Title

A single-institution phase II trial of radiation, temozolomide, erlotinib, and bevacizumab for initial treatment of glioblastoma

Journal

Neuro-Oncology, 16(7)

ISSN

1522-8517

Authors

Clarke, Jennifer L

Molinaro, Annette M

Phillips, Joanna J

et al.

Publication Date

2014-07-01

DOI

10.1093/neuonc/nou029

Peer reviewed

Neuro-Oncology

Neuro-Oncology 16(7), 984–990, 2014
doi:10.1093/neuonc/nou029
Advance Access date 16 March 2014

A single-institution phase II trial of radiation, temozolomide, erlotinib, and bevacizumab for initial treatment of glioblastoma

Jennifer L. Clarke, Annette M. Molinaro, Joanna J. Phillips, Nicholas A. Butowski, Susan M. Chang, Arie Perry, Joseph F. Costello, Ashley A. DeSilva, Jane E. Rabbitt, and Michael D. Prados

Department of Neurological Surgery, University of California, San Francisco, San Francisco, California (J.L.C., A.M.M., J.J.P., N.A.B., S.M.C, A.P., J.F.C., A.A.D., J.E.R, M.D.P); Department of Neurology, University of California, San Francisco, San Francisco, California (J.L.C.); Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California (A.M.M.); Department of Pathology, University of California, San Francisco, San Francisco, California (A.P., J.J.P.)

Corresponding Author: Jennifer L. Clarke, MD, MPH, Assistant Professor, Department of Neurological Surgery, Division of Neuro-oncology, 400 Parnassus Ave, A808, Box 0372, San Francisco, CA 94143-0372 (clarkej@neurosurg.ucsf.edu).

Background. Both the epidermal growth factor receptor and vascular endothelial growth factor pathways are frequently overexpressed in glioblastoma multiforme. This study combined bevacizumab, a vascular endothelial growth factor inhibitor, and erlotinib, an epidermal growth factor receptor inhibitor, with standard radiation and temozolomide (TMZ), with the goal of improving overall survival (OS).

Methods. Treatment consisted of fractionated radiotherapy to 60 Gy, with daily TMZ at 75 mg/m^2/d and erlotinib 150–200 mg/d (or 500–600 mg/d for patients on enzyme-inducing antiepileptic drugs). Bevacizumab was given at 10 mg/kg every 2 weeks, starting $\geq$4 weeks after surgery. After radiotherapy, adjuvant TMZ was given at 200 mg/m^2/d $\times$ 5d per 28-day cycle, with unchanged erlotinib and bevacizumab doses. Treatment continued until progression or for 12 months. Efficacy was compared against an institutional historical control. A sample of 55 patients was calculated to provide 85% power to detect a hazard ratio of 0.67 for OS.

Results. Fifty-nine patients were enrolled for efficacy analysis after a 15-patient safety lead-in. For the efficacy group, median age was 54 years; median KPS was 90. Gross total and subtotal resections were achieved in 33% and 53%, respectively. The most frequent related grade 3/4 adverse effects were lymphopenia, thrombocytopenia, neutropenia, diarrhea, weight loss, and fatigue. One patient died of disseminated aspergillosis. Median OS was 19.8 months (vs 18 mo for HC, $P = .33$) and median progression-free survival was 13.5 months (vs 8.6 mo for HC, $P = .03$).

Conclusions. The combination of bevacizumab, erlotinib, TMZ, and radiotherapy appears to be well tolerated and improved progression-free survival but did not reach the primary endpoint of improved OS.

Keywords: bevacizumab, erlotinib, glioblastoma, radiation, temozolomide.

Glioblastoma (GBM) is the most common and most aggressive primary malignant brain tumor in adults. Despite improvements in survival, it remains largely incurable. The current standard of care includes radiation therapy (RT) in combination with low-dose daily temozolomide (TMZ), followed by at least 6 cycles of adjuvant TMZ, based on the seminal phase III study by the European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada.[1] Alterations in epidermal growth factor receptor (*EGFR*) are common in GBM and include overexpression, amplification, and mutation. Indeed, *EGFR* is amplified in ~45% of GBM tumors.[2] GBM is also among the most highly vascularized human tumors, and a major driver of microvascular proliferation is vascular endothelial growth factor (VEGF).[3]

We previously reported the results of a phase II study adding erlotinib (an *EGFR* inhibitor) to standard initial treatment with RT and TMZ, showing a modest improvement in survival over a historical control.[4] Phase II studies of bevacizumab (an antibody targeting VEGF) plus RT/TMZ have also been reported,[5,6] showing improved progression-free survival (PFS) but not overall survival (OS), and phase III studies testing this combination are in the process of being reported as well.[7,8] Both *EGFR* and VEGF pathways are known to be upregulated by radiation, so combining inhibitors of either pathway with RT may be highly effective. In addition,

Received 28 November 2013; accepted 14 February 2014

preclinical data suggest that a multitargeted approach may have more impact on GBM than treatment with a single agent.[9] As such, the presented study combined standard RT and TMZ with both erlotinib and bevacizumab to evaluate whether this combination would be more effective than standard therapy. Because the full combination of RT/TMZ/erlotinib/bevacizumab has not been previously tested, the study was designed with a 15-patient safety lead-in adding bevacizumab and erlotinib to TMZ after standard RT/TMZ, to confirm that there was no unexpected toxicity to the 3-drug combination prior to combining the 3 drugs with radiation.

Materials and Methods

Drug Supply

Bevacizumab and erlotinib were supplied by Genentech.

Patient Population

See Table 1 for a summary of the eligibility criteria. Use of enzyme-inducing antiepileptic drugs (EIAEDs) was strongly discouraged but not prohibited. All patients signed informed consent forms approved by the University of California, San Francisco (UCSF) Institutional Review Board, Committee on Human Research, which also approved the overall study.

Treatment Plan

For the primary efficacy group, RT was administered in daily doses of 1.8–2.0 Gy delivered 5 days per week over ~6 weeks, to a total dose of 59.4 to 60 Gy. During RT, patients not taking EIAEDs received erlotinib at 150 mg/d on a continuous basis 7 days per week. Those taking EIAEDs received erlotinib at 500 mg/d. The dose of erlotinib was escalated on day 15 (±3 d) to 200 mg/d for patients not on EIAEDs and to 600 mg/d for patients on EIAEDs, assuming that they did not experience any grade 3 or intolerable grade 2 rash, or grade 2 diarrhea despite treatment with loperamide. Bevacizumab was dosed at 10 mg/kg and was started in week 2 of RT, between days 8 and 13, to ensure that it was not started until at least 4 weeks after surgery; it was continued every 2 weeks (±3 d) during radiation. All patients were given TMZ at 75 mg/m^2/d continuously 7 days per week.

Table 1. Major eligibility criteria for efficacy population*

Inclusion criteria
• Age ≥18 y
• KPS ≥60
• Newly diagnosed, surgically confirmed GBM or gliosarcoma, with study treatment starting 3–5 wk after open surgery or 2–5 wk after biopsy
• Adequate bone marrow, liver, and kidney function
Exclusion criteria
• Proteinuria (UPC >1.0 or >1 g protein in a 24-hr urine collection)
• Uncontrolled hypertension
• Prior history of hypertensive crisis or encephalopathy or of stroke
• Significant cardiac, valvular, or vascular disease
• Significant recent hemorrhage on baseline scan or history of bleeding diathesis/coagulopathy
• Known HIV, other cancer requiring treatment within 3 y, or serious nonhealing wound, ulcer, or bone fracture
• Recent history of abdominal fistula, abdominal abscess, or gastrointestinal perforation

*Eligibility for the safety lead-in cohort included all of these items, plus patients had to have stable disease on their postradiation MRI.

For both the primary efficacy group and the safety lead-in, after the completion of RT, patients were treated with TMZ 200 mg/m^2/d for 5 days every 28 days (+7 d) and bevacizumab 10 mg/kg every 2 weeks; cycles were 4 weeks in length. Patients not on EIAEDs received erlotinib at a continuous daily dose of 150 or 200 mg/d; patients on EIAEDs began erlotinib at a dose of 500 or 600 mg/d. Dosing of erlotinib was based on prior phase I dose-finding and pharmacokinetics studies and was confirmed in our prior phase II study adding erlotinib to radiation and TMZ.[4]

The pretreatment evaluation included a complete history and physical and neurologic examination. Prestudy laboratory tests, obtained within 14 days of treatment, included a complete blood count (CBC) with differential and platelets, protime, prothrombin time, serum creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, anticonvulsant level (if applicable), urine protein: creatinine ratio (UPC) or urine dipstick, and serum pregnancy test for women of childbearing potential.

During radiation, a CBC with differential and platelets was performed every 2 weeks, while blood urea nitrogen, AST, total bilirubin, and UPC were done on day 28. During adjuvant chemotherapy, CBC with differential, creatinine, blood urea nitrogen, total bilirubin, AST, and UPC measurements were performed prior to each 4-week cycle, and an additional CBC with differential was performed on approximately day 21 of each cycle. Brain MRI was performed as a baseline 2–3 weeks after the completion of radiation, and then every 8 weeks while patients were receiving treatment. Prophylaxis for *Pneumocystis jerovecii* pneumonia was encouraged for patients on corticosteroids and during radiation with TMZ but was left to the discretion of the treating physician. The intent was to treat up to 12 months after RT; additional treatment beyond 12 months was allowed at the discretion of the treating physician, assuming no significant toxicity and with the consent of the patient. Treatment beyond 24 months was not allowed. All patients were observed for OS; after disease progression, patients were contacted every 3 months to determine survival.

Pathology slides from the most recent surgical material were submitted for confirmatory pathology review, as well as to evaluate molecular abnormalities in the tumor, including *EGFR* by fluorescent in situ hybridization (FISH), *EGFR* variant (v)III by immunohistochemistry (IHC), phosphate and tensin homolog (*PTEN*) by IHC, and methylguanine methyltransferase (*MGMT*) gene promoter region cytosine–phosphate–guanine island hypermethylation testing using a methylation-specific PCR-based assay. To assess the mutation status of isocitrate dehydrogenase 1 (IDH1), DNA was extracted from paraffin-embedded tumor tissue and sequenced as previously described.[10] Immunohistochemistry for IDH1R132H was performed when sufficient tumor DNA was available, as described previously.[11] The IHC assays were scored using a 0 to 3+ scoring system. No positive staining was scored 0; 1% to 25% immunoreactivity of cells was scored 1+; 26%–75% was scored 2+; and 76% or greater was scored

3+. Analyses of results were done using the actual IHC score, and the level of positivity was included as part of the assessment. Thus, any level of positivity was considered positive, but the range was taken into account.

Trial Design and Statistics

This was a single-arm, single-institution, open-label phase II trial. The primary endpoint was OS as measured from the date of surgical diagnosis. Secondary endpoints included PFS and the evaluation of safety of the combination of bevacizumab, erlotinib, and TMZ. Results were compared with results of comparable patients treated at UCSF from 2 prior prospective clinical trials ($n = 133$), one combining erlotinib with TMZ during and after RT, and the other combining enzastaurin with TMZ during and after RT.[4,12]

The protocol was written with a safety lead-in adding bevacizumab and erlotinib to TMZ after completion of radiation to rule out unexpected toxicity of the combination of drugs. Assuming no unexpected toxicity, patients were to be enrolled in the main protocol, which was to form the basis of the primary efficacy analysis. The safety lead-in patients were not included in the efficacy analyses but were included in the safety analyses.

Consistent with the phase II nature of this study, the hypothesis that the new therapy is worthy of further study was tested using a 1-sided test with alpha = 0.1. For the purpose of the calculation, we assumed that survival followed an exponential distribution. Under this assumption, with a sample size of 55 patients and the above-described control group, there was expected to be ~85% power to detect an improvement in survival if the hazard ratio of experimental treatment/historical control was 0.67. Up to 10% overaccrual was allowed to ensure an adequate sample size in case any adjustment for ineligible patients was needed. The relationship of molecular subtypes to outcome was assessed in an exploratory fashion.

A stopping rule was used for the main arm of the study to monitor for the possibility of toxicity from treatment-related intracranial hemorrhage. Specifically, if the lower end of the 95% confidence bound for the estimated probability of treatment-related intracranial hemorrhage were to exceed 5%, considerations would be made to either modify the current doses of treatment or suspend the trial, in consultation with the UCSF Data Safety and Monitoring Committee. The total number of accrued patients and the corresponding thresholds for stopping are shown in Table 2.

Table 2. Stopping rule for intracranial hemorrhage

Number of patients	14–16	17–28	29–40	41–53	54–67	68–70
Stop if $\geq n$ toxicities	3	4	5	6	7	8

Table 3. Baseline patient characteristics

Parameter	Current Study ($n = 59$) Number (%)	Historical Control ($n = 133$) Number (%)
KPS		
Median	90	90
Range	60–100	60–100
Age, y		
Median	54	56
Range	21–76	23–80
Extent of resection		
Biopsy	8 (14)	19 (14)
Subtotal	30 (53)	68 (52)
Gross total	19 (33)	45 (34)
Number of patients taking EIAEDs	10 (17)	37 (28)

Evaluation of Response

This study was written prior to the development of the Revised Assessment in Neuro-Oncology guidelines. As such, for this protocol, the following imaging guidelines were used to evaluate progression: (i) 25% increase in the sum of products of all measurable lesions over the smallest sum observed (over baseline if no decrease) using the same techniques as baseline; (ii) clear worsening of any assessable disease; (iii) appearance of any new lesion/site; and (iv) clear clinical worsening or failure to return for evaluation as a result of death or deteriorating condition (unless clearly unrelated to this cancer). Progression-free survival was defined from the date of diagnosis to the date that progressive disease was first observed on imaging, or the date at which nonreversible neurologic progression or permanently increased corticosteroid requirement, death from any cause, or early discontinuation of treatment. Overall survival was defined from the date of diagnosis to date of death from any cause.

Results

Baseline Characteristics

A total of 15 patients in the safety lead-in arm were enrolled from September 18, 2007 to November 12, 2008, and 59 patients were enrolled in the main study arm between January 8, 2009 and September 8, 2010. Two patients had previously been diagnosed with lower-grade tumors but had not received any treatment besides surgery; for both these patients, survival was measured from the date of diagnosis of glioblastoma. All 59 patients were eligible; median age was 54 years (range 21–76) and median KPS was 90 (range 60–100). See Table 3 for detailed patient characteristics.

Safety/Toxicity

Both the safety lead-in group and the efficacy group were included in toxicity evaluations. Toxicity from this regimen was moderate overall (summarized in Table 4). The majority of the treatment-specific adverse events were expected in type and severity. Hematologic abnormalities were presumed due to TMZ, while rash and diarrhea were presumed due to erlotinib. Fatigue and weight loss were presumed due to both drugs, with fatigue also presumed due to radiation. Venous thromboembolic events were presumed due to both bevacizumab and underlying disease. Arterial ischemic events were presumed due to bevacizumab.

There was one CNS hemorrhage, which was a grade 2 subarachnoid hemorrhage associated with trauma. A few of the

Table 4. Treatment-specific adverse events

	Grade 3	Grade 4	Grade 5
Hematologic abnormalities			
Lymphopenia	39	9	
Thrombocytopenia	10	6	
Neutropenia	3	5	
Liver function abnormality	5		
Infection	8	1	1
Pneumonitis, noninfectious	2		
Weight loss	8		
Diarrhea	9	0	
Fatigue	7	1	
Rash	5	0	
Vascular events			
Venous thromboembolic events	3	3	
Stroke		1	
Myocardial infarction	1		
Hypertension	2		
Fistula, bronchial	1		
Wound complication, noninfectious	1		

infections were opportunistic, including one grade 5 infection with disseminated aspergillosis and one case of herpes esophagitis from HSV1. In addition, there was one case of aspergillus infection of the vocal cords (grade 2). One patient experienced pneumonitis due to TMZ (initially attributed to erlotinib but confirmed due to TMZ by drug rechallenge), while a second patient experienced pneumonitis due to either erlotinib or pneumocystis pneumonia; the diagnosis was never pathologically confirmed due to concurrent thrombocytopenia.

Efficacy

In the current study, median PFS was 13.5 months (95% confidence interval [CI]: 12.2–17.0 mo), and median OS was 19.8 months (95% CI: 17.1–28.6 mo) (Figs. 1 and 2). For the historical control group of 133 patients, median PFS was 8.6 months (95% CI: 7.6–10.6 mo) and median OS was 18.0 months (95% CI: 15.2–19.6 mo). After adjusting for age, KPS, and extent of resection, there was a difference for the current study versus the historical control in PFS ($P = .03$) but not in OS ($P = .33$). Results for the safety lead-in group were similar to those for the primary efficacy group, with PFS of 12.3 months (95% CI: 8.4–45.4 mo) and OS of 15.6 months (95% CI: 13.1 – not reached); as outlined above, these patients were not included in the primary efficacy group.

Molecular studies were done on tissue from a majority of the patients treated in the study; paraffin blocks were not available for all patients and a few patients did not have sufficient tissue to analyze for all markers. Summarized in Table 5 are results for *MGMT* methylation status, presence of IDH1 mutation, *EGFR* amplification (by FISH), presence of the EGFRvIII mutation (by IHC), and *PTEN* deletion (by IHC). Exploratory survival analyses were undertaken for specific molecular subgroups as described below.

Within the current study, there was no clear survival advantage for patients whose tumors had methylated *MGMT* promoters

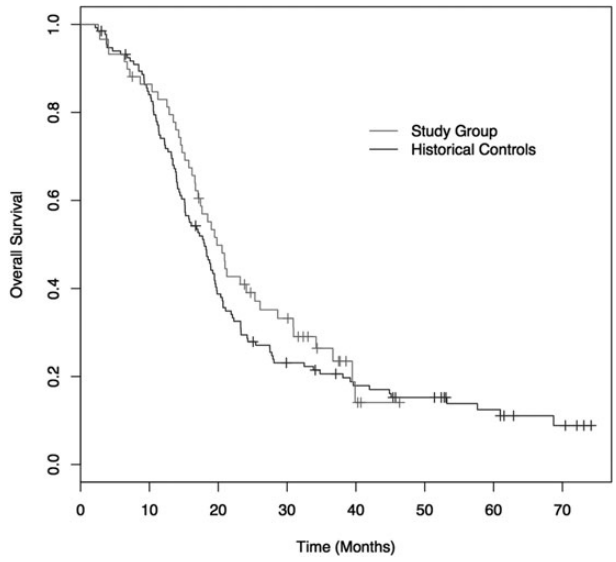

Fig. 1. OS, all patients; log-rank $P = .332$.

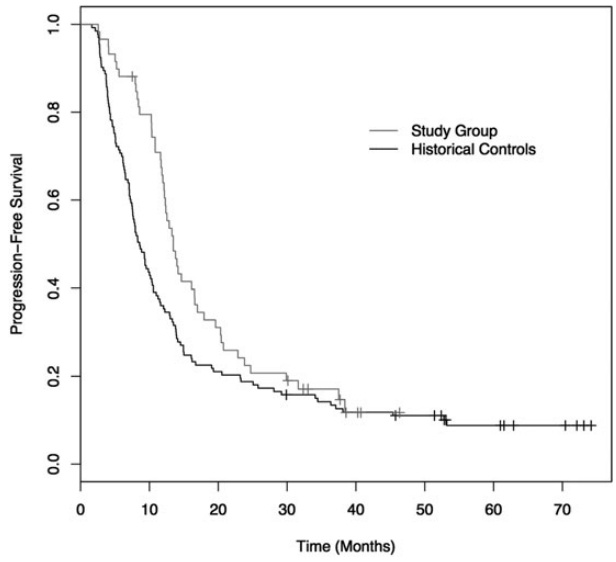

Fig. 2. PFS, all patients; log-rank $P = .031$.

over those whose tumors were unmethylated or of unknown status (median OS: 20.6 mo vs 17.5 mo vs 25.4 mo, respectively). However, when the subgroup of patients with unmethylated tumors in the current study was compared with the same subgroup in the historical control group, there was no clear difference in PFS (median PFS: 12.4 vs 7.5 mo, $P = .17$) or OS (median OS: 17.5 vs 16.9 mo, $P = .68$). There was also no difference in OS or PFS between the current study group and the control group for the subgroup of patients with methylated tumors. There was no clear difference by *PTEN* status, either, and numbers were too limited to do a subset analysis of the group of patients with IDH1 mutant tumors.

Within the current study, there was no difference in PFS (median: 13.3 vs 17.3 mo, $P = .16$) or OS (median: 19.8 vs 24.1 mo,

Table 5. Molecular characterization

Molecular Marker	Value, score	Number of Patients (%)
MGMT promoter methylation status ($n = 59$)	Methylated	15 (25)
	Unmethylated	26 (44)
	Unknown	18 (31)
PTEN (IHC) ($n = 53$)	0	20 (38)
	1+	9 (17)
	2+	14 (26)
	3+	10 (19)
EGFR (FISH) ($n = 55$)	No (not amplified)	16 (29)
	Yes (amplified)	39 (71)
EGFRvIII (IHC) ($n = 53$)	0	43 (81)
	1+	5 (9)
	2+	4 (8)
	3+	1 (2)
IDH1 mutation ($n = 39$)	No	34 (87)
	Yes	5 (13)

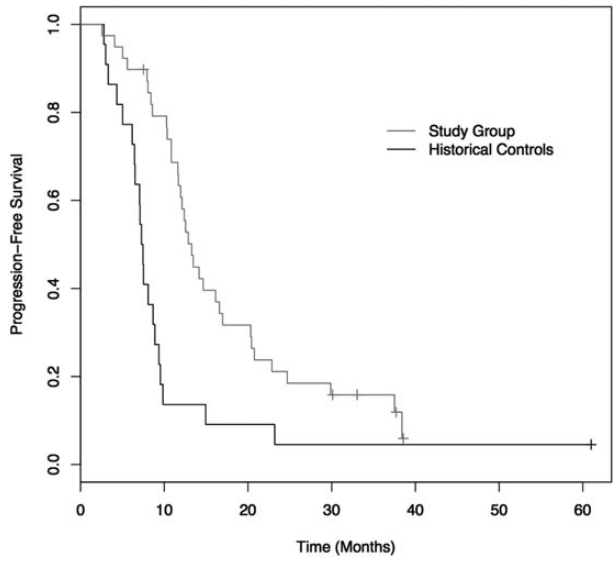

Fig. 4. PFS in *EGFR* amplified (by FISH) subgroup; log-rank $P = .001$.

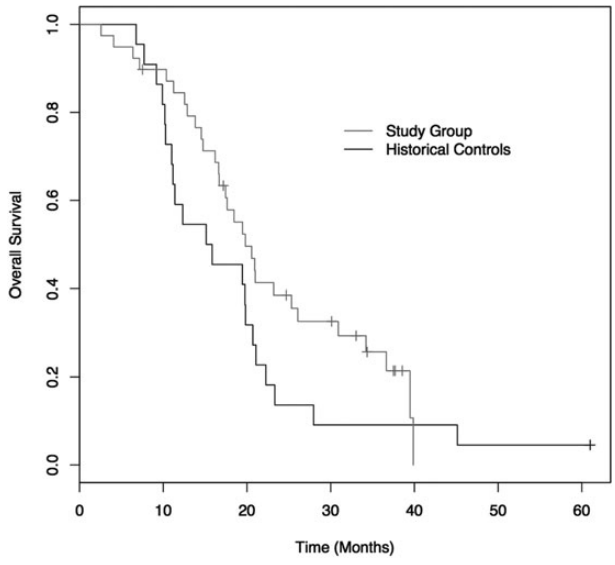

Fig. 3. OS in *EGFR* amplified (by FISH) subgroup; log-rank $P = .145$.

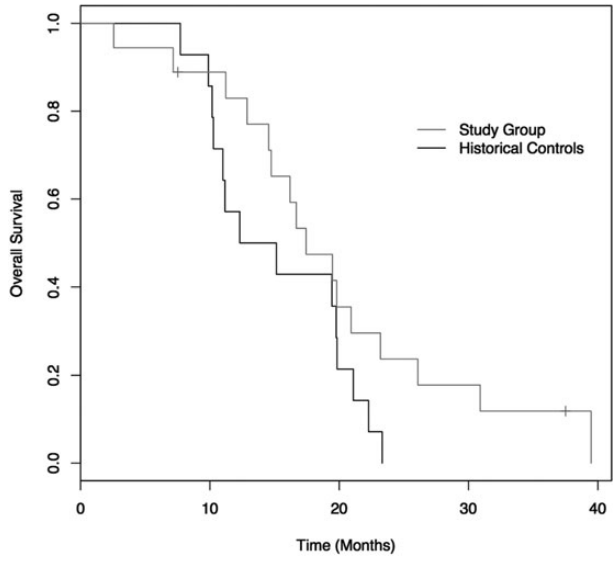

Fig. 5. OS in *EGFR* amplified and *MGMT* unmethylated subgroup; log-rank $P = .118$.

$P = .19$) for patients whose tumors had *EGFR* amplification compared with those whose tumors were not amplified. Of note, for the subset of patients whose tumors had *EGFR* amplification within the current study versus the same subset in the historical control, there was improvement in PFS (median: 13.3 vs 7.4 mo, $P = .001$) and a trend toward improvement in OS (median: 19.8 vs 15.5 mo, $P = .145$) (Figs. 3 and 4). Moreover, the subset of patients ($n = 18$) whose tumors both were unmethylated and had *EGFR* amplification showed significantly better PFS and a trend toward improved OS ($P = .0004$ and $P = .12$, respectively; Figs. 5 and 6) versus the same molecular subgroup in the control group. Numbers were too limited to do subset analyses of the group of patients whose tumors manifested the EGFRvIII mutation. Interestingly, there was no clear correlation among loss of *PTEN* protein expression, *EGFR* amplification, and improved survival (the number of EGFRvIII mutant tumors was too small for subset analysis), in contrast to previously reported data in recurrent malignant gliomas treated with EFGR kinase inhibitors (data not shown).[13]

Discussion

Overall, the combination of RT/TMZ/erlotinib/bevacizumab was tolerable and demonstrated modest efficacy, with improved PFS but not improved OS compared with a recent historical control. It is certainly possible that some of the improvement in PFS is related to suppression of pseudoprogression by use of bevacizumab during radiation. However, the substantial improvement in

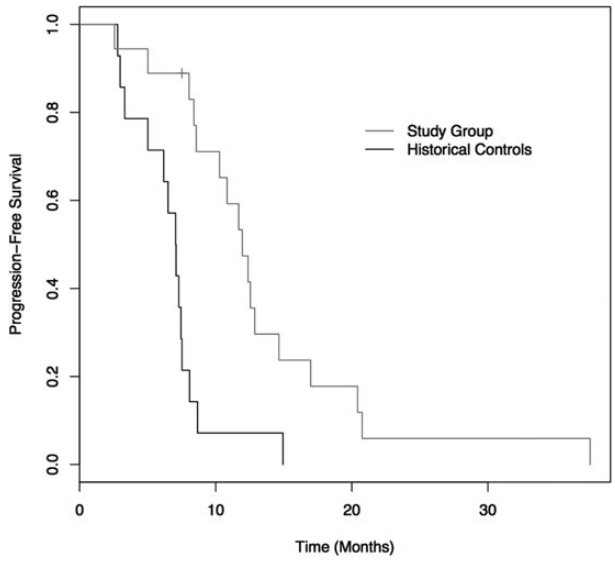

Fig. 6. PFS in *EGFR* amplified and *MGMT* unmethylated subgroup; log-rank $P = .00036$.

PFS, which corroborates the improvement seen in other upfront clinical trials including bevacizumab,[5–8] goes beyond the expected timeframe for pseudoprogression, which is typically in the first 3–6 months post-RT. As such, it more likely represents true improvement in PFS.

If so, this raises the question of why the observed benefit in PFS does not translate into a corresponding improvement in OS. It has been noted that most single-arm phase II studies testing new agents in combination with RT and TMZ for newly diagnosed GBM have demonstrated a modest improvement in OS[14] relative to what was seen in the original phase III study that led to approval of TMZ as part of upfront treatment.[1] The consistency of this finding across multiple regimens argues against agent-specific improvements in OS; rather, it suggests that the baseline against which upfront phase II studies such as this one should be compared is a median OS in the 18- to 20-month range. Our historical control appropriately fits that category. The reason for this improvement over the original phase III OS result of 14.6 months remains unclear but may reflect improvements in overall clinical care over time or a better prognosis for populations of patients who enroll in phase II studies at specialty centers compared with those who enroll in phase III studies.

Alternatively, the historical control population we used was being treated for recurrence around the time that bevacizumab came into common use for recurrent GBM at many academic centers, and many of those patients would have been treated with bevacizumab at recurrence. Therefore, it may be that there is a small benefit in OS with the use of bevacizumab for GBM but that the benefit is accrued whether it is used as part of initial treatment or at recurrence, so that there is no differential advantage seen in the current study population. In that case, however, a similar benefit in OS should have been seen in both arms of each of the recently reported phase III studies testing upfront bevacizumab, and OS in these studies was only 15–16 months.[8]

Even without clear benefit to OS, there may be benefit from a quality-of-life standpoint for some patients treated with bevacizumab up front. This study did not evaluate steroid requirements, neurocognitive outcomes, or quality-of-life parameters, all of which are increasingly recognized as important clinical outcomes for neuro-oncology patients. Interpretation of the results for these ancillary outcome measures from the recently reported phase III studies of bevacizumab/RT/TMZ is being actively debated among the neuro-oncology community at this time.[7,15,16]

The subset of patients in the current study whose tumors were *EGFR* amplified appeared to benefit from this combination, with improvement in PFS and a trend toward improvement in OS relative to the same subset of the historical control. Those whose tumors were both *EGFR* amplified and unmethylated showed further improvement in both PFS and OS relative to the historical control. Of note, the same subgroup (*EGFR* amplified, unmethylated) also demonstrated improved PFS and OS in the prior study testing erlotinib, RT, and TMZ. Given that half of the control group for the current study consisted of patients from that study, these results may indicate that the combination of bevacizumab and erlotinib with RT and TMZ is synergistic or at least has added efficacy in the setting of *EGFR* amplification, especially in the setting of an unmethylated *MGMT* promoter. It is important to acknowledge that the subset analyses reported here were post hoc and exploratory in nature; the study was not powered to do such subset analyses.

As we move toward molecular characterization rather than morphological characterization alone, it becomes likely that different subtypes of GBM will be treated differently. Our results show that the addition of bevacizumab and erlotinib to upfront treatment improves PFS but not OS in an unselected GBM population, similar to the results seen in the other upfront studies of bevacizumab-containing regimens. However, though they must be interpreted with caution, given the small size and single-arm nature of our study as well as the post hoc nature of the analysis, our results also indicate that there may be utility in aggressively treating patients with *EGFR*-amplified, unmethylated GBM up front with this combination. Continued effort to tailor treatment by molecular profile will be critical to ongoing efforts to more effectively treat this challenging disease.

Funding

This work was partially funded by Genentech, Inc.

Acknowledgments

Preliminary results for this study were presented in abstract form at the American Society for Clinical Oncology (ASCO) annual meeting, 2012.

Final results for this study were presented in abstract form at the Quadrennial World Federation of Neuro-oncology (WFNO)/Society for Neuro-oncology (SNO) meeting, 2013.

Conflict of interest statement. None declared. Dr Michael Prados is on the advisory panel for Genentech/Roche.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.

2. The Cancer Genome Atlas Research Network. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. 2008;455(7216):1061–1068. Erratum in *Nature*. 2013;494:506.
3. Kaur B, Tan C, Brat DJ, et al. Genetic and hypoxic regulation of angiogenesis in gliomas. *J Neurooncol*. 2004;70(2):229–243.
4. Prados MD, Chang SM, Butowski N, et al. Phase II study of erlotinib plus temozolomide during and after radiation therapy in patients with newly diagnosed glioblastoma multiforme or gliosarcoma. *J Clin Oncol*. 2009;27(4):579–584.
5. Lai A, Tran A, Nghiemphu PL, et al. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol*. 2011; 29(2):142–148.
6. Hainsworth JD, Shih KC, Shepard GC, et al. Phase II study of concurrent radiation therapy, temozolomide, and bevacizumab followed by bevacizumab/everolimus as first-line treatment for patients with glioblastoma. *Clin Adv Hematol Oncol*. 2012;10(4): 240–246.
7. Henriksson R, Bottomley A, Mason W, et al. Progression-free survival (PFS) and health-related quality of life (HRQoL) in AVAglio, a phase III study of bevacizumab (Bv), temozolomide (T), and radiotherapy (RT) in newly diagnosed glioblastoma (GBM) [abstract]. *J Clin Oncol*. 2013; 31(suppl, abstr 2005).
8. Gilbert MR, Dignam J, Won M, et al. RTOG 0825: phase III double-blind placebo-controlled trial evaluating bevacizumab (Bev) in patients (Pts) with newly diagnosed glioblastoma (GBM) [abstract]. *J Clin Oncol*. 2013;31(suppl, abstr 1).
9. Prasad G, Sottero T, Yang X, et al. Inhibition of PI3K/mTOR pathways in glioblastoma and implications for combination therapy with temozolomide. *Neuro Oncol*. 2011;13(13):384–392.
10. Christensen BC, Smith AA, Zheng S, et al. DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma. *J Natl Cancer Inst*. 2011;103(2):143–153.
11. Elkhaled A, Jalbert LE, Phillips JJ, et al. Magnetic resonance of 2-hydroxyglutarate in IDH1-mutated low-grade gliomas. *Sci Transl Med*. 2012;4(116):116ra5.
12. Butowski N, Chang SM, Lamborn KR, et al. Phase II and pharmacogenomics study of enzastaurin plus temozolomide during and following radiation therapy in patients with newly diagnosed glioblastoma multiforme and gliosarcoma. *Neuro Oncol*. 2011;13(12):1331–1338.
13. Mellinghoff IK, Wang MY, Vivanco I, et al. Molecular determinants of the response of glioblastomas to *EGFR* kinase inhibitors. *N Engl J Med*. 2005;353(19):2012–2024.
14. Grossman SA, Ye X, Piantadosi S, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. *Clin Cancer Res*. 2010;16(8): 2443–2449.
15. Wefel J, Pugh S, Armstrong T, et al. Neurocognitive function (NCF) outcomes in patients with glioblastoma (GBM) enrolled in RTOG 0825 [abstract]. *J Clin Oncol*. 2013;31(suppl, abstr 2004).
16. Armstrong T, Wefel J, Won M, et al. Comparative impact of treatment on patient reported outcomes (PROs) in patients with glioblastoma (GBM) enrolled in RTOG 0825 [abstract]. *J Clin Oncol*. 2013;31(suppl, abstr 2003).