Original Article

NRG/RTOG 1122: A Phase 2, Double-Blinded, Placebo-Controlled Study of Bevacizumab With and Without Trebananib in Patients With Recurrent Glioblastoma or Gliosarcoma

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BACKGROUND: Targeting vascular endothelial growth factor (VEGF) alone does not improve overall survival (OS) in recurrent glioblastoma (rGBM). The angiopoiein (Ang)–TIE2 system may play a role in tumor survival under VEGF inhibition. We conducted a phase 2, double-blinded, placebo-controlled trial of bevacizumab plus trebananib (a novel Fc fusion protein that sequesters Ang1/Ang2) over bevacizumab alone in rGBM. **METHODS:** Patients ≥18 years of age with a Karnofsky performance status ≥70 and GBM or variants in first or second relapse were randomized to bevacizumab 10 mg/kg every 2 weeks plus trebananib 15 mg/kg every week or bevacizumab plus placebo. The primary endpoint was 6-month progression-free survival (PFS). **RESULTS:** After an initial 6-patient lead-in cohort confirmed the safety of combining bevacizumab and trebananib, 115 eligible patients were randomized to the control (n = 58) or experimental treatment (n = 57). In the control arm, 6-month PFS was 41.1%, median survival time was 11.5 months (95% CI, 8.4-14.2 months), median PFS was 4.8 months (95% CI, 3.8-7.1 months), and radiographic response (RR) was 5.9%. In the experimental arm, 6-month PFS was 22.6%, median survival time was 7.5 months (95% CI, 6.8-10.1 months), median PFS was 4.2 months (95% CI, 3.7-5.6 months), and RR was 4.2%. The rate of severe toxicities was not significantly different between arms. **CONCLUSION:** The combination of bevacizumab and trebananib was well tolerated but did not significantly improve 6-month PFS rate, PFS, or OS for patients with rGBM over bevacizumab alone. The shorter PFS in the experimental arm with a hazard ratio of 1.51 (P = .04) suggests that the addition of trebananib to bevacizumab is detrimental. ***Cancer* 2020;0:1-8**. © *2020 American Cancer Society*.

KEYWORDS: angiogenesis, angiopoietin, bevacizumab, glioblastoma, trebananib.

INTRODUCTION

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is frequently used to treat patients with recurrent glioblastoma (GBM) and has received US Food and Drug Administration approval for this indication.[1,2] Although randomized, phase 3 trials in newly diagnosed GBM suggest an improvement in progression-free survival (PFS), the addition of bevacizumab to standard therapy is not associated with an improvement in overall survival (OS) compared with standard therapy alone.[3,4] Indeed, GBMs often develop resistance to bevacizumab treatment within months of starting therapy.[1,5] Targeting VEGF alone may not be sufficient for durable responses. Intrinsic and acquired resistance may be due to the redundancy of angiogenesis stimulators.[6,7]

Angiopoietins (Ang) may play a role in mediating resistance to anti-VEGF therapy in GBM. In a phase 2 clinical trial of cediranib (a pan-VEGF receptor [VEGFR] inhibitor) in recurrent GBM, progression on cediranib correlated with increases in the soluble form of the Ang-binding TIE2 receptor.[8,9] In a U87 glioma xenograft model, dual inhibition

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of VEGFR and Ang2 inhibited tumor growth, prolonged vessel normalization compared to VEGFR inhibition alone, and improved survival through reprogramming of tumor-associated macrophages toward an antitumor phenotype.[10,11] In addition, a subset of GBM patients on anti-VEGF therapy develops a nonenhancing tumor pattern of progression, believed to represent a more invasive phenotype.[5,12,13] Upregulation of Ang2 correlates with the invasiveness of gliomas.[14,15] Blockade of Ang2 may decrease the invasiveness of gliomas and abrogate an escape mechanism for anti-VEGF therapy. Data from a colon cancer xenograft model suggest that combined Ang1/Ang2 inhibition confers better tumor suppression than Ang2 inhibition alone.[16] Furthermore, in the same models, Ang1/Ang2 inhibition plus bevacizumab mediated better tumor suppression than Ang2 inhibition plus bevacizumab. For these reasons, dual inhibition of the VEGF and Ang–TIE2 signaling pathways is an attractive therapeutic strategy in the recurrent GBM population.

Trebananib is a novel peptide-Fc fusion protein that sequesters Ang1 and Ang2, thereby preventing their interaction with TIE2 and inhibiting tumor endothelial cell proliferation and tumor growth. We performed a phase 2, double-blinded, placebo-controlled trial in patients with recurrent GBM comparing bevacizumab plus trebananib versus bevacizumab plus placebo.

MATERIALS AND METHODS

Patients

Eligibility criteria included age ≥18 years at registration with a histologic diagnosis of GBM or variants (gliosarcoma, glioblastoma with oligodendroglial features, giant cell glioblastoma) in first or second relapse with unequivocal radiographic evidence for tumor progression ≤14 days prior to registration. Patients with a secondary GBM were also eligible as long as GBM had been histologically proven. For patients with a recent tumor resection for progressive disease, registration on study could not occur any sooner than 28 days from surgery. Additional eligibility criteria included supratentorial disease only; Karnofsky performance status (KPS) ≥70; and adequate renal, hepatic, and bone marrow function.

No prior treatment with VEFG inhibitors including bevacizumab or with Ang–TIE2 inhibitors was allowed. Exclusion criteria also included magnetic resonance imaging evidence of recent intracranial hemorrhage, history of bleeding diathesis or coagulopathy, clinically significant cardiovascular disease including myocardial infarction and stroke within 180 days prior to registration, and uncontrolled hypertension. Therapeutic or prophylactic therapy with aspirin, a low-molecular weight heparin, or a factor Xa inhibitor was allowed, but not warfarin.

All patients provided written informed consent. The study was approved by the institutional review board or an equivalent panel at each study center before patient enrollment and is registered at ClinicalTrials.gov (NCT01609790).

Study Design, Treatment, and Endpoints

For the phase 2 portion, under the permuted block design,[17] patients were stratified by age (<50 vs ≥50 years), KPS (70-80 vs 90-100), and recent resection (Yes vs No/Biopsy) and then randomly assigned to receive trebananib or placebo with a 1:1 allocation ratio. All patients received bevacizumab at a dose of 10 mg/kg every 2 weeks. Trebananib (or placebo) was administered intravenously at a dose of 15 mg/kg every week until disease progression or severe treatment-related toxicity. At the time of tumor progression, patients were unblinded. Those who received bevacizumab monotherapy were allowed to cross over and to receive treatment with bevacizumab and trebananib, provided that they still met eligibility criteria.

The primary endpoint was 6-month progression-free survival rate (6-month PFS) and was confirmed by central review (EQL, ERG). Secondary endpoints included PFS, OS, radiographic response (RR), and safety. Toxic effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Radiographic assessments were performed by the local investigator and were based on the Response Assessment in Neuro-Oncology (RANO) criteria.[18] Additional details regarding study design can be found in the supplement.

Statistical Methods

The primary endpoint was 6-month PFS. Based on a March 2009 US Food and Drug Administration briefing,[19] 6-month PFS for bevacizumab monotherapy in recurrent GBM patients is 36%. We hypothesized that the addition of trebananib to bevacizumab in bevacizumab-naïve patients would result in a 6-month PFS rate of 55%. Assuming exponential distribution for PFS time, these rates corresponded to a median PFS time of 4.1 and 7 months for the control and experimental arm, respectively, with a hazard ratio (HR) of 0.59. With a 1-sided significance level at $P = .15$, a total of 114 patients (57 per arm) would yield an 85% power to detect the projected effect size on 6-month PFS, based on a 2-sample test on proportions. To guard against an ineligible rate up

to 10%, 127 patients were required to be accrued for the phase 2 portion of the study.

An interim futility analysis on 6-month PFS was designed to be performed when 50% of the total required eligible patients had a minimum of 6-month follow-up. The analysis followed the principle of intent-to-treat, with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The decision rule was that if the 6-month PFS rate for the experimental arm was worse than that for the control arm by any amount, the study would be stopped and reported early.

PFS was measured from the date of randomization to the date of first progression or death, whichever came first, or the last follow-up date on which the patient was reported alive without experiencing disease progression. OS was measured from the date of randomization to the date of death or the last follow-up date on which the patient was reported alive. OS and PFS rates by treatment arm were estimated using the Kaplan-Meier method. The HRs for the treatment effects on OS and PFS were estimated using the Cox proportional hazard model and tested using the log-rank test. Multivariate analyses with the Cox proportional hazard model were performed with the stratification factors and other patient pretreatment characteristics as covariates. Differences in the rate of reported severe toxicities and RR between treatment arms were tested using a chi-square test. For all the secondary endpoints, 2-sided tests with a significance level of $P = .05$ were used in the analyses.

The efficacy (as measured by OS, PFS, RR and 6-month PFS) of the salvage treatment for patients who crossed over from the control arm to receive the experimental drug after disease progression was investigated as an exploratory endpoint. For this group of patients, OS and PFS were measured from the date of initial progression (before crossover). OS and PFS rates were similarly estimated using the Kaplan-Meier method. The incidence rates of RR and the reported severe toxicities were also calculated.

RESULTS

Patients

One hundred thirty patients were enrolled across 41 centers in the United States through NRG oncology and randomized on the phase 2 portion of the study between March 2013 and September 2014 (Fig. 1; CONSORT diagram), of whom 15 (11.5%) were subsequently found to be ineligible. In total, 58 and 57 eligible patients randomized to the control and experimental arms, respectively, were included in the analyses. Table 1 shows the distributions of pretreatment characteristics by treatment arm. The distributions of the stratification factors were balanced between the 2 treatment arms.

Outcomes

The interim futility analysis was performed in March 2015. Out of the 27 and 30 eligible patients from the experimental and control arms, 7 (25.9%) and 11 (36.7%) patients, respectively, were progression-free at 6 months after randomization. Of note, the total accrual to the study had already been reached, and all patients had had 6-month follow-up by the time of this analysis. The report of this analysis was reviewed by the NRG Oncology Data Monitoring Committee, and it was recommended to unblind protocol treatment and to report the final analyses based on the data from all the randomized and eligible patients.

One hundred nine (94.8%) patients were evaluable for 6-month PFS (Table 2). Twelve of the 53 (22.6%) patients in the experimental arm were progression-free at 6 months after randomization compared with 23 of the 56 (41.1%) patients in the control arm (1-sided $P = .98$).

The median follow-up time for the patients who were still alive at the time of analysis was 15 months (range, 2.5-26.4 months). The median survival time was 11.5 months (95% CI, 8.4-14.2 months) for the control arm and 7.5 months (95% CI, 6.8-10.1 months) for the experimental arm, with an HR of 1.46 (95% CI, 0.95-2.27; $P = .09$) (Fig. 2A). The median PFS time was 4.8 months (95% CI, 3.8-7.1 months) for the control arm and 4.2 months (95% CI, 3.7-5.6 months) for the experimental arm, with an HR of 1.51 (95% CI, 1.02-2.24; $P = .04$) (Fig. 2B). After adjusting for the stratification factors and other patient pretreatment characteristics, the adjusted HR of the treatment effect on OS was 1.46 (95% CI, 0.94-2.26; $P = .09$) and that for PFS was 1.50 (95% CI, 1.01-2.23; $P = .05$).

Table 2 also presents the best RR by RANO criteria. Overall, 99 (86.1%) patients were evaluable. For the 51 patients in the control arm, 3 (5.9%) achieved a partial response. For the 48 patients in the experimental arm, 2 (4.2%) achieved partial response. No patient in either treatment arm achieved a complete response. No significant difference was found between the 2 treatment arms.

Safety

Information for adverse events without regard to attribution is presented by treatment arm for all the randomized

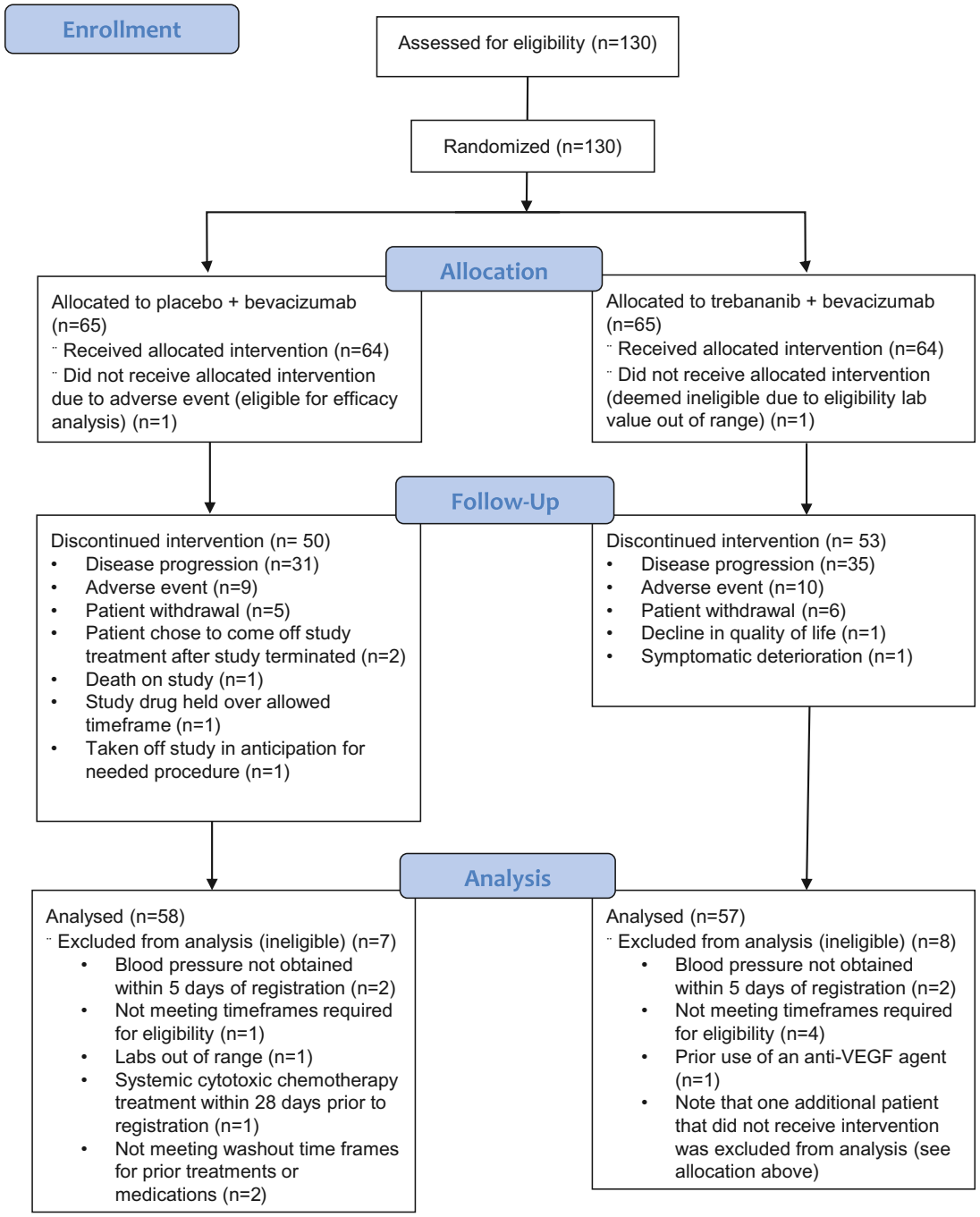

Figure 1. CONSORT diagram. Enrollment into the safety run-in portion of the study began on June 4, 2012, and closed temporarily on October 2, 2012, when the target accrual of 7 patients for the safety run-in component was met. Enrollment into the randomized portion of the study began on March 13, 2013, and accrual was competed on September 2, 2014. VEGF, vascular endothelial growth factor.

and eligible patients who received protocol treatment (Supporting Table S1). Although the proportion of patients with grade 3+ adverse events was numerically higher for the control arm (80.7% vs 64.9% for the experimental arm), this difference did not reach statistical significance ($P = .06$). Similarly, the proportion of patients with grade 3+ adverse events attributed to study treatment (36.8% of patients in the control arm vs 35.1% in the experimental arm) was not significantly different ($P = .85$). Overall, there were 2 (3.5%) patients in the

TABLE 1. Patient and Tumor Characteristics at Baseline for all Eligible Patients

Characteristic	Bevacizumab + Placebo (n = 58)	Bevacizumab + Trebananib (n = 57)
Age, y		
Median (range)	58 (22-79)	57 (30-80)
<50	17 (29.3)	14 (24.6)
≥50	41 (70.7)	43 (75.4)
Sex		
Men	36 (62.1)	32 (56.1)
Women	22 (37.9)	25 (43.9)
Race		
Asian	2 (3.4)	0 (0.0)
Black or African American	3 (5.2)	2 (3.5)
White	53 (91.4)	53 (93.0)
Unknown or not reported	0 (0.0)	2 (3.5)
Ethnicity		
Hispanic or Latino	3 (5.2)	2 (3.5)
Not Hispanic or Latino	55 (94.8)	54 (94.7)
Unknown	0 (0.0)	1 (1.8)
Karnofsky performance status		
70-80	31 (53.4)	34 (59.6)
90-100	27 (46.6)	23 (40.4)
Neurologic Function		
No symptoms	12 (20.7)	11 (19.3)
Minor symptoms	32 (55.2)	27 (47.4)
Moderate symptoms (fully active)	10 (17.2)	16 (28.1)
Moderate symptoms (required assistance)	4 (6.9)	3 (5.3)
Surgery (initial brain tumor)		
Biopsy only	8 (13.8)	3 (5.3)
Subtotal resection	19 (32.8)	12 (21.1)
Gross total resection	30 (51.7)	42 (73.7)
Other	1 (1.7)	0 (0.0)
Recent resection		
No/biopsy only	30 (51.7)	30 (52.6)
Yes	28 (48.3)	27 (47.4)
Histologic tumor type		
Glioblastoma	53 (91.4)	53 (93.0)
Gliosarcoma	2 (3.4)	2 (3.5)
Glioblastoma with oligodendroglial features	2 (3.4)	1 (1.8)
Giant cell glioblastoma	0 (0.0)	1 (1.8)
Other	1 (1.7)	0 (0.0)

Data are presented as n (%) unless noted otherwise.

control arm and 5 (8.8%) patients in the experimental arm with reported grade 5 adverse events, all of which were deemed unrelated to protocol treatment.

Crossover Study

A total of 25 patients crossed over from the control arm to receive open-label trebananib and bevacizumab after disease progression (Table 2). Twenty-two (88.0%) of these patients were evaluable for 6-month PFS, and only 1 (4.5%) patient was progression-free at 6 months after initial disease progression on bevacizumab. Nine (36.0%) patients were evaluable for the best RR, all with progressive disease based on the RANO criteria. The median survival time from the date of initial progression was 4.9 months (95% CI, 3.8-8.4 months), and the median PFS was 2.3 months (95% CI, 2.1-3.2 months). No grade 5 adverse events were reported in the crossover cohort, and 1 (4.0%) patient experienced grade 4 sepsis.

Pharmacokinetics

Four of 6 patients in cohort 1 and 17 of 25 patients in the crossover arm participated in the optional PK and antitrebananib antibody studies. The peak and trough concentrations of trebananib on days 1 and 8 of cycle 2 were comparable to those from previous studies.[20] Minimal variability of trebananib concentrations were observed between days 1 and 8 of cycle 2, suggesting that the steady state pharmacokinetics had been reached.

DISCUSSION

The combination of trebananib and bevacizumab did not significantly improve the 6-month PFS rate for patients with recurrent GBM in first or second relapse compared with bevacizumab alone. Indeed, the median PFS was longer in the control arm than in the experimental arm. Compared with other randomized studies comparing bevacizumab alone with in combination with another systemic agent (such as carboplatin,[21] dasatinib,[22] or onartuzumab[23]) in recurrent GBM, our study similarly fails to demonstrate a survival advantage to combination therapy. We also examined the benefit of adding trebananib to bevacizumab in patients who progressed on bevacizumab monotherapy. Survival times were similar to prior studies examining the role of combining bevacizumab with a systemic agent after progression on bevacizumab.[1]

The best RR was similar for the 2 treatment arms (~5.0%), but lower than the historical benchmarks from prior bevacizumab studies (35% in Kreisl et al[1] and 46.4%-65.8% in Friedman et al[2]). This is partly explained by differences in RR assessment methods, with the historical benchmark studies using Macdonald criteria[24] and our study using RANO criteria.[18] When the results reported by Friedman et al were reassessed by independent reviewers using RANO criteria, the RR dropped to 33.1%.[25] The even lower RR seen in our study could reflect a heightened understanding that decreased contrast enhancement on bevacizumab may not reflect true antitumor responses.[18] In addition, RR assessment was performed by a local investigator, some of whom were not neurooncologists or neuroradiologists and may have been more apt to declare progression earlier than investigators in prior benchmark studies.

TABLE 2. Study Outcomes

Outcome	Randomized Cohort			Crossover Cohort
	Bevacizumab + Placebo	Bevacizumab + Trebananib	*P*	Bevacizumab + Trebananib
6-Month PFS, n, %	23/56 (41.1)	12/53 (22.6)	.98	1/22 (4.5)
OS, mo, median (95% CI)	11.5 (8.4, 14.2)	7.5 (6.8, 10.1)	.09	4.9 (3.8, 8.4)
PFS, mo, median (95% CI)	4.8 (3.8, 7.1)	4.2 (3.7, 5.6)	.04	2.3 (2.1, 3.2)
RR for evaluable patients			.99[a]	
Complete response	0/0 (0)	0/0 (0)		0/0 (0)
Partial response	3/51 (5.9)	2/48 (4.2)		0/0 (0)
Stable disease	16/51 (31.4)	9/48 (18.8)		0/0 (0)
Progressive disease	32/51 (62.7)	37/48 (77.1)		9/9 (100)

Abbreviations: OS, overall survival; PFS, progression free survival; RR, radiographic response.
[a]Determined using Fisher's exact test for partial response versus stable disease/progressive disease by treatment arm.

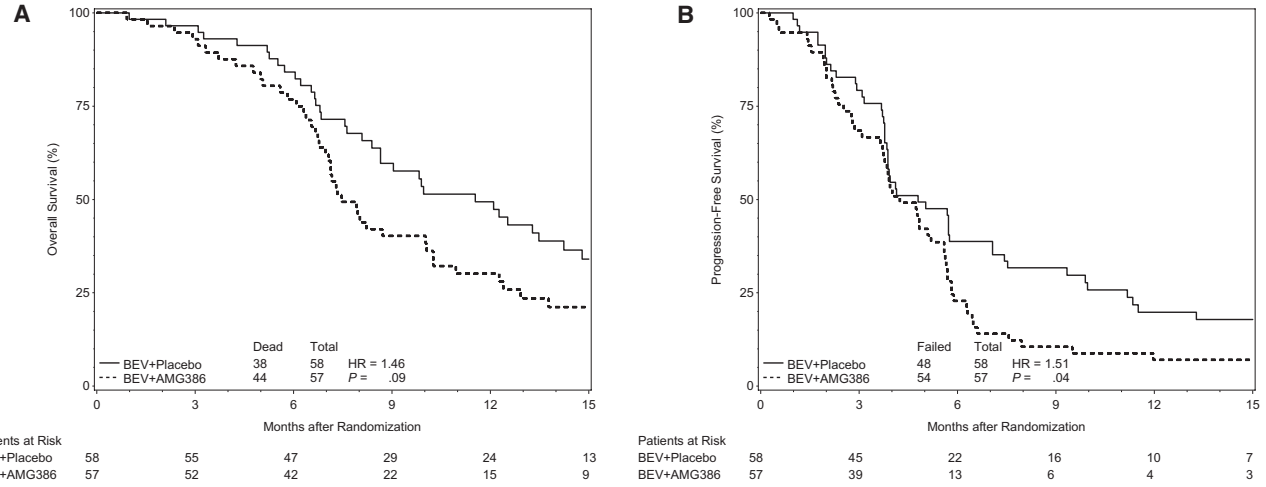

Figure 2. Overall survival (A) and progression-free survival (B) by treatment arm. AMG386, trebananib; BEV, bevacizumab; HR, hazard ratio.

The median survival time of 11.5 months in the control arm was numerically but not statistically significantly longer than the experimental arm (7.5 months). Although PFS was numerically similar (4.8 months in the control arm versus 4.2 months in the experimental arm), PFS was significantly longer in the control arm ($P = .04$). Except for the protocol-specified salvage treatment (placebo arm participants crossing over to experimental arm) and nonprotocol surgery (6 patients who progressed on the placebo arm underwent nonprotocol surgery compared with 0 patients on the experimental arm), there was no significant difference in reported nonprotocol treatments given after disease progression between the 2 arms (Supporting Table S2). When comparing patients in the control arm who crossed over (n = 25) to receive the experimental treatment versus those who did not cross over (n = 33), the patients who did not cross over lived longer (with a median survival time of 12.1 months versus 9.9 months). These data suggest that adding trebananib to bevacizumab could be detrimental compared with bevacizumab alone. In a separate study of trebananib with or without bevacizumab, there was no clear benefit from either trebananib alone or in combination with bevacizumab.[26] In the trebananib plus bevacizumab arm of that study, outcomes were similar to our study, with a 6-month PFS of 24.3%, median OS of 9.5 months, and median PFS of 3.6 months.

It is unclear why patients receiving bevacizumab alone fared better than patients receiving bevacizumab plus trebananib. One potential reason relates to the complex interactions between Ang1 and Ang2. Ang2 can act as a TIE2 antagonist or partial agonist depending on cellular context.[27] Therefore, depending on the balance of Ang1 and Ang2, targeting the Ang–TIE2 pathway has the potential to promote or inhibit tumor growth.[27] Several studies examining the effects of Ang1 or Ang2 blockade

suggest that Ang2 may play a more important role in tumor angiogenesis.[27] In addition, tumor models of several cancers suggest that Ang1 overexpression reduces tumor growth.[28] It is possible that the Ang1 blocking effects of trebananib may somehow counteract or negate the antitumor effects of the Ang2–VEGF blockade.

Another possible explanation for the lack of benefit from combined therapy is upregulation of alternative proangiogenic pathways. Other mechanisms that have been implicated in angiogenesis resistance include upregulation of alternative proangiogenic pathways such as the basic fibroblast growth factor pathway, the hepatocyte growth factor–cMET pathway, and SDF-1α; recruitment of bone marrow–derived proangioenic cells; and increased pericyte coverage of tumor vessels leading to vessel cooption.[29,30] It is possible that coinhibition of the VEGF and Ang–TIE2 pathways is still insufficient to prevent angiogenesis escape.

In conclusion, the combination of bevacizumab and trebananib failed to demonstrate improvements in 6-month PFS, PFS, OS, or RR compared with bevacizumab alone.

Careful consideration should be given to future trials of Ang inhibitors in combination with bevacizumab given the possible detrimental effects of Ang1 in this study. Dual inhibitors of Ang2 and VEGFR are in development and may have therapeutic potential for glioblastoma.

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CONFLICT OF INTEREST DISCLOSURES

Eudocia Q. Lee has been a consultant for Eli Lilly and has received royalties from Up to Date, Inc. Peixin Zhang is an employee of Jazz Pharmaceuticals. Patrick Y. Wen has received grant/research/clinical trial support from Lilly USA, Agios, AstraZeneca, Beigene, Eli Lily, ImmunocellularTherapeutics, Kazia, Kadmon, Karyopharm, Merck, Novartis, Oncoceutics, Sanofi-Aventis, Vascular Biogenics, and VBI Vaccines; is on the speaker's bureau for Merck; has received speaker fees from Prime Oncology; has been a consultant for Roche, Taiho Oncology, Novartis, and Agios Pharmaceuticals; and has served on the advisory board for Merck, Puma, Abbvie, Astra Zeneca, Bayer, Blue Earth Diagnostics, Eli Lilly, Deciphera, Genentech/Roche, GW Pharmaceuticals, Immunomic Therapeutics, Kadmon, Kiyatec, Vascular Biogenics, VBI Vaccines, Ziopharm, Taiho Oncology, DSMB Monteris, and Tocagen. David A. Reardon has received grants from Agenus, Celldex, EMD Serono, Inovio, Acerta Pharmaceuticals, Incyte, Inocia, Midatech, Omniox, and Tragara and has received personal fees from Agenus, Celldex, EMD Serono, Inovio, Abbvie, Advantagene, Amgen, Bayer, Bristol-Myers Squibb, DelMar, Genentech/Roche, Merck, Merck KGaA, Monteris, Novocure, Oncorus, Oxigene, Regeneron, Stemline, and Taiho Oncology. Jeffrey J. Raizer owns stock in Celldex and Agenus, owns stock options in Astra-Zeneca, and is employed by Astellas. Minesh P. Mehta has received grants from Novocure; has received personal fees from Karyopharm, Insys, Remedy, IBA, Varian, Celgene, Abbvie, AstraZeneca, Tocagen, and Blue Earth Diagnostics; and is on the Board of Directors for Oncoceutics. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Eudocia Q. Lee: study concept and design; data analysis/interpretation; writing–original draft; writing–review and editing. **Peixin Zhang:** study concept and design; data analysis/interpretation; writing–original draft; writing–review and editing. **Patrick Y. Wen:** study concept and design; writing–original draft; writing–review and editing. **Elizabeth R. Gerstner:** study concept and design; writing–original draft; writing–review and editing. **David A. Reardon:** study concept and design; writing–original draft; writing–review and editing. **Kenneth D. Aldape:** study concept and design; writing–original draft; writing–review and editing. **John F. deGroot:** study concept and design; writing–original draft; writing–review and editing. **Edward Pan:** implementation of data; writing–original draft; writing–review and editing. **Jeffrey J. Raizer:** implementation of data; writing–original draft; writing–review and editing. **Lyndon J. Kim:** implementation of data; writing–original draft; writing–review and editing. **Steven J. Chmura:** implementation of data; writing–original draft; writing–review and editing. **H. Ian Robins:** implementation of data; writing–original draft; writing–review and editing. **Jennifer M. Connelly:** implementation of data; writing–original draft; writing–review and editing. **James D. Battiste:** implementation of data; writing–original draft; writing–review and editing. **John L. Villano:** implementation of data; writing–original draft; writing–review and editing. **Naveed Wagle:** implementation of data; writing–original draft; writing–review and editing. **Ryan T. Merrell:** implementation of data; writing–original draft; writing–review and editing. **Merideth M. Wendland:** implementation of data; writing–original draft; writing–review and editing. **Minesh P. Mehta:** study concept and design; data analysis/interpretation; writing–original draft; writing–review and editing.

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