

Phase II Study to Evaluate the Efficacy and Safety of Rilotumumab and Bevacizumab in Subjects with Recurrent Malignant Glioma

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01113398
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- **Principal Investigators:** Mary Lou Affronti, Katherine B. Peters
- **IRB Approved:** Yes

LESSONS LEARNED

- Due to evolving imaging criteria in brain tumors and variation in magnetic resonance imaging evaluation, it is not ideal to use response rate as a primary objective. Future studies involving antiangiogenic agents should use overall survival.
- Disease-expected toxicities should be considered when defining the clinical significance of an adverse event. For example, vascular thromboembolic events are common in brain tumor patients and should not be attributed to the study drug in the safety analysis.

ABSTRACT

Background. Recurrent malignant glioma (rMG) prognosis is poor, with a median patient survival of 3–11 months with bevacizumab (BEV)-containing regimens. BEV in rMG has 6-month progression free survival (PFS-6) of ~40% and an objective response rate of 21.2%. BEV-containing regimens improve PFS-6 to 42.6%–50.3%, indicating that BEV combination therapies may be superior to single agent. Rilotumumab, a hepatocyte growth factor (HGF) antibody, inhibits angiogenesis and expression of angiogenic autocrine factors (e.g., vascular endothelial growth factor [VEGF]) by c-Met inhibition. Combination of rilotumumab with BEV to block vascular invasion and tumor proliferation may synergistically inhibit tumor growth.

Methods. Thirty-six BEV-naïve rMG subjects received rilotumumab (20 mg/kg and BEV (10 mg/kg) every 2 weeks. Endpoints included objective response rate (using Response Assessment in Neuro-Oncology [RANO] criteria), PFS-6, overall survival (OS), and toxicity.

Results. Median patient follow-up was 65.0 months. Objective response rate was 27.8% (95% confidence interval [CI]: 15.7%–44.1%). Median OS was 11.2 months (95% CI: 7–17.5). PFS-6 was 41.7% (95% CI: 25.6%–57.0%). Most frequent treatment-related grade ≤ 2 events included weight gain, fatigue, allergic rhinitis, and voice alteration; grade ≥ 3 events included venous

thromboembolism (four patients), including one death from pulmonary embolism.

Conclusion. Rilotumumab with BEV did not significantly improve objective response compared with BEV alone, and toxicity may preclude the use of rilotumumab in combination BEV regimens. *The Oncologist* 2018;23:889–e98

DISCUSSION

This study's hypothesis was that rilotumumab plus BEV, a humanized anti-VEGF-A antibody, would work synergistically to block vascular invasion and tumor proliferation causing tumor growth inhibition. Previous studies demonstrate a positive association between HGF and glioma grade. Additionally, abnormal expression of HGF contributes to glioma progression, showing the importance of the HGF mechanism in malignant glioma. Rilotumumab is an antibody that blocks the interaction of HGF with the c-Met receptor, resulting in reduced tumor cell proliferation and migration. This study was designed to differentiate between a 20% and 40% radiographic response rate using RANO criteria. This study combination resulted in an objective response of 27.8% (complete response: 2.8% plus partial response: 25%), therefore not meeting the threshold for concluding that the regimen merits further investigation.

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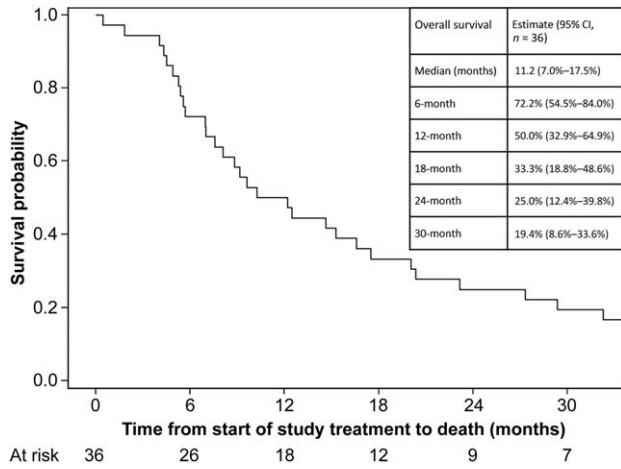


Figure 1. Kaplan-Meier curve of overall survival of patients treated with rilotumumab in combination with bevacizumab. The inset table shows the overall survival specifications for this regimen. Abbreviation: CI, confidence interval.

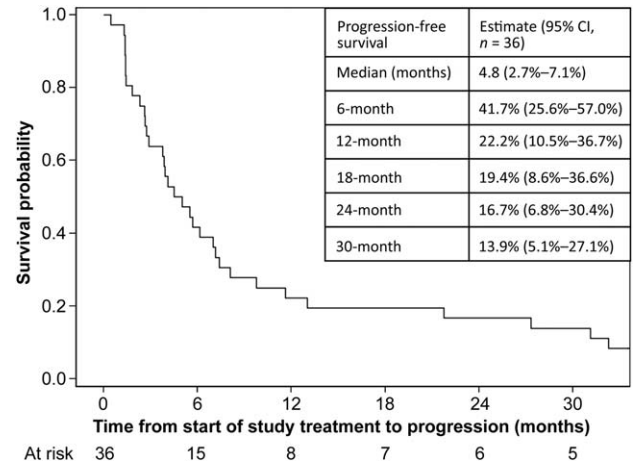


Figure 2. Kaplan-Meier curve of progression-free survival in patients treated with rilotumumab in combination with bevacizumab. The inset table shows the progression-free survival specifications for this regimen. Abbreviation: CI, confidence interval.

A previous study treating rMG patients with rilotumumab alone demonstrated a median OS of 6.5 months and a median PFS of 4.1 weeks. The statistical comparator study of single-agent BEV in rMG showed a median OS of ~7.8 months (95% CI: 5.3–13.5) and a median PFS of 4 months (95% CI: 3–6). In the present study, BEV plus rilotumumab modestly increased the median OS to 11.2 months (95% CI: 7.0–17.5) and the median PFS to 4.8 months (95% CI: 2.7–7.1), see Figures 1 and 2, respectively. Although BEV plus rilotumumab showed ~3–4-month improvement in median survival over the individual agents, it did not increase the PFS of BEV alone. The improvement in median OS should be balanced with the toxicity of the

combination regimen. Occurrences of grade (GR) ≥ 2 central nervous system (CNS) hemorrhage or GR4/5 nonhematologic treatment-related toxicity were determined unacceptable, a priori. “Unacceptable” toxicity rates of $\leq 5\%$ were desirable, whereas rates $\geq 20\%$ were undesirable. There were no GR2 CNS hemorrhages, although 6% of patients had GR4/5 nonhematologic treatment-related toxicity (one GR4 prolonged QTc; one GR4 pulmonary embolism [PE]; one lethal PE). Although venous thromboembolic events are expected in gliomas, and the combination did not exceed unacceptable toxicity, four patients (11%) had grade > 3 PE, which is clinically significant.

TRIAL INFORMATION

Disease	World Health Organization (WHO) grade IV malignant glioma
Stage of Disease/Treatment	Adjuvant
Prior Therapy	No designated number of regimens
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Toxicity

Additional Details of Endpoints or Study Design

Primary endpoint: radiological response rate as determined by RANO criteria.

Secondary endpoints: overall survival and 6-month progression-free survival. Incidence and severity of CNS hemorrhage and systemic hemorrhage. Incidence of grade > 4 hematologic and grade > 3 nonhematologic toxicities.

Sample size justification: A minimax two-stage design was used to assess the radiographic response rate (i.e., complete response [CR] + partial response [PR]) of rilotumumab and Avastin in the treatment of patients with advanced malignant glioma [1]. The randomized phase II trial, AVF3708g, investigating Avastin versus Avastin plus irinotecan demonstrated a radiographic response rate to Avastin of approximately 20%. Hence, the current study was designed to differentiate between a 20% (null hypothesis) and a 40% (alternative hypothesis) response rate, assuming type I and II error rates of 0.10. If 10 or fewer of the total 36 patients had a radiographic response, the AMG 102 and Avastin treatment combination was to be considered not worthy of further research.

Analytic methods: The primary endpoint, radiographic response rate, was assessed using RANO criteria. Brain magnetic resonance imaging scans were obtained on patients after each 4-week treatment cycle, and complete and partial responses were confirmed at least 4 weeks later. The response rate was calculated with Wald confidence intervals. Secondary endpoints of OS and PFS were estimated using Kaplan-Meier methods; corresponding 95% confidence intervals were calculated using Greenwood's formula. OS was defined as the time between the initiation of study treatment and death or last follow-up, if alive at the time of analysis; PFS was defined as the time between the initiation of study treatment and the first occurrence of disease progression or death. Patients alive and progression free at the time of analysis were censored as of the date of last follow-up. Common Terminology Criteria for Adverse Events version 4.0 was used to assess adverse events for safety endpoints. SAS 9.4 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Investigator's Analysis

Active but results overtaken by other developments

DRUG INFORMATION**Drug 1**

Generic/Working Name	Bevacizumab
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Trade Name	Avastin
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Company Name	Genentech
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Drug Type	Antibody
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Drug Class	Angiogenesis—VEGF
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Dose	10 mg/kg
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Route	IV
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Schedule of Administration	Every 2 weeks for up to 12 cycles. Each cycle was 6 weeks, which included three infusions of Avastin every 2 weeks.
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Drug 2

Generic/Working Name	Rilotumumab
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Trade Name	AMG102
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Company Name	Amgen, Inc.
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Drug Type	Antibody
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Drug Class	MET—cMET
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Dose	20 mg/kg
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Route	IV
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Schedule of Administration	Rilotumumab was administered every 2 weeks following the administration of Avastin for up to 12 cycles. Each cycle was 6 weeks and included three administrations of Avastin at 10 mg/kg followed by rilotumumab at 20 mg/kg.
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PATIENT CHARACTERISTICS

Number of Patients, Male	22
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Number of Patients, Female	14
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Age	Median (range): 55.5 (27–74)
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Number of Prior Systemic Therapies	Median (range): 1 (1–3)
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Performance Status: ECOG	0 — 0
	1 — 33
	2 — 3
	3 — 0
	Unknown — 0

Cancer Types or Histologic Subtypes	Recurrent malignant glioma WHO grade IV
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PRIMARY ASSESSMENT METHOD

Title	Total patient population
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Number of Patients Screened	42
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Number of Patients Enrolled	36
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Number of Patients Evaluable for Toxicity	36
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Number of Patients Evaluated for Efficacy	36
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Evaluation Method	RANO
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Response Assessment CR	<i>n</i> = 1 (2.8%)
Response Assessment PR	<i>n</i> = 9 (25.0%)
Response Assessment SD	<i>n</i> = 17 (47.2%)
Response Assessment PD	<i>n</i> = 6 (16.7%)
Response Assessment OTHER	<i>n</i> = 3 (8.3%)
(Median) Duration Assessments PFS	4.8 months, CI: 95%
(Median) Duration Assessments OS	11.2 months, CI: 95%

ADVERSE EVENTS							
All Cycles							
Name	NC/NA	1	2	3	4	5	All grades
Alanine aminotransferase increased	80%	17%	3%	0%	0%	0%	20%
Alkaline phosphatase increased	86%	14%	0%	0%	0%	0%	14%
Allergic rhinitis	69%	28%	3%	0%	0%	0%	31%
Anal hemorrhage	89%	11%	0%	0%	0%	0%	11%
Arthralgia	81%	11%	8%	0%	0%	0%	19%
Aspartate aminotransferase increased	83%	17%	0%	0%	0%	0%	17%
Blood bilirubin increased	94%	6%	0%	0%	0%	0%	6%
Cough	92%	8%	0%	0%	0%	0%	8%
Diarrhea	91%	6%	3%	0%	0%	0%	9%
Dry mouth	92%	8%	0%	0%	0%	0%	8%
Dyspnea	89%	11%	0%	0%	0%	0%	11%
Edema limbs	70%	19%	8%	3%	0%	0%	30%
Edema trunk	94%	3%	3%	0%	0%	0%	6%
Electrocardiogram QT corrected interval prolonged	89%	8%	0%	0%	3%	0%	11%
Epistaxis	89%	11%	0%	0%	0%	0%	11%
Fatigue	42%	36%	19%	3%	0%	0%	58%
Flushing	94%	6%	0%	0%	0%	0%	6%
Hypertension	77%	14%	6%	3%	0%	0%	23%
Hypoalbuminemia	67%	22%	8%	3%	0%	0%	33%
Hypocalcemia	92%	8%	0%	0%	0%	0%	8%
Hypokalemia	91%	6%	0%	3%	0%	0%	9%
Myalgia	89%	11%	0%	0%	0%	0%	11%
Nausea	92%	8%	0%	0%	0%	0%	8%
Pain in extremity	94%	3%	0%	3%	0%	0%	6%
Platelet count decreased	91%	6%	3%	0%	0%	0%	9%
Proteinuria	88%	6%	6%	0%	0%	0%	12%
Seizure	94%	3%	3%	0%	0%	0%	6%
Thromboembolic event	85%	0%	3%	6%	3%	3%	15%
Urinary frequency	91%	6%	3%	0%	0%	0%	9%
Vascular disorders—Other, specify	94%	6%	0%	0%	0%	0%	6%
Voice alteration	63%	31%	3%	3%	0%	0%	37%
Vomiting	94%	3%	3%	0%	0%	0%	6%
Weight gain	64%	25%	11%	0%	0%	0%	36%

Adverse events possibly, probably, or definitely related to the study drug regimen (bevacizumab and/or rilotumumab) that occurred in >5% of the patients at any time during treatment on the study.

Abbreviation: NC/NA, no change from baseline/no adverse event.

SERIOUS ADVERSE EVENTS		
Name	Grade	Attribution
Death not otherwise specified	5	Unrelated
Electrocardiogram QT corrected interval prolonged	4	Probable
Fracture	3	Unrelated
Hypotension	3	Possible
Musculoskeletal and connective tissue disorder—Fall	3	Unrelated
Seizure	3	Unrelated
Venous thromboembolic event	3	Probable
Venous thromboembolic event	3	Probable
Venous thromboembolic event	4	Probable
Venous thromboembolic event	5	Probable

All serious adverse events that occurred in patients treated on study.

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Active but results overtaken by other developments

Patients with recurrent malignant glioma (rMG) have improved progression-free survival (PFS) with bevacizumab (BEV), a humanized monoclonal antibody that inhibits vascular endothelial growth factor-A (VEGF-A). In a 2009 study, single-agent BEV, followed by BEV plus irinotecan, in rMG resulted in a median overall survival (OS) of 7.8 months (95% confidence interval [CI]: 5.3–13.5) and a median PFS of 4 months (95% CI: 3–6) [2]. The BELOB trial showed single-agent BEV to have a similar median OS of 8 months (95% CI: 6–9) but showed an increase in median OS to 12 months (95% CI: 8–13) when combined with lomustine [3]. However, overall survival benefits were not seen in a phase III study of BEV combined with lomustine compared with single-agent lomustine (median OS 9.1 months vs. 8.6 months, respectively), although the combination improved PFS by 2.7 months over lomustine alone [4]. Observations from other phase II studies show improved PFS with BEV-containing regimens, with no significant impact on OS [2, 5]. Even with such increases in PFS, the prognosis of rMG remains poor with low survival outcomes.

Numerous studies are testing BEV combination therapies in attempts to increase survival [6–8]. One component that may provide synergy with BEV is rilotumumab, a hepatocyte growth factor (HGF)-inhibiting antibody that blocks HGF, which prevents activation of the c-Met receptor, resulting in downstream prevention of tumor cell growth and survival. In addition to the effect on cell growth, HGF is also associated with tumor grade in gliomas [9–11], and abnormal expression of HGF contributes to glioma progression, showing the importance of the HGF activation mechanism in malignant glioma [12–15]. By itself, rilotumumab is not as effective as BEV, with phase II study results of single-agent rilotumumab in rMG patients demonstrating a median OS of 6.5 months and a median PFS of 4.1 weeks [16]. With rilotumumab's ability to inhibit a molecule that is associated with malignant glioma and BEV's impact on PFS in rMG, it was suspected that these two drugs may work synergistically to improve survival outcomes of rMG patients through multipathway tumor growth inhibition.

This clinical trial enrolled 36 rMG subjects to receive rilotumumab (20 mg/kg) and BEV (10 mg/kg) every 2 weeks. Of the 36 subjects, 27 (75%) were at their first recurrence and 33 (91.7%) had a Karnofsky Performance Status \geq 80. Based on an earlier BEV-alone study in rMG, the current study was designed to differentiate between a 20% and 40% response rate. Overall best responses included 1 (2.8%) complete response, 9 (25.0%) partial responses, 17 (47.2%) patients with stable disease, and 6 (16.7%) with progressive disease. The resulting objective response rate (complete or partial response) of 27.8% did not meet the study threshold needed to deem the BEV/rilotumumab combination worthy of further investigation. However, objective response is not a robust measure of efficacy due to the intricacies and evolving criteria for analyzing magnetic resonance images of brain tumor patients who have received BEV. Future studies in this patient population would benefit from using OS as the primary outcome instead of the response rate.

The BEV plus rilotumumab study regimen resulted in a median OS of 11.2 months (95% CI: 7.0–17.5). This is a small, nonsignificant improvement in OS over recently published results by Wick and colleagues, which showed the median OS for BEV with lomustine (9.1 months [95% CI: 8.1–10.1]) was not superior to single-agent lomustine (8.6 months [95% CI: 7.6–10.4]) [4]. With a median PFS of 4.8 months (95% CI: 2.7–7.1), our study of BEV plus rilotumumab did not show any improvement in PFS over BEV alone. In this study, it is difficult to attribute the extended OS exclusively to the BEV plus rilotumumab regimen given that many subjects progressed quickly and proceeded to receive other therapies that could influence OS. Additionally, the small increase in median OS should be balanced with the toxicity caused by the regimen. Occurrences of grade (GR) \geq 2 central nervous system (CNS) hemorrhage or GR4/5 nonhematologic treatment-related toxicity were determined unacceptable, a priori. "Unacceptable" toxicity rates of \leq 5% were desirable, whereas rates \geq 20% were undesirable. There were no GR2 CNS hemorrhages, although 6% of patients had a GR4/5 nonhematologic-related toxicity (one GR4 prolonged

electrocardiogram QT corrected interval; one GR4 pulmonary embolism [PE]; one GR5 PE). Although venous thromboembolic events are expected in gliomas, and the combination did not exceed unacceptable toxicity, four patients (11%) had \geq GR3 PE, which is clinically significant. Other common treatment-related side effects experienced by \geq 20% of patients were fatigue (58%), voice alteration (37%), weight gain (36%), hypoalbuminemia (33%), and allergic rhinitis (31%). Overall, BEV plus rilotumumab resulted in an increase of side effects, both expected and new. Ultimately, the BEV plus rilotumumab combination was not further explored in rMG due to a decision made by the Principal Investigator after an ongoing clinical trial in gastric cancer (RILOMET-1) was terminated early due to an increased number of deaths on the rilotumumab arm compared with the placebo-controlled arm [17, 18]. Although the BEV plus rilotumumab regimen was not excessively toxic in the rMG patients in this study, there was concern for the safety of the patients due to the number of venous thromboembolisms that occurred in the rMG patients on this study and the increased number of deaths on the rilotumumab arm in the RILOMET-1 study. No further studies of rilotumumab alone or in combination with BEV have been done in rMG patients.

In conclusion, rilotumumab in combination with BEV did not significantly improve objective response, OS, or PFS com-

pared with BEV alone. Nonetheless, given the improvement of OS (although statistical significance was not evaluated), rilotumumab plus BEV was an active treatment regimen in rMG patients. The toxicity profile of rilotumumab in combination with BEV precludes this regimen from being used in rMG patients.

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DISCLOSURES

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