of treatment with the other active study drugs. The overall treatment outcomes for the study population compared favorably with the historical performance of first-line mFOLFOX6/bevacizumab [9, 10]. Hence, it appears unlikely that any potential activity of parsatuzumab was confounded by study conduct that resulted in compromised delivery or efficacy of the reference regimen.

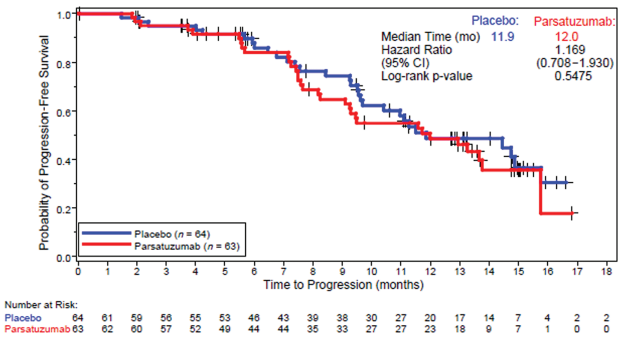

Figure 1. Kaplan-Meier estimates of progression-free survival. Placebo (blue) = mFOLFOX6 + bevacizumab + placebo. Parsatuzumab (red) = mFOLFOX6 + bevacizumab + parsatuzumab. +, indicates censored value on graph.

Abbreviations: CI, confidence interval; mFOLFOX6, modified FOLFOX6 (folinic acid, 5-fluorouracil, and oxaliplatin).

Although anti-EGFL7 therapy was active in preclinical models, our data in patients with previously untreated mCRC suggest that anti-EGFL7 therapy does not add significant clinical benefit in this patient population. Any further clinical development of anti-EGFL7 is likely to require new mechanistic insights and biomarker development for antiangiogenic agents.

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Trial Information

Disease	Colorectal cancer
Stage of disease/treatment	Metastatic/Advanced
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Randomized
ORR	*p*-value = 0.715. Difference in ORR (95% CI): −5% (−22% to 12%)
PFS	*p*: .548, HR: 1.17
Response duration	*p*: .33, HR: 1.41
Primary Endpoint	PFS
Secondary Endpoint	Safety
Secondary Endpoint	Tolerability
Secondary Endpoint	Overall Survival
Secondary Endpoint	Overall Response Rate
Secondary Endpoint	Duration of objective response
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Immunogenicity

Additional Details of Endpoints or Study Design

Patients. Patients with histologically or cytologically confirmed mCRC and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, who had not been previously treated with chemotherapy for mCRC and were not candidates for potentially curative resection were eligible for participation in this study. Other inclusion criteria included an age of at least 18 years; an 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 mCRC (adjuvant systemic therapy or radiotherapy more than 12 months before study entry was permitted), malignancies other than CRC within 5 years, radiotherapy 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 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).

Study Design. Eligible patients were randomly assigned 1:1 to receive modified FOLFOX6 (mFOLFOX6) (oxaliplatin 85 mg/m^2, 5-fluorouracil 400 mg/m^2 bolus followed by 2,400 mg/m^2 continuous infusion over 46 hours, folinic acid 400 mg/m^2), bevacizumab 5 mg/kg, and placebo or mFOLFO-X6 (as above), bevacizumab 5 mg/kg, and parsatuzumab 400 mg iv on day 1 of each 14-day cycle. Randomization was stratified by ECOG performance status (0 vs. 1), number of affected organs (1 vs. >1), and prior adjuvant chemotherapy (yes vs. no). Therapy was continued until disease progression or unacceptable toxicity for a maximum of 24 months, with the exception of oxaliplatin, which was administered for up

to 8 cycles. 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 8–9 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 serious adverse events (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 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 was assessed by using a bridging enzyme-linked immunosorbent assay (ELISA) developed and validated to detect antibodies against parsatuzumab (antitherapeutic antibodies, ATA). The specificity of ATA-positive samples was confirmed by competition inhibition with unlabeled parsatuzumab. Pharmacokinetics were assessed by using a sandwich ELISA developed and validated to quantitate parsatuzumab in human serum. There was no interference from coadministered bevacizumab. Parsatuzumab concentrations were measured at baseline and at peak and trough during cycles 1 and 2, and at trough levels during cycle 7 after steady state was achieved. A sparse collection scheme was used for assessing bevacizumab, oxaliplatin, and 5-fluorouracil PK. Gene expression analysis was performed on archival tumor specimens using the BioMark HD real-time PCR Platform (Fluidigm, South San Francisco, CA, http://www.fluidigm.com) as per the manufacturer's protocol. For each specimen, expression levels were determined for a panel of angiogenesis-related genes that included the following: *ACVRL1, ANGPT1, ANGPT2, APLN, AREG, ARF5, BGN, BNIP3, CD247, CD274, CD28, CD34, CD36, CD3E, CD4, CD68, CD8A, CDH5, CEACAM5, CLEC5a, Col4a1, CRP D15, CRPD21, CTPS2, CXCL1, CXCL11, CXCL12, CXCR4, CXCR5, DLL4, EFNB2, EGF, Egfl7, EpCAM, EphB4, ERCC2, ERG, ESM1, FAP, FBLIM1, FGF2, FLT1, FN1, FOXP3, GUSB, GZMK, Hey1, HeyL, HGF, HHEX, Hif1A, HMBS, ICAM1, ICOS, IL6, IL8, JAG1, KDR, KISS1R, KRT14, KRT19, KRT20, LAMA4, LDHB, Map4k4, MET, MFAP5, MKi67, MMP10, MMP3, MSH2, MYCN, NID2, Notch1, NRP1, PDGFRb, PECAM1, PGF, PODXL, PPP1R13L, RGS5, SELE, SERPINF1, SP2, TGFb1, THBS1, TIMP1, TMEM55B, TOP1, TXNDC5, TYMS, VCAM1, VEGF121, VEGF165, VEGFC, VIM, VPS33B,* and *ZEB1*. Expression levels for each transcript were determined with respect to a geometric mean of four reference genes (*SP2, GUSB, TMEM55B,* and *VPS33B*). Median mRNA expression levels across patients were used as cutoffs to define high versus low expression. Of the 127 randomly assigned patients, 115 submitted archival tissue that was adequate for gene expression analysis.

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). For the 10 patients (6 in the placebo arm, 4 in the parsatuzumab arm) who underwent surgical resection of metastasis on study (because of reassessment of resectabiity following response to study treatment), data were censored at the time of the last tumor assessment before the resection. An exploratory sensitivity analysis of PFS in which time points subsequent to metastasectomy were included was also performed. 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 (oxaliplatin, 5-fluorouracil, bevacizumab, or parsatuzumab/placebo). The study was intended to enroll approximately 120 patients, and the primary analysis was to be performed after approximately 60 investigator-assessed PFS events. The emphasis of the efficacy analyses was on estimation of the magnitude of the treatment effect rather than hypothesis testing. Interim analyses were conducted by an internal monitoring committee (IMC). The IMC performed a blinded interim safety analysis after 12 patients had been treated for at least four full cycles. An interim efficacy analysis accompanied by a review of safety data was performed after all patients had been followed for a minimum of 8 months (i.e., after the occurrence of approximately two thirds of the 60 PFS events required for the primary analysis). The study was not stopped after the planned interim efficacy analysis but rather after the prespecified primary analysis that was to occur after 60 PFS events. The final data cutoff (August 29, 2013) reflected 62 PFS events.

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

Drug Information Arm A: Placebo arm

Drug 1	
Generic/Working name	Placebo
Dose	400 milligrams (mg) per flat dose
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity
Drug 2	
Generic/Working name	Bevacizumab
Drug class	Angiogenesis - VEGF
Dose	5 milligrams (mg) per kilogram (kg)
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity.
Drug 3	
Generic/Working name	5-fluorouracil
Dose	400 milligrams (mg) per squared meter (m^2)
Route	i.v., bolus, 2400 mg/m^2 infusion
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity

Drug 4	
Generic/Working name	Folinic acid
Dose	400 milligrams (mg) per squared meter (m^2)
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity.
Drug 5	
Generic/Working name	Oxaliplatin
Drug class	Platinum compound
Dose	85 milligrams (mg) per squared meter (m^2)
Route	i.v.
Schedule of Administration	Every 2 weeks for 8 cycles

Drug Information Arm B: Parsatuzumab arm	
Drug 1	
Generic/Working name	Parsatuzumab
Drug class	Angiogenesis
Dose	400 milligrams (mg) per flat dose
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity.
Drug 2	
Generic/Working name	Bevacizumab
Drug class	Angiogenesis - VEGF
Dose	5 milligrams (mg) per kilogram (kg)
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity
Drug 3	
Generic/Working name	5-fluorouracil
Dose	400 milligrams (mg) per squared meter (m^2)
Route	i.v., bolus, 2400 mg/m^2 infusion
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity
Drug 4	
Generic/Working name	Folinic acid
Dose	400 milligrams (mg) per squared meter (m^2)
Route	i.v.
Schedule of Administration	Every 2 weeks until disease progression or unacceptable toxicity.
Drug 5	
Generic/Working name	Oxaliplatin
Drug class	Platinum compound
Dose	85 milligrams (mg) per squared meter (m^2)
Route	i.v.
Schedule of Administration	Every 2 weeks for 8 cycles

Patient Characteristics	
Number of patients, male	74 (58.7%)
Number of patients, female	52 (41.3%)
Stage	Stage I: 1 (0.8%) Stage IIA: 4 (3.2%) Stage IIB: 4 (3.2%) Stage IIIA: 2 (1.6%)

	Stage IIIB: 14 (11.2%)
	Stage IIIC: 6 (4.8%)
	Stage IV: 94 (75.2%)
Age	Median (range): 62 (32–80)
Number of prior systemic therapies	Median (range): See Table 1
Performance Status: ECOG	0 — 66 (52.0%)
	1 — 61 (48.0%)
	2 —
	3 —
	unknown —
Other	See Table 1

Primary Assessment Method

Arm A: Placebo Arm: Total Patient Population

Number of patients enrolled	64
Number of patients evaluable for toxicity	62
Number of patients evaluated for efficacy	64
Response assessment CR	*n* =3 4.8%
Response assessment PR	*n* =37 58.7%
(Median) duration assessments PFS	11.9 months, CI: 9.6, 15.8 (95% CI)
(Median) duration assessments duration of treatment	9.1 months

Arm B: Parsatuzumab Arm: Total Patient Population

Number of patients enrolled	63
Number of patients evaluable for toxicity	63
Number of patients evaluated for efficacy	63
Response assessment CR	*n* = 3 4.8%
Response assessment PR	*n*= 34 54.0%
(Median) duration assessments PFS	12 months, CI: 9.1, 15.8 (95% CI)
(Median) duration assessments OS	19 months, CI: 17.3, 19.0 (95% CI)
(Median) duration assessments response duration	9.9 months
(Median) duration assessments duration of treatment	9.2 months

Adverse Events

	Placebo (*n* = 62)	Parsatuzumab (*n* = 63)
Patients with any AEs, *n* (%)	62 (100%)	63 (100%)
Patients with AEs grade ≥3	47 (75.8%)	41 (65.1%)
Patients with SAEs	24 (38.7%)	22 (34.9%)
AEs leading to discontinuation of parsatuzumab or placebo	11 (17.7%)	14 (22.2%)
AEs leading to death	3 (4.8%)	4 (6.3%)
Grade 5 disease progression	2 (3.2%)	3 (4.8%)
Grade 5 large intestine perforation	1 (1.6%)	-
Grade 5 neutropenic enterocolitis	-	1 (1.6%)

	Placebo All AEs	Placebo ≥G3 AEs	Parsatuzumab All AEs	Parsatuzumab ≥G3 AEs
Patients with AEs of special interest	55 (88.7%)	30 (48.4%)	51 (81.0%)	18 (28.6%)
Hemorrhage	29 (46.8%)	1 (1.6%)	31 (49.2%)	0 (0%)
Gastrointestinal perforation	2 (3.2%)	2 (3.2%)	4 (6.3%)	2 (3.2%)
Wound healing	2 (3.2%)	1 (1.6%)	2 (3.2%)	0 (0%)
Hypertension	21 (33.9%)	7 (11.3%)	18 (28.6%)	4 (6.3%)

Proteinuria	5 (8.1%)	0 (0%)	5 (7.9%)	1 (1.6%)
Arterial thromboembolism	0 (0%)	0 (0%)	1 (1.6%)	1 (1.6%)
Venous thromboembolism	12 (19.4%)	3 (4.8%)	5 (7.9%)	3 (4.8%)
Neutropenia	24 (38.7%)	20 (32.3%)	20 (31.7%)	13 (20.6%)
Posterior reversible encephalopathy syndrome	1 (1.6%)	1 (1.6%)	0 (0%)	0 (0%)

Pharmacokinetics/Pharmacodynamics

Notes

Observed parsatuzumab pharmacokinetics data were generally similar to population model predictions based on phase Ia monotherapy data [11]. Observed bevacizumab levels were similar to population model predictions for both treatment groups. Similar 5-fluorouracil and oxaliplatin levels were observed for both treatment arms.

Immunogenicity: Confirmed ATAs were detected in 6 of 127 (4.7%). Of these, 3 patients were positive at baseline and negative following administration of parsatuzumab; 2 patients were positive at baseline as well as after drug administration but with no evidence of an increased ATA titer; 1 patient was negative at baseline but positive following drug administration. Therefore, 1 of 127 (0.8%) patients was considered to have treatment-emergent ATA. The impact of ATA on clinical endpoints was not determinable.

Pharmacodynamics comments: Pharmacodynamic biomarker analyses were not performed.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated reason	Company stopped development
Pharmacokinetics/Pharmacodynamics	Not Collected
Investigator's Assessment	Inactive because results did not meet primary endpoint

Antiangiogenesis therapy has shown important clinical benefits, leading to approvals of multiple VEGF/VEGF receptors inhibitors in a wide variety of tumor types. In mCRC, bevacizumab has been shown to improve overall survival and other clinical endpoints when combined with fluorouracil-based chemotherapy as first-line and second-line therapy, and when continued past first progression [12–14]. Complementary targeting of other angiogenesis factors is a rational strategy to improve these outcomes; epidermal growth factor-like domain 7 (EGFL7) has emerged as such a target. EGFL7 is a vascular-restricted extracellular matrix protein that promotes endothelial cell adhesion and survival under stress [1–5]. EGFL7 is produced by endothelial cells in nascent blood vessels in tumors and other proliferating tissues, but is absent or expressed at low levels in healthy quiescent vessels and in many nonvascular cell types [2, 4, 5, 15]. 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 [1, 6, 16–19].

Parsatuzumab (also known as MEGF0444A) is a humanized IgG_1 monoclonal antibody that selectively blocks the interaction between EGFL7 and endothelial cells [6]. In preclinical models, the addition of anti-EGFL7 enhanced the antiangiogenesis, tumor growth control, and survival associated with anti-VEGF monotherapy [7]. Favorable tolerability and promising evidence of pharmacodynamic modulation and antitumor activity was observed in a phase Ib trial that evaluated parsatuzumab in combination with bevacizumab and bevacizumab/paclitaxel [8]. These results led to concurrent phase II trials of parsatuzumab in combination with bevacizumab and chemotherapy in patients with mCRC in this study and in patients with advanced non-small cell lung cancer in another study (manuscript in preparation), respectively.

In this study, 127 patients with previously untreated mCRC who were not candidates for curative-intent metastasectomy and had no contraindications to bevacizumab were randomized to receive parsatuzumab or placebo in addition to mFOLFOX6/bevacizumab every 2 weeks until disease progression or unacceptable toxicity. Oxaliplatin was capped at 8 cycles in order to minimize discontinuation of the study regimen due to chemotherapy-related adverse events, as the duration of treatment with bevacizumab appears to be important to maximize its therapeutic benefit [10]. The protocol-specified primary analysis was performed after the occurrence of 62 PFS events and a minimum of 12.5 months of follow-up for all patients. The PFS hazard ratio was 1.17 (95% confidence interval [CI], 0.71–1.93; $p = .548$), with median PFS of 12 months for the parsatuzumab arm versus 11.9 months for the placebo arm. An exploratory analysis that included time points subsequent to metastasectomy for the 10 patients (6 in the placebo arm and 4 in the parsatuzumab arm) who became eligible for resection while on study treatment was also performed. The results of this sensitivity analysis were similar to those of the primary analysis (PFS hazard ratio of 1.11; median PFS of 12.9 months for the parsatuzumab arm versus 12.6 months for the placebo arm). With a total of 27 deaths reported, the immature overall survival (OS) hazard ratio was 0.97 (95% CI, 0.46–2.1; $p = .943$). The overall response rate was 59% in the parsatuzumab arm and 64% in the placebo arm. Furthermore, the PFS hazard ratio was not

statistically significant in subgroups defined by ECOG performance status (0 vs. 1), history of adjuvant therapy (yes vs. no), or number of metastatic sites at baseline (1 vs. >1) or *KRAS* genotype (wild-type vs. mutant); however, *KRAS* status was available for only 64 of the 127 patients. Based on a prior phase Ib study in which high tumor EGFL7 expression was found to be associated with lack of response (data on file), subgroup analysis was also performed based on EGFL7 expression measured in archival tumor specimens (above median vs less than or equal to median), but with no significant difference in PFS hazard ratio observed.

The adverse event profiles of the parsatuzumab and placebo arms, including the number of protocol-specified adverse events of interest and events leading to treatment discontinuation, were similar to each other and consistent overall with the established profile of mFOLFOX6/bevacizumab in mCRC patients [12]. There was no evidence that the concomitant administration of parsatuzumab altered the duration or intensity of treatment with the other active study drugs. No difference in bevacizumab, 5-fluorouracil, or oxaliplatin pharmacokinetics was observed between the treatment arms. Moreover, the overall treatment outcomes for the study population compared favorably with the historical performance of first-line mFOLFOX6/bevacizumab [9, 10]. Hence, it appears unlikely that any potential activity of parsatuzumab was confounded by study conduct that resulted in compromised delivery or efficacy of the reference regimen.

These data highlight the challenge in achieving meaningful improvement in front-line outcomes for patients with mCRC, a disease for which no new therapeutic class has been introduced since the U.S. Food and Drug Administration approvals of bevacizumab (anti-VEGF) and cetuximab (anti-epidermal growth factor receptor) in 2004. These phase II results for parsatuzumab underscore the difficulty of developing agents whose mechanism predicts (1) activity only in combinations (i.e., with bevacizumab) but not as a single agent and (2) enhanced survival in the absence of increased response rates. Neither validated pharmacodynamic biomarkers that reflect modulation of the targeted pathway nor strong predictive biomarker hypotheses were available to guide the development of parsatuzumab. Despite intensive efforts, such biomarkers for anti-VEGF agents in colorectal cancer have remained elusive. Any further clinical development of anti-EGFL7 is likely to require new mechanistic insights and biomarker development for antiangiogenic agents.

Disclosures

Rocío García-Carbonero: Roche, Merck, Amgen, Eli Lilly, Bayer, Novartis, Ipsen, Boerhinger (C/A); **Eric van Cutsem**: Roche (RF); **Fernando Rivera**: Amgen, Merck-Serono, Sanofi-Aventis, Bayer, Celgene (C/A), Roche, Merck-Serono, Amgen, Sanofi-Aventis, Bayer (RF); **Jacek Jassem**: Amgen, Astra-Zeneca, Roche, Bristol-Myers Squibb, Merck, Pfizer (C/A); **Ira Gore**: Genentech, Puma, Bristol-Myers Squibb (RF); **Niall Tebbutt**: Roche (C/A, RF); **Fadi Braiteh**: Genentech (CA); **Zev A. Wainberg**: Genentech, Amgen (C/A), Genentech (H), Novartis, Merck (RF); **Roel Funke**: Roche (E, IP, OI); **Maria Anderson**: Genentech (E, OI); **Bruce McCall**: Genentech (E), Roche (OI); **Mark Stroh**: Genentech (E); **Eric Wakshull**: Genentech (E), Roche (OI); **Priti Hegde**: Genentech (E, OI); **Weilan Ye**: Genentech (E), Roche (OI); **Ilsun Chang**: Genentech (E, OI); **Ina Rhee**: Genentech (E), Roche (OI); **Herbert Hurwitz**: Genentech/Roche, Bristol-Myers Squibb, Eli Lilly, Novartis, Incyte, TRACON Pharma, Acceleron Pharma, GlaxoSmithKline, OncoMed (C/A); Genentech/Roche, Eli Lilly/ImClone (H), Genentech/Roche, GlaxoSmithKline, Novartis, TRACON Pharma, Bristol-Myers Squibb, Regeneron, Eli Lilly, Macrogenics (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

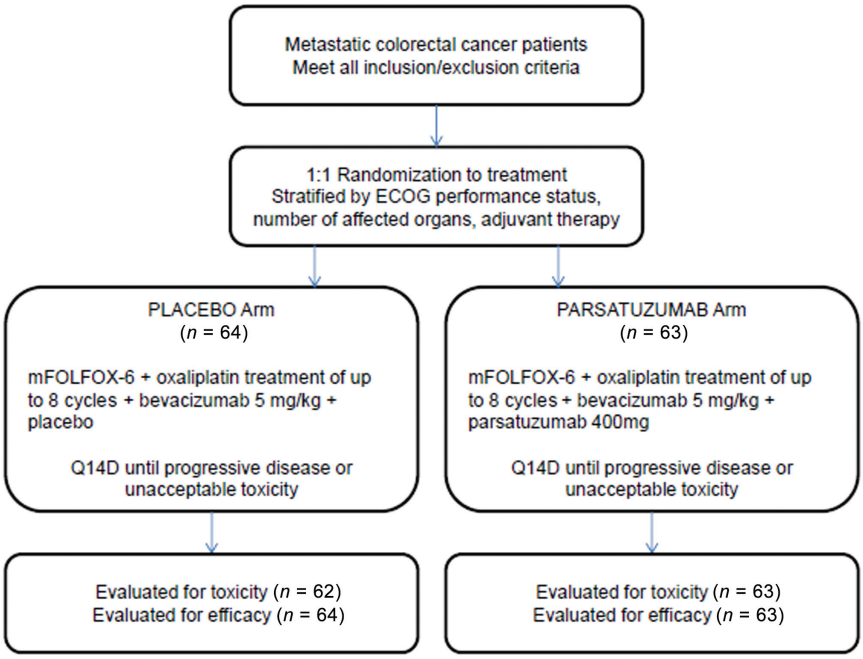

Figure 2. Study design.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mFOLFOX6, oxaliplatin 85 mg/m^2, 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 continuous infusion over 46 hours, folinic acid 400 mg/m^2; Q14D, each 14-day cycle.

Table 1. Baseline patient and disease characteristics

Characteristic	Placebo ($n = 64$)	Parsatuzumab ($n = 63$)	All patients ($n = 127$)
Median age (range), yr	64 (32–78)	61 (37–80)	62 (32–80)
Sex, *n* (%)			
Male	36 (57.1)	38 (60.3)	74 (58.7)
Female	27 (42.9)	25 (39.7)	52 (41.3)
Ethnicity, *n* (%)			
Hispanic or Latino	2 (3.2)	4 (6.3)	6 (4.8)
Not Hispanic or Latino	61 (96.8)	59 (93.7)	120 (95.2)
Race, *n* (%)			
Asian	2 (3.2)	2 (3.2)	4 (3.2)
Black or African American	3 (4.8)	3 (4.8)	6 (4.8)
White	58 (92.1)	58 (92.1)	116 (92.1)
ECOG performance status, *n* (%)			
0	36 (56.3)	30 (47.6)	66 (52.0)
1	28 (43.8)	33 (52.4)	61 (48.0)
Adjuvant therapy, *n* (%)			
No	56 (88.9)	53 (84.1)	109 (86.5)
Yes	7 (11.1)	10 (15.9)	17 (13.5)
Median time from primary diagnosis (range), months	1.4 (−0 to 81)	1.4 (0–79)	1.4 (−0 to 81)
Histology grade, *n* (%)			
Moderately differentiated	35 (55.6)	35 (55.6)	70 (55.6)
Poorly differentiated	8 (12.7)	8 (12.7)	16 (12.7)
Unknown	12 (19.0)	10 (15.9)	22 (17.5)
Well differentiated	8 (12.7)	10 (15.9)	18 (14.3)
AJCC/UICC stage at original diagnosis, *n* (%)			
Stage 1	1 (1.6)	0 (0)	1 (.8)
Stage IIA	0 (0)	4 (6.5)	4 (3.2)
Stage IIB	1 (1.6)	3 (4.8)	4 (3.2)
Stage IIIA	1 (1.6)	1 (1.6)	2 (1.6)
Stage IIIB	9 (14.3)	5 (8.1)	14 (11.2)
Stage IIIC	2 (3.2)	4 (6.5)	6 (4.8)
Stage IV	49 (77.8)	45 (72.6)	94 (75.2)
Disease type, *n* (%)			
Metastatic disease	63 (100)	63 (100)	126 (100)
Median time from diagnosis (range), months	1.0 (0–7)	1.0 (0–25)	1.0 (0–25)
Number of sites of metastatic disease, *n* (%)			
1	24 (38.1)	29 (46.0)	53 (42.1)
2	31 (49.2)	22 (34.9)	53 (42.1)
3	7 (11.1)	10 (15.9)	17 (13.5)
4	1 (1.6)	2 (3.2)	3 (2.4)
Prior systemic therapy, *n* (%)			
No	57 (89.1)	53 (84.1)	110 (86.6)
Yes	7 (10.9)	10 (15.9)	17 (13.4)
Prior surgery, *n* (%)			
No	25 (39.1)	19 (30.2)	44 (34.6)
Yes	39 (60.9)	44 (69.8)	83 (65.4)
Prior radiotherapy, *n* (%)			
No	62 (96.9)	57 (90.5)	119 (93.7)
Yes	2 (3.1)	6 (9.5)	8 (6.3)

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; UICC, Union for International Cancer Control.