A Multicenter, Phase II, Randomized, Noncomparative Clinical Trial of Radiation and Temozolomide with or without Vandetanib in Newly Diagnosed Glioblastoma Patients

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Abstract

Purpose: Vandetanib, a tyrosine kinase inhibitor of KDR (VEGFR2), EGFR, and RET, may enhance sensitivity to chemotherapy and radiation. We conducted a randomized, noncomparative, phase II study of radiation (RT) and temozolomide with or without vandetanib in patients with newly diagnosed glioblastoma (GBM).

Experimental Design: We planned to randomize a total of 114 newly diagnosed GBM patients in a ratio of 2:1 to standard RT and temozolomide with (76 patients) or without (38 patients) vandetanib 100 mg daily. Patients with age $\geq$ 18 years, Karnofsky performance status (KPS) $\geq$ 60, and not on enzyme-inducing antiepileptics were eligible. Primary endpoint was median overall survival (OS) from the date of randomization. Secondary endpoints included median progression-free survival (PFS), 12-month PFS, and safety. Correlative studies included pharmacokinetics as well as tissue and serum biomarker analysis.

Results: The study was terminated early for futility based on the results of an interim analysis. We enrolled 106 patients (36 in the RT/temozolomide arm and 70 in the vandetanib/RT/temozolomide arm). Median OS was 15.9 months [95% confidence interval (CI), 11.0–22.5 months] in the RT/temozolomide arm and 16.6 months (95% CI, 14.9–20.1 months) in the vandetanib/RT/temozolomide (log-rank $P = 0.75$).

Conclusions: The addition of vandetanib at a dose of 100 mg daily to standard chemoradiation in patients with newly diagnosed GBM or gliosarcoma was associated with potential pharmacodynamic biomarker changes and was reasonably well tolerated. However, the regimen did not significantly prolong OS compared with the parallel control arm, leading to early termination of the study. *Clin Cancer Res; 1–9.* ©2015 AACR.

Introduction

Despite standard therapy with surgery, radiation (RT), and temozolomide, the prognosis for newly diagnosed glioblastoma (GBM) remains poor with a median overall survival (OS) of approximately 15 months (1). The advent of molecularly targeted drugs for cancer has brought new promise that molecular pathways important for gliomagenesis and progression could be targeted to further increase survival. Aberrant EGF receptor (EGFR) signaling is common in GBM with EGFR amplification (reported up to 50% of tumors; ref. 2) and may potentially play a role in resistance to radiation (3, 4) and chemotherapy (4). In addition, GBMs are highly vascularized tumors, with the VEGF/VEGF receptor 2 (VEGFR-2) pathway acting as an important mediator of angiogenesis (5) and radioresistance (6) in GBM. However, VEGF blockade with bevacizumab was not associated with added survival benefit over chemoradiation alone in two recent phase III trials (7, 8). Moreover, the role of EGFR blockade in GBM remains unclear.

Vandetanib is an orally bioavailable 4-anilinoquinazoline which selectively inhibits KDR (VEGFR-2), EGFR, and RET. Vandetanib has shown efficacy in preclinical models of glioma (9, 10) and potentiated the effects of RT (9, 11–15). We previously demonstrated that vandetanib could be safely combined with RT and temozolomide in a phase I study of patients with newly diagnosed GBM (16). We designed a randomized,

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

This randomized, noncomparative phase II trial examined the efficacy of adding vandetanib (an inhibitor of VEGFR2, EGFR, and RET) to radiation and temozolomide in patients with newly diagnosed glioblastoma. We performed exploratory correlative analyses of serum and tissue biomarkers to investigate whether these biomarkers could predict response to treatment. Serum angiogenesis studies were largely supportive of previous biomarker studies of anti-VEGFR agents and suggested that vandetanib is a weak inhibitor of VEGFR2. Archival tissue testing did not reveal statistically significant differences in progression-free survival or overall survival based on EGFRvIII mutation, EGFR amplification, or PTEN staining pattern. Limited pharmacokinetic testing was also consistent with prior studies of vandetanib at similar dosing. The addition of vandetanib to standard chemoradiation did not significantly prolong survival compared with historical controls.

noncomparative, phase II trial of standard chemoradiation with or without vandetanib in patients with newly diagnosed GBM or gliosarcoma.

Materials and Methods

Patients

Patients age 18 years or older with histologically confirmed GBM or gliosarcoma who had received no prior chemotherapy or radiation were eligible. Other inclusion criteria included Karnofsky performance status (KPS) $\geq$ 60, life expectancy $\geq$ 12 weeks, adequate bone marrow function (WBC $\geq$ 3,000/μL, ANC $\geq$ 1,500/mm^3, platelet count $\geq$ 100,000/mm^3, and hemoglobin $\geq$ 10 gm/dL), adequate liver function [SGOT, SGPT $\leq$ 2.5 times upper limit of normal (ULN); bilirubin $\leq$ 1.5 times ULN], and adequate renal function (creatinine < 1.5 mg/dL, and/or serum creatinine $\leq$ 1.5$\times$ ULN, and/or creatinine clearance >30 mL/minute, calculated by Cockcroft–Gault formula). At least 10 unstained slides or 1 tissue block from a prior biopsy or surgery was required for correlative studies. Patients with clinically significant cardiovascular events, cardiac arrhythmias including QT prolongation or left bundle branch block, significant intratumoral or peritumoral hemorrhage, or those taking enzyme inducing antiepileptics or coumadin were excluded. Approval from institutional review boards and/or independent ethics committees was obtained at each site. All patients provided written, informed consent. This study was registered on clinicaltrials.gov (NCT00441142).

Treatment and study design

This was a randomized, noncomparative, open-label, multicenter phase II study that enrolled patients between February 2009 and June 2011 (CONSORT diagram; Fig. 1). Patients were randomly assigned 2:1 at registration to receive RT and temozolomide with or without vandetanib. Patients were required to begin treatment 21 to 35 days after surgical resection or 14 to 35 days after stereotactic biopsy. Patients underwent radiation with concurrent temozolomide 75 mg/m^2 daily for 6 weeks (termed the "induction" phase), followed by 4 to 6 weeks of rest

(termed the "rest" phase), and then temozolomide "maintenance" for 12 cycles dosed at 150 mg/m^2/day on days 1 to 5 of the first 28-day cycle, and if well tolerated, dosed at 200 mg/m^2/day on days 1 to 5 of each subsequent 28-day cycle. RT was administered via external beam to a partial brain field in daily fractions of 180 to 200 centiGray (cGy), to a planned total dose to the tumor of approximately 6000 cGy. For those randomized to the vandetanib arm, vandetanib 100 mg was taken once daily beginning 5 to 7 days before initiating radiation and continuing until removal from study treatment. Vandetanib was supplied by AstraZeneca. Treatment continued until progressive disease or unacceptable toxicity.

Patients were evaluated every 2 weeks during the "induction" and "rest" phases and then every 4 weeks during the maintenance phase. Imaging (brain MRI with gadolinium preferred) was obtained before initiation of study treatment, before cycle 1 of adjuvant temozolomide, and then every 8 weeks thereafter.

The primary endpoint was median OS. Secondary objectives included median progression-free survival (PFS), 12-month PFS (PFS12), and safety. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0. Radiographic assessments were based on modified Macdonald Criteria (17) as this study was initiated before the development of Response Assessment in Neuro-Oncology (RANO) criteria (18). Macdonald Criteria for partial response (PR) and stable disease (SD) was modified to require that the steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy. Survival analysis was based on Kaplan–Meier estimates and was based on treated patients (as survival information was not collected on patients who were randomized but withdrew from the study before initiating treatment). In exploratory studies, we planned to evaluate the changes in plasma angiogenic biomarkers and their associations with outcomes in a patient receiving vandetanib/RT/temozolomide.

Pharmacokinetics

Blood collection for limited pharmacokinetics was mandatory for all patients randomized to the vandetanib arm. Pharmacokinetic samples were collected at baseline (before starting therapy on day 1), on day 22 ($\pm$1 day) of "induction" treatment with chemoradiation, on day 8 ($\pm$1 day) of the rest phase between concurrent temozolomide and adjuvant temozolomide, and on day 1 ($\pm$2 days) of the first cycle of temozolomide "maintenance" therapy.

Human plasma concentrations of vandetanib using lithium heparin as anticoagulant were determined by high-performance liquid chromatography and tandem mass spectrometry (HPLC/MS-MS). The bioanalytical method for vandetanib has been reported previously (19). The analysis was performed by Bio-Analytical Systems (BASi). The standard curves of vandetanib in plasma ranged from 5 to 1000 ng/mL. Samples were stored at $-80°$C until analysis. The precision (%CV) and accuracy (% bias) for the quality control (QC) samples were $\leq$9.9%CV and within -1.0% to 1.9% bias. However, the results for a number of samples were generated outside of demonstrated long-term stability window, and these results should be used for informational purposes only. With these exceptions, the results of analysis of vandetanib in lithium heparinized human plasma are valid.

Figure 1.
CONSORT flow diagram of patients enrolled on study. TMZ, temozolomide.
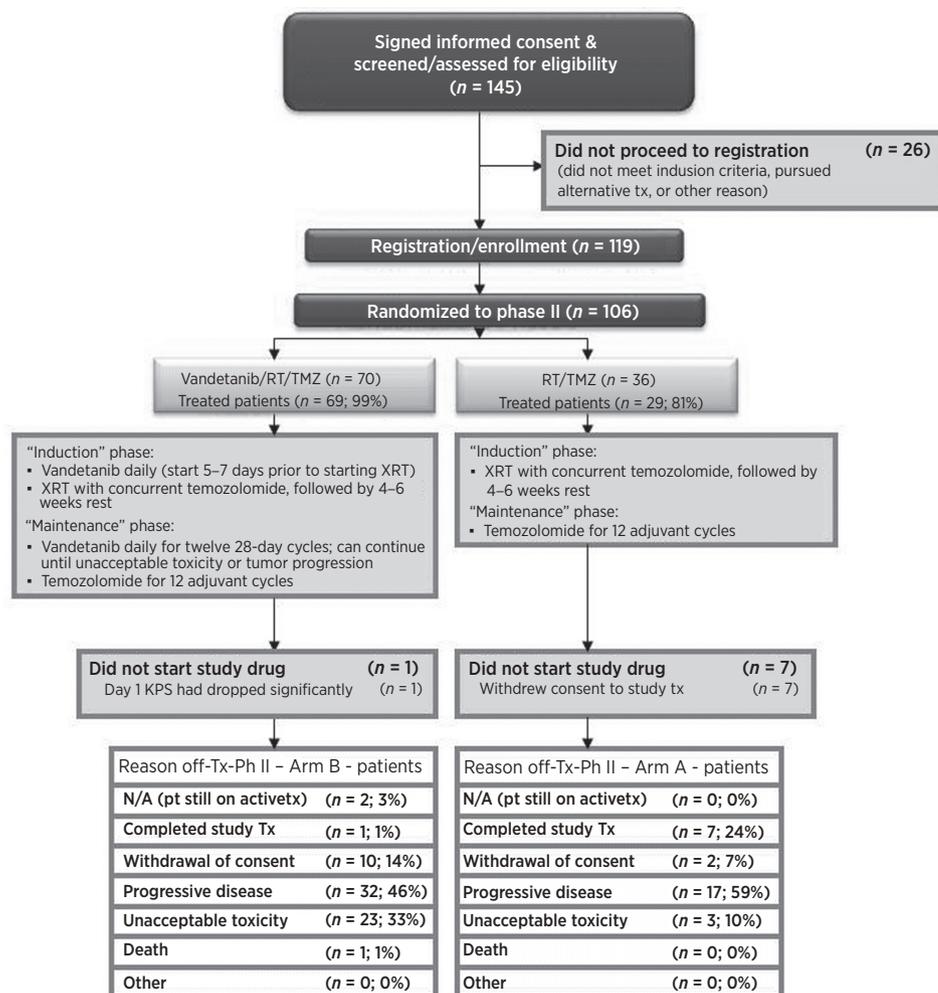
Plasma and tissue biomarkers

Blood collection for plasma angiogenic biomarkers was mandatory for all patients randomized to the vandetanib arm. Samples were collected at various time points: baseline (before starting therapy on day 1), at 4 and 24 hours after first dose of vandetanib, on days 8 and 22 during chemoradiation, and on day 1 of every odd numbered cycle of maintenance therapy. Plasma protein measurements were performed using multiplex array (Meso Scale Discovery) or standard ELISA kits (R&D Systems) as previously described (20).

Submission of tissue from their original surgery demonstrating GBM was mandatory for all patients. Diaminobenzidine, bright-field staining was performed according to standard protocols on 5 μm thick paraffin sections (21) using the following primary antibodies: PTEN (Cell Signaling Technology, #9559), activated NOTCH1-specific antibody (Cell Signaling Technology, #4147), VEGFR2 (Cell Signaling Technology, #2479), and IDH1 (R132H) (Dianova, DIA-H05). EGFR amplification status was determined by silver *in situ* hybridization (Ventana 760-1216), while EGFRvIII RNA was detected by the previously described Nanostring assay (22) MGMT methylation was performed according to standard pyrosequencing protocols (23). FISH for 1p/19q utilized Vysis LSI1p36/LSI1q25 Dual Color Probe Set 1 and LSI19p13/LSI19q13 Dual Color Probe Set 2 (Abbott Molecular).

Statistical analysis

We planned to enroll a total of 114 eligible patients randomized in a ratio of 1:2 to standard therapy with RT/temozolomide (38 patients) versus vandetanib/RT/temozolomide (76 patients). Patients were randomized at time of registration, before the start of RT. Assuming an exponential distribution and testing for a decreased hazard compared with historical controls, the study was powered to detect an increase of 15% in OS rates at the 15 months evaluation time point attributed to the addition of vandetanib. With 76 patients in the vandetanib arm, the study had 88% power to detect such an increase, using a one-sided binomial hypothesis test with significance level of 0.1. A null of no difference would be rejected if at least 46 patients are alive by 15 months. The study was not powered or designed to be comparative. While a concurrent control group has been included to validate that the outcome for this patient group does not differ substantially from what would be expected historically, the numbers are too small to make a decision on the success of this combined therapy based on a statistical hypothesis test comparing the two treatment groups.

Plasma biomarker changes were expressed as ratios, reported as median with interquartile intervals, and tested using exact paired Wilcoxon test. Correlations of biomarkers with response rate (RR) and OS were quantified as Kendall correlation

coefficients. *P* values were obtained from the Jonckheere–Terpstra test. All *P* values < 0.05 were considered statistically significant.

For tissue biomarkers, the Kaplan–Meier method was used to calculate the PFS and OS point and quartile estimates and the log-rank test was used to determine the *P* value for the comparison between the respective biomarker levels.

As both the tissue and plasma markers were exploratory analyses, there were no prespecified hypotheses associated with these correlative studies.

Results

Patient characteristics

We enrolled 106 patients (36 in the RT/temozolomide arm and 70 in the vandetanib/RT/temozolomide arm) before early termination of the trial. Median ages were 55 (range 23–73) and 59 (range 23–83), respectively (Table 1). Median KPS was 90 (range: 60–100) in both arms. All patients had a diagnosis of GBM or gliosarcoma. There was no imbalance in baseline characteristics between the two groups.

Eight patients randomized to a treatment arm did not start treatment on study (Fig. 1). Seven patients in the standard therapy arm withdrew consent upon learning they were randomized to the RT/temozolomide arm. One patient on the vandetanib arm did not start treatment due to a dramatic clinical decline before initiating treatment. There were no apparent differences in baseline characteristics between those patients who did not start treatment on trial and those who did start treatment on trial (results not shown).

Efficacy and safety

Because of slow accrual and concern for futility, an unplanned interim analysis was performed. This study was terminated early for futility based on the results of the interim analysis.

Median OS and PFS as well as radiographic RRs were similar between the two arms (Table 2). Median OS was 15.9 months (95% CI, 11.0–22.5 months) in the RT/temozolomide arm and 16.6 months (95% CI, 14.9–20.1 months) in the vandetanib/RT/temozolomide (log-rank *P* = 0.75; Fig. 2). Median PFS was 6.2 months (95% CI, 3.9–10.4 months) and 7.7 months (95% CI, 5.5 months–10.1 months), respectively, in each arm (log-rank *P* = 0.61). The overall response rate (CR + PR) was 17.9% in the RT/temozolomide arm and 25.4% in the vandetanib/RT/temozolomide arm.

As of June 2013, 2 patients (2.9%) on the vandetanib arm remain on vandetanib monotherapy after completing the 12

adjuvant cycles of vandetanib/temozolomide. One patient (1.4%) on the vandetanib arm completed the minimum 12 adjuvant cycles and decided not to receive further vandetanib monotherapy. Seven patients (24%) on standard therapy completed 12 adjuvant cycles of temozolomide and remain on observation. Thirty-two patients (46%) on the vandetanib arm and 17 patients (59%) on the standard therapy arm have developed progressive disease on study.

In the vandetanib arm, the most frequent grade 3 or higher adverse events (AEs) at least possibly related to study treatment were lymphopenia (43.5%), leukopenia (11.6%), neutropenia (11.6%), ALT/SGPT elevation (8.7%), and thrombocytopenia (7.2%) (Table 3). In the standard therapy arm, lymphopenia (27.6%), thrombocytopenia (17.2%), neutropenia (10.3%), and ALT/SGPT elevation (10.3%) were the most common AEs at least possibly related to study treatment. Twenty-three patients (33%) on the vandetanib arm were taken off study due to unacceptable toxicity, compared with 3 patients (10%) on the standard therapy arm. Rash was more often seen in the vandetanib arm. Three different patients on the vandetanib arm experienced grade 3 or 4 rashes with desquamation. Two patients were also characterized as developing grade 3 or 4 erythema multiforme at least possibly related to study treatment. There were no grade 3 or 4 rashes at least possibly related to study treatment seen in the standard therapy arm. There was one patient with colonic fistula (1.4%), one patient with colonic perforation (1.4%), 3 patients with thrombosis/thrombus/embolism (4.3%), and one patient with a cerebrovascular ischemic event (1.4%) at least possibly related to study treatment in the vandetanib arm; none of these toxicities were reported as grade 3 or higher and at least possibly related to

Table 1. Patient characteristics

	RT/temozolomide N = 36	Vandetanib/RT/ temozolomide N = 70	P
Median age, y (range)	55 (23–73)	59 (23–83)	
Median KPS (range)	90 (60–100)	90 (60–100)	
Gender, Female	19 (52.8%)	26 (37.1%)	0.1
Race			0.7
White	32/36 (88.9%)	64/70 (91.4%)	
African American	1/36 (2.8%)	2/70 (2.9%)	
Asian	2/36 (5.6%)	1/70 (1.4%)	
Other	1/36 (2.8%)	3/70 (4.3%)	
Extent of Resection			0.4
Gross total resection	10/29 (34.5%)	38/67 (56.7%)	
Subtotal resection	13/29 (44.8%)	16/67 (23.9%)	
Biopsy	6/29 (20.7%)	13/67 (19.4%)	

Table 2. Outcomes

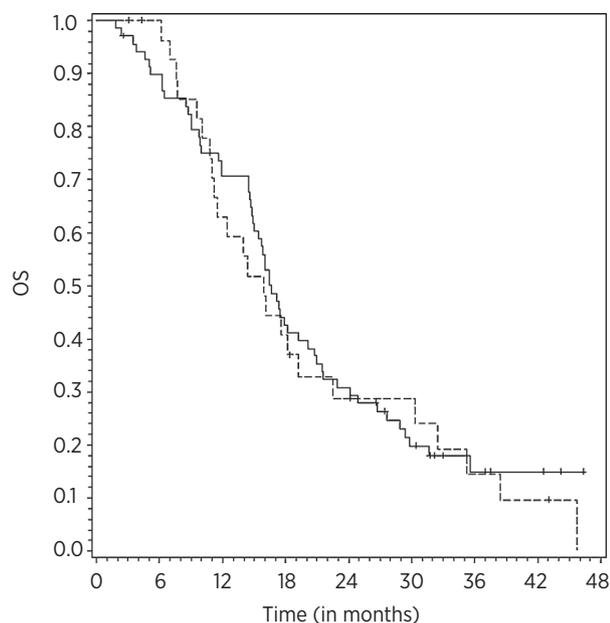|	RT/temozolomide (N = 29)	Vandetanib/RT/temozolomide (N = 69)	P
OS, months, median (95% CI)	15.9 months (11.0–22.5)	16.6 months (14.9–20.1)	0.8
PFS, months, median (95% CI)	6.2 months (3.9–10.4)	7.7 months (5.5–10.1)	0.6
OS12 rate (95% CI)	0.56 (0.40–0.80)	0.68 (0.56–0.81)	
PFS12 rate (95% CI)	0.39 (0.20–0.57)	0.25 (0.15–0.37)	
PFS6 rate (95% CI)	0.57 (0.37–0.73)	0.58 (0.44–0.68)	
Best radiographic response			
CR	1/28 (3.6%)	4/51 (7.8%)	
PR	4/28 (14.3%)	9/51 (17.6%)	
SD	18/28 (64.3%)	27/51 (52.9%)	
Pseudoprogression	0	3/51 (5.9%)	
Progressive disease	5/28 (17.9%)	8/51 (1%)	

Figure 2.
OS by treatment arm, solid line (vandetanib/RT/temozolomide), dashed line (RT/temozolomide).

study treatment in the standard therapy arm. There was one grade 5 pneumonia at least possibly related to study treatment seen in the vandetanib arm. There were no grade 5 toxicities at least possibly related to study treatment in the standard arm.

Plasma biomarkers

The concentration of several plasma biomarkers of angiogenesis changed significantly after vandetanib/RT/temozolomide. PlGF dropped at 4 hours but was moderately increased by 6% to 40% on day 2, day 8, and day 22 ($P < 0.05$) and sVEGFR2 moderately decreased at all time points by 4% to 8% ($P < 0.05$, Table 4). In addition, plasma SDF1α and sTie2 dropped at 4 hours and plasma VEGF and SDF1α increased at day 22. Plasma Ang2, sVEGFR1, CAIX, bFGF, and collagen IV showed no significant change over time. Exploratory studies showed a direct correlation between more favorable radiographic responses with (i) low plasma bFGF at baseline; (ii) decreases in CAIX at 4 hours; and (iii) decreases in sVEGFR2 and increases in collagen IV at day 2 (Supplementary Table S1). In addition, OS was directly associated with plasma sVEGFR1 at baseline and inversely with the change in plasma sVEGFR2 and PlGF at day 2 (Supplementary Table S2). No other association was seen for the other biomarkers and time points.

Pharmacokinetics

Limited pharmacokinetic analysis was performed in patients randomized to the vandetanib arm. Mean concentrations of 231 (SD ± 79), 292 (SD ±135), and 295 (SD ±125) ng/mL were achieved at nominal days 22, 55, and 80 (Supplementary Fig. 1). Mean concentrations increased between days 22 and 55 and were stable between days 55 and 80 indicating that steady state was reached by day 55. This is consistent with the long half life of vandetanib and the time to reach steady state in other trials. The steady-state mean concentration of approximately 300 ng/mL is

Table 3. Grade 3 or 4 or 5 AEs possibly, probably, or definitely related to treatments, according to arm

	RT/temozolomide (N = 29)	Vandetanib/RT/temozolomide (N = 69)
Hematologic		
Anemia	0	2 (2.9%)
Leukopenia	2 (6.9%)	8 (11.6%)
Lymphopenia	8 (27.6%)	30 (43.5%)
Neutropenia	3 (10.3%)	8 (11.6%)
Thrombocytopenia	5 (17.2%)	5 (7.2%)
Dermatology/skin		
Pruritis/itching	0	1 (1.4%)
Rash–acneiform	0	1 (1.4%)
Rash–desquamation	0	3 (4.3%)
Rash–erythema multiforme	0	2 (2.9%)
Gastrointestinal		
Colonic fistula	0	1 (1.4%)
Colonic perforation	0	1 (1.4%)
Diarrhea	0	1 (1.4%)
Hepatobiliary/pancreas		
Cholecystitis	0	1 (1.4%)
Infection	2 (6.9%)	2 (2.9%)
Metabolic/laboratory		
ALT/SGPT elevation	3 (10.3%)	6 (8.7%)
AST/SGOT elevation	1 (3.4%)	3 (4.3%)
Hyperbilirubinemia	0	2 (2.9%)
Hyperglycemia	0	1 (1.4%)
Hyponatremia	0	1 (1.4%)
Hypophosphatemia	0	3 (4.3%)
Nervous system disorders		
CNS cerebrovascular ischemia	0	1 (1.4%)
Dizziness	0	1 (1.4%)
Headache	1 (3.4%)	0
Imbalance/weakness	0	1 (1.4%)
Pulmonary/upper respiratory		
Dyspnea	0	3 (4.3%)
Hypoxia	0	1 (1.4%)
Vascular disorders		
Hypertension	0	1 (1.4%)
Thrombosis/thrombus/embolism	0	3 (4.3%)
Fatigue	1 (3.4%)	4 (5.8%)

in good agreement with steady state achieved in other trials employing 100 mg once daily dosing (24).

Tissue biomarkers

By log-rank testing, there was a statistically significant increase in PFS (not reached vs. 0.65 years; $P = 0.03$) and OS (not reached vs. 1.38 years; $P = 0.03$) in the vandetanib arm by IDH1 (R132) mutation status (Supplementary Table S3). In the standard therapy arm, there was a trend towards increased PFS (1.90 vs. 0.63 years; $P = 0.3$) and OS (3.18 vs. 1.32 years; $P = 0.09$) in patients with IDH1 (R132H) mutations, but the difference was not statistically significant. Similarly, there was a nonsignificant trend towards improved OS in patients with methylated MGMT promoter in both treatment arms. There were no statistically significant differences in PFS or OS based on EGFRvIII mutation, EGFR amplification, PTEN staining pattern, or activated NOTCH staining pattern in tumor cells.

Discussion

This randomized, noncomparative study evaluated the VEGFR2/EGFR inhibitor vandetanib in combination with

Table 4. Plasma cytokines (pg/mL) that significantly change (increase italicized, decrease in bold) in the vandetanib/RT/temozolomide arm

Plasma biomarker	Pretreatment	4 hours	Day 2	Day 8	Day 22
VEGF	110 (76–147; N = 68)	105 (82–135; N = 60)	92 (75–140; N = 57)	115 (89–142; N = 62)	*134 (97–165; N = 58)*
P	N/A	0.4	0.4	0.6	*0.02*
PlGF	21 (18–27; N = 68)	**19 (17–22; N = 60)**	*22 (19–27; N = 57)*	*25 (20–28; N = 62)*	*29 (25–36; N = 58)*
P	N/A	**0.0001**	*0.02*	*<0.0001*	*<0.0001*
bFGF	18 (6–44; N = 68)	14 (5–32; N = 60)	16 (5–41; N = 57)	18 (5–45; N = 62)	19 (8–36; N = 58)
P	N/A	0.4	0.8	0.8	0.6
sVEGFR1	117 (94–142; N = 68)	117 (93–154; N = 60)	104 (92–137; N = 57)	110 (90–136; N = 62)	109 (85–137; N = 58)
P	N/A	0.7	0.9	0.07	0.7
sVEGFR2	8,414 (7,201–9,781; N = 68)	**7,719 (6,786–9,411; N = 60)**	**8,235 (6,963–9,188; N = 57)**	**8,305 (6,958–9,305; N = 62)**	**7,445 (6,467–9,123; N = 58)**
P	N/A	**0.002**	**0.001**	**0.03**	**0.0003**
Ang2	2,234 (1,500–2,854; N = 68)	2,044 (1,481–2,499; N = 60)	2,190 (1,517–2,814; N = 57)	2,263 (1,569–3,140; N = 62)	1,986 (1,588–2,809; N = 58)
P	N/A	0.6	0.2	0.2	0.4
sTie2	18 (14–20; N = 68)	**17 (14–20; N = 60)**	18 (15–20; N = 57)	17 (15–20; N = 62)	17 (15–20; N = 58)
P	N/A	**0.006**	0.7	0.8	0.7
SDF1α	1,576 (1,243–1,858; N = 68)	**1,478 (1,131–1,803; N = 60)**	1,455 (1,190–1,915; N = 57)	1,525 (1,166–1,778; N = 62)	*1,587 (1,347–1,929; N = 58)*
P	N/A	**0.0001**	0.2	0.2	*0.01*
Collagen IV	0.31 (0.22–0.38; N = 68)	0.27 (0.20–0.36; N = 60)	0.28 (0.22–0.33; N = 57)	0.28 (0.21–0.38; N = 62)	0.29 (0.23–0.36; N = 58)
P	N/A	0.4	0.4	0.8	0.8
Plasma CAIX	46 (23–70; N = 68)	47 (25–67; N = 60)	39 (25–61; N = 57)	39 (30–68; N = 62)	48 (27–67; N = 58)
P	N/A	0.7	0.4	0.4	0.7

NOTE: Data are shown as medians and interquartile ranges (in parentheses) and are compared with baseline (pretreatment) levels. *P* values (adjusted for multiple comparisons) are from the paired exact paired Wilcoxon test.

standard therapy for patients with GBM or gliosarcoma, but did not meet its primary endpoint of statistically significant prolongation of OS compared with historical controls or the parallel control arm. Treatment with vandetanib 100 mg daily in combination with RT and temozolomide was generally well tolerated with expected toxicities from EGFR and VEGFR-2 inhibition. Although lymphopenia and leukopenia occurred in slightly higher frequency in the vandetanib arm compared with the standard therapy arm, such hematologic toxicities were not seen in studies of vandetanib monotherapy (25–28).

The changes in plasma biomarkers over time were consistent with previous studies of vandetanib and other anti-VEGFR tyrosine kinase inhibitors (TKI). For example, we observed significant increases in plasma PlGF and decreases in plasma sVEGFR2, potential pharmacodynamic biomarkers for anti-VEGF therapy. However, the magnitude of these changes was modest for vandetanib (6%–40% for PlGF and 4%–8% for sVEGFR2) compared with more potent anti-VEGFR TKIs such as cediranib in newly diagnosed GBM patients (31%–263% for PlGF and 7%–24% for sVEGFR2; ref. 29). Moreover, plasma Ang2 levels were not significantly changed after vandetanib/RT/temozolomide treatment in contrast to the decrease seen after cediranib with RT/temozolomide (29). These biomarker studies strongly suggest a weak VEGF pathway inhibition of 100 mg/day of vandetanib.

Exploratory correlative studies were also generally consistent with previous reports. As previously seen with cediranib (30) and vatalanib (31) in GBM, a rapid increase in circulating collagen IV, a biomarker of vascular normalization after VEGF inhibition, was associated with a better response to vandetanib/RT/temozolomide treatment. Along the same lines, a decrease in the circulating levels of the hypoxia biomarker CAIX at 4 hours was also associated with a better response. Finally, better treatment responses were also associated with lower levels of bFGF (a proangiogenic marker) at baseline as well as greater decreases in sVEGFR2 (consistent with its potential pharmacodynamic marker for VEGFR2 TKIs; ref. 32). The extent of sVEGFR2 decrease was also associated with OS in these patients. OS was also associated with baseline plasma sVEGFR1 levels. sVEGFR1 is an endogenous

inhibitor of the VEGF and PlGF, previously found to inversely correlate with the response to anti-VEGF agents, including vandetanib with cetuximab and chemotherapy in colorectal cancer (33). This discrepancy may be due to vandetanib's ability to efficiently block the VEGF pathway, particularly in the face of rising concentrations of circulating PlGF and VEGF. Indeed, an early increase in plasma PlGF was associated with poor survival. Of note, an increase in sVEGFR1 over time tended to associate with worse outcome (Supplementary Table S2 and data not shown) as previously seen with cediranib in GBM patients (20, 29). Taken together, these exploratory studies are largely supportive of previous biomarker studies of anti-VEGFR agents and suggest that one reason for the lack of benefit from vandetanib in GBM is the weak anti-VEGFR2 activity (32).

With regard to tissue biomarkers, none of the biomarkers tested was associated with improved PFS or OS except for IDH1 (R132H) mutation. The improvement in PFS in the vandetanib arm likely reflects the prognostic value of IDH1 mutations, and it is unlikely that IDH1 status predicts response to treatment. There was a trend towards improved OS in the standard therapy arm as well but the difference was not statistically significant, likely due to the small numbers of patients with IDH1 (R132H) mutation (n = 4).

Possible explanations for the lack of efficacy from adding vandetanib to standard therapy is inadequate blood–brain barrier (BBB) penetration and the limited benefit of VEGFR2 and/or EGFR inhibition in newly diagnosed GBM. Surrogate blood/serum biomarkers may not represent relevant intratumoral actions of vandetanib. *In vivo* brain distribution studies in mice indicated that vandetanib penetration into the brain is restricted by both P-glycoprotein (P-gp) and breast cancer resistance protein (Bcrp1) mediated active efflux at the BBB (34). Preclinical data suggest that combining vandetanib with elacridar, a dual P-gp/BCRP inhibitor, or with everolimus may help increase the BBB of vandetanib (34).

In addition, although preclinical studies suggest a beneficial role for EGFR and VEGFR2 blockade, clinical trials of EGFR or VEGF inhibitors have not demonstrated a definitive survival

advantage in GBM. Phase II studies of standard chemoradiation with the EGFR inhibitor erlotinib (35–37) or with erlotinib and bevacizumab (38) did not include a comparison arm of standard chemoradiation. Two recent randomized phase III trials of standard chemoradiation with or without bevacizumab in newly diagnosed GBM [AVAglio and Radiation Therapy Oncology Group (RTOG) 0825] did not demonstrate an OS benefit with the addition of bevacizumab (7, 8). In *post hoc* molecular analysis of the AVAglio study, the addition of bevacizumab conferred a significant OS benefit in patients with IDH1 wild-type proneural tumors (39). Because of limited tissue availability in our study, we did not perform testing for the proneural subtype.

Although the study was not designed to be comparative, the concurrent standard therapy arm was included to validate that the outcome for this patient group does not differ substantially from what would be expected historically. The median OS of the standard therapy arm was 15.9 months, which is slightly improved compared with the median OS of 14.9 months in Stupp and colleagues study that established radiation and temozolomide as standard of care for newly diagnosed GBM (1). Without the comparative arm, one might be misled into thinking that a median OS of 16.6 months in the vandetanib arm represents an improvement over standard therapy. Indeed, these results are comparable to the standard therapy arms in AVAglio, RTOG 0825, and RTOG 0525 (40). This argues in favor of randomized phase II clinical trial designs. However, the obvious disadvantage of noncomparative trial designs is the limited power to formally compare the two arms. Some, including the RANO group, have argued against the use of noncomparative randomized studies for this reason, except in limited circumstances (41).

This study also highlights the challenges of combining targeted molecular agents with radiation and temozolomide in patients with newly diagnosed GBM. In the preliminary phase I study, the maximum tolerated dose of vandetanib with chemoradiation was 100 mg daily, rather than the 300 mg daily that has been used in many single-agent trials with vandetanib (42–44). The low dose of vandetanib used in this trial likely contributed to the weak VEGFR2 inhibition and lack of efficacy. Given the marginal benefit of temozolomide in GBM patients with unmethylated MGMT promoter status (45), there is increasing interest in neuro-oncology in conducting trials in this patient population with the targeted agent and radiation alone, without temozolomide, potentially allowing higher doses of the targeted agent to be used.

Another limitation of our study is that we did not collect information on the impact of vandetanib on cerebral edema or contrast enhancement. Pseudoresponses and improvement in cerebral edema partly related to normalization of abnormally permeable tumor vessels as opposed to true antiglioma effect has been reported with other VEGF and VEGFR inhibitors such as bevacizumab (18). However, since plasma angiogenic biomarker changes in this study suggest very weak VEGFR2 inhibition, we suspect that vandetanib at the doses used in this study may be a weak angiogenesis inhibitor and therefore less likely to produce pseudoresponses or affect cerebral edema.

Although reasonably well tolerated, the addition of vandetanib to standard chemoradiation in patients with newly diagnosed GBM may not significantly prolong OS compared with the parallel control arm. Plasma angiogenic biomarker changes suggest very weak VEGFR2 inhibition at a vandetanib dose of 100 mg/day. From the limited pharmacokinetic analysis, the exposure and attainment of steady-state approximate experiences from prior studies of vandetanib at 100 mg/day dosing in other solid tumors. Further testing of vandetanib in GBM is not recommended.

Disclosure of Potential Conflicts of Interest

A.B. Lassman is a consultant/advisory board member for Agenus, Amgen, Celgene, Foundation Medicine, Genentech, Heron, Kyowa Hakko Kirin Pharma, Merck Sharp & Dohme, Midatech, Novartis, Roche, Sigma Tau, and Stemline. R. Beroukhim has ownership interest (including patents) in AstraZeneca. T. Batchelor reports receiving commercial research grants from AstraZeneca, Millennium, and Pfizer; speakers bureau honoraria from Champions Biotechnology, Educational Concepts Group, Imedex, Oakstone Publishing, Research to Practice, Robert Michael Educational Institute, and Up to Date, Inc; and is a consultant/advisory board member for Agenus, Amgen, Kirin, Merck, Novartis, Proximagen, Roche, and Spectrum. P.Y. Wen reports receiving other research grants from AbbVie, Agios, Angiochem, Ascular Biogenics, AstraZeneca, Cubist, Exelixis, Genentech/Roche, GlaxoSmithKline, Karyopharm, Merck, Novartis, and Sanofi-Aventis; speakers bureau honoraria from Merck; and is a consultant/advisory board member for AbbVie, Celldex, Genentech/Roche, Midatech, Momenta, Novartis, Novocure, Sigma Tau, and Vascular Biogenics. No potential conflicts of interest were disclosed by the other authors.

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A Multicenter, Phase II, Randomized, Noncomparative Clinical Trial of Radiation and Temozolomide with or without Vandetanib in Newly Diagnosed Glioblastoma Patients

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