

The impact of bevacizumab treatment on survival and quality of life in newly diagnosed glioblastoma patients

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Abstract: Glioblastoma multiforme (GBM) remains one of the most devastating tumors, and patients have a median survival of 15 months despite aggressive local and systemic therapy, including maximal surgical resection, radiation therapy, and concomitant and adjuvant temozolomide. The purpose of antineoplastic treatment is therefore to prolong life, with a maintenance or improvement of quality of life. GBM is a highly vascular tumor and overexpresses the vascular endothelial growth factor A, which promotes angiogenesis. Preclinical data have suggested that anti-angiogenic treatment efficiently inhibits tumor growth. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor A, and treatment has shown impressive response rates in recurrent GBM. In addition, it has been shown that response is correlated to prolonged survival and improved quality of life. Several investigations in newly diagnosed GBM patients have been performed during recent years to test the hypothesis that newly diagnosed GBM patients should be treated with standard multimodality treatment, in combination with bevacizumab, in order to prolong life and maintain or improve quality of life. The results of these studies along with relevant preclinical data will be described, and pitfalls in clinical and paraclinical endpoints will be discussed.

Keywords: primary treatment, VEGF, quality of life, monoclonal antibody, patient survival, vascular tumor

Introduction

Glioblastoma multiforme (GBM) remains one of the most lethal tumors, and newly diagnosed patients have a median survival of 15 months despite aggressive therapy including maximal surgical resection, radiation therapy (RT), and concomitant and adjuvant temozolomide.¹ GBM is characterized by excessive and aberrant angiogenesis, which is thought to be linked to expression of the prominent angiogenic promoter – the vascular endothelial growth factor A (VEGF).^{2,3} Bevacizumab (BVZ) (Avastin[®]; Genentech, Inc., South San Francisco, CA, USA), a humanized monoclonal antibody targeting VEGF, has been suggested as a feasible anti-angiogenic drug. BVZ inhibits angiogenesis by clearing circulating VEGF and thereby preventing interaction of VEGF with its target receptors on the surface of endothelial cells. Consequently, BVZ does not have to cross the blood–brain barrier (BBB) in order to be active. Preclinical and clinical studies suggest that anti-angiogenic therapies such as BVZ, in part elicit their anti-tumor activity by transiently “normalizing” the tumor vasculature by inhibiting the formation of new blood vessels, thereby improving the efficacy of both chemotherapy and RT.^{4,5}

Several phase II studies in GBM patients with recurrent disease have shown impressive response rates varying from 30% to 50%, prolongation of life in responders,

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as well as improved quality of life (QOL).^{6–10} These studies have led to a number of investigations in newly diagnosed GBM patients,^{11–17} including well conducted prospective randomized phase III trials^{18–20} testing the hypothesis that GBM patients for first line therapy should be treated with standard multimodality treatment in combination with BVZ. In this paper we will discuss the results of these recent investigations of combining BVZ and standard treatment in newly diagnosed patients with primary GBM.

Anti-angiogenic therapy rationale

GBM tumor cells are known to produce VEGF primarily as a result of hypoxia, glucose deprivation, oxidative and mechanical stress, and mutations in both oncogenes and tumor suppressor genes.² VEGF binds to its receptors on endothelial cells, resulting in new blood vessel formation, which facilitates tumor growth. Therefore, 4 decades ago, Judah Folkman hypothesized that anti-angiogenic therapy by vessel pruning would be an effective treatment strategy in cancer.²¹ Now, this hypothesis is widely accepted, and a variety of drugs targeting VEGF or its receptors have been shown to effectively prevent or reduce the growth of experimental mouse tumors and xenografts.²²

However, the promising results from preclinical animal studies in GBM have not been translated into the clinic, suggesting that the mechanisms of angiogenesis are complicated and that escape mechanisms during single anti-angiogenic drug treatment with drugs such as BVZ occur.^{22–25} More recently, Rakesh K Jain formulated a new hypothesis which suggested that anti-angiogenic therapy elicits its anti-tumor activity by transiently normalizing the abnormal structure and function of tumor vasculature to make it more efficient for delivery of oxygen and chemotherapeutic agents.²⁶ Evidence from several preclinical studies has confirmed that the temporary vascular normalization as a result of anti-angiogenic therapy, improves tumor blood perfusion, which consequently increases the delivery of chemotherapy and oxygen, and this potentially enhances the efficacy of both chemotherapy and RT.^{27–30} Recently, Batchelor et al provided clinical proof of concept that improved tumor blood perfusion, as a consequence of vascular normalization, was related to longer overall survival (OS) in newly diagnosed GBM patients treated with a combination of anti-angiogenic therapy (Cediranib) (Recentin™; AstraZeneca plc, London, UK) and standard treatment.⁵ These data remain to be validated, but strongly suggest that part of the beneficial response mechanisms of anti-angiogenic therapy in GBM patients is due to vascular normalization.

In addition to the paracrine stimulation of endothelial cells, recent data indicate that the GBM cells themselves also possess VEGF receptors and that autocrine stimulation of these receptors promotes tumor growth (Michaelsen et al, unpublished data, 2014).³¹ However, whether BVZ therapy has a directly disrupting effect on the autocrine growth stimulation of glioma cells in the perivascular niche, remains to be studied further.

BVZ in newly diagnosed GBM Efficacy

Over the years, seven phase II (including two randomized)^{11–17} and three phase III randomized studies^{18–20} with BVZ as part of the treatment of newly diagnosed GBM patients have been published. In three studies, BVZ was given as neoadjuvant treatment,^{11,12,14} while it was given as concomitant and adjuvant treatment in combination with RT in the remaining studies^{13,15–20} (Table 1). The response rates were comparable in both the neoadjuvant and adjuvant setting, and 23% to 38% responded to treatment, which is comparable to patients treated for recurrent disease.³²

Progression free survival (PFS) at 6 months varied from 52% to 85%, and median PFS from 7.3 to 14.2 months. Finally, median OS varied from 11.7 to 23 months. The studies^{11–20} varied in baseline characteristics such as patient age, performance status, degree of surgical resection, steroid use, and epigenetic silencing of *MGMT* (O6-methylguanine-DNA methyltransferase), which have been shown previously to have prognostic value,^{33,34} and this may explain some of the observed variations in response, PFS, and OS.

Among the published studies^{11–20} were two randomized Phase III studies, AVAGlio¹⁸ and RTOG 0825,¹⁹ which compared standard treatment versus standard treatment plus BVZ. Both studies included newly diagnosed GBM patients in good performance status having *MGMT* methylated as well as non-methylated tumors. Known prognostic factors were comparable in the two studies except surgery, since more patients had debulking surgery in the RTOG 0825 study compared to the AVAGlio study. Both studies found significant increase in median PFS in the BVZ treatment arm compared to the placebo treatment arm (AVAGlio: 6.2 months to 10.6 months, ~71% increase, and RTOG 0825: 7.3 months to 10.7 months, ~47% increase). In contrast, no difference in OS was observed in either of the studies.

In both the AVAGlio¹⁸ and the RTOG 0825¹⁹ studies, the patients were allowed to cross over to BVZ-containing treatment at progression, and this occurred frequently. However, independently of whether BVZ was given as early treatment or as late treatment at recurrence, only a marginal, clinical

Table 1 Efficacy of bevacizumab in newly diagnosed GBM

Reference	Study design and population	Regimen	n	Response rate				PFS6 (%)	PFS (mo)	OS (mo)
				CR (%)	PR (%)	SD (%)	PD (%)			
Neoadjuvant bevacizumab										
Hofland et al ¹²	Phase II, randomized Biopsy/partial resection: 8%/92% Median age: 61 years Median KPS: 90 Randomization stratified for center Response criteria: ^a	A: Neoadjuvant BVZ and Iri for 8 weeks Concomitant standard RT, BVZ, and Iri Adjuvant BVZ and Iri for 8 weeks. B: Neoadjuvant BVZ and TMZ for 8 weeks Concomitant RT, BVZ, and TMZ Adjuvant BVZ and TMZ for 8 weeks.	31	0	23	54	23	52	7.3 95% CI (5.0-9.3) 7.7 95% CI (5.1-10.2)	15.1 95% CI (9.6-20.6) 11.8 95% CI (8.2-15.3)
Chauffert et al ¹¹	Phase II, randomized 100% unresectable Median age: ~60 years Median KPS: 80 Randomization stratified for Mini Mental Status, MRC neurological status, sex, age and center Response criteria: ^b	A: Neoadjuvant BVZ and Iri for 8 weeks Concomitant RT, BVZ, and TMZ Adjuvant BVZ and Iri. B: Standard treatment: concomitant RT and TMZ + adjuvant TMZ.	60	NA	NA	NA	NA	62 95% CI (48%-73%) 42 95% CI (29%-54%)	7.1 95% CI (5.5-9.2) 5.2 95% CI (4.3-6.8)	11.1 (no significant difference between A and B)
Lou et al ¹⁴	Phase II 100% unresectable Median age: 59 years Median KPS: 80 Steroids (yes): 34% Response criteria: ^c	Neoadjuvant BVZ + TMZ for 16 weeks Standard treatment: concomitant RT and TMZ + adjuvant TMZ.	41	0	24	68	2	NA	NA	11.7 95% CI (7.4-15.6)
First line treatment										
Vredenburg et al ¹⁷	Phase II Complete resection/partial resection: 40%/35% Median age: 56 years Median KPS: 90 Steroids (yes): 71% Response criteria: ^c	Concomitant RT, BVZ, and TMZ Adjuvant TMZ, BVZ, and Iri for 6-12 cycles.	75	NA	NA	NA	NA	NA	14.2 95% CI (12-16) PFS12: 63 95% CI (51%-73%)	21.2 95% CI (17.2-25.4)
Lai et al ¹³	Phase II Complete resection/partial resection: 40%/57% Median age: 57 years Median KPS: 85 Response criteria: ^d	Concomitant RT, BVZ, and TMZ Adjuvant TMZ and BVZ until progression or for a maximum of 24 cycles.	70	NA	NA	NA	NA	NA	13.6 95% CI (11.1-16.5)	19.6 95% CI (16.1-23.3)
Narayana et al ¹⁵	Phase II Complete resection: 71% Median age: 54 years Median KPS: 90 Response criteria: ^a	Concomitant RT, TMZ and BVZ Adjuvant TMZ 150 mg/m ² day 1-7, and BVZ on days 8 and 22.	51	NA	NA	NA	NA	85	13	23 95% CI: NA

(Continued)

Table 1 (Continued)

Reference	Study design and population	Regimen	n	Response rate				PFS6 (%)	PFS (mo)	OS (mo)
				CR (%)	PR (%)	SD (%)	PD (%)			
Omuro et al ¹⁶	Phase II Complete resection: NA Median age: 55 years Median KPS: 90 Response criteria: ^b Double blinded phase III, randomized 1:1 Randomization stratified for RPA class and center Complete resection/partial resection: 42%/47% Median age: 56.5 years Median KPS: 90–100 Steroids (yes): 76% Response criteria: ^a	Hypofractionated stereotactic RT (6*6 Gy to contrast-enhancing tumor and 6*4 Gy to FLAIR) was administered concomitant with BVZ and TMZ. A: Concomitant RT, TMZ and BVZ B: Concomitant RT, TMZ, and placebo followed by BVZ monotherapy (15 mg/kg) every 3 weeks until progression. C: Concomitant RT, TMZ, and placebo followed by placebo monotherapy every 3 weeks until progression.	40	27	63	3	7	NA	11 95% CI (9–15)	NA
Chinot et al (AVAGlio) ¹⁸	Double blinded phase III, randomized 1:1 Randomization stratified for RPA class and center Complete resection/partial resection: 42%/47% Median age: 56.5 years Median KPS: 90–100 Steroids (yes): 76% Response criteria: ^a	Adjuvant BVZ and TMZ for 6 cycles followed by BVZ monotherapy (15 mg/kg) every 3 weeks until progression. A: Concomitant RT, TMZ and BVZ followed by BVZ monotherapy (15 mg/kg) every 3 weeks until progression. B: Concomitant RT, TMZ, and placebo followed by BVZ monotherapy (15 mg/kg) every 3 weeks until progression.	458	38	49	6	NA	10.6	16.8	
Gilbert et al (RTOG 0825) ¹⁹	Double blinded phase III, randomized 1:1 Randomization stratified for MGMT-status and 9-gene expression profile Complete resection/partial resection: 61%/36% Median age: 59 years Median KPS: 90–100 Response criteria: ^b	A: 3 weeks concomitant RT and TMZ followed by 3 weeks concomitant RT, TMZ, and BVZ B: 3 weeks concomitant RT and TMZ followed by 3 weeks concomitant RT, TMZ, and placebo C: 3 weeks concomitant RT and TMZ followed by 3 weeks concomitant RT, TMZ, and placebo	312	NA	NA	NA	NA	10.7	6.2 HR =0.64 95% CI (0.55–0.74) P<0.0001	16.7 HR =0.88 95% CI (0.76–1.02) P=0.0987 15.7
Herrlinger (GLARIUS) ²⁰	Open label phase III, randomized 2:1 MGMT-nonmethylated Randomization stratified for KPS and extent of resection and center Complete resection/partial resection: 49%/50% Median age: 56 years Median KPS: 90–100 Response criteria: ^b	A: Concomitant RT, BVZ, and Iri B: Standard treatment: concomitant RT and TMZ + adjuvant TMZ for 6 months.	116	NA	NA	NA	NA	80 95% CI (71%–86%)	9.7 95% CI (9.0–11.6)	16.6 16.1 HR =1.13 95% CI (0.93–1.37) P=0.21

Notes: Unless otherwise stated: BVZ 10 mg/kg administered on days 1 and 14. Irinotecan 125 mg/m² administered on days 1 and 14. RT is 60 Gy/30 fractions. Neoadjuvant and adjuvant temozolomide doses are 200 mg/m² administered on days 1 to 5. Concomitant TMZ 75 mg/m²/day. Adjuvant treatment for 6 cycles (28-day cycles). Response evaluations: ^athe modified MacDonald response criteria;⁴⁸ the MacDonald response criteria;⁴⁹ the Radiologic Assessment in Neuro-Oncology (RANO) criteria;⁴⁹ and ^bthe modified Levin criteria.¹⁰⁵

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS6, progression-free survival at 6 months; PFS12, progression-free survival at 12 months; PFS, median progression free survival; n, number of patients; mo, months; OS, median overall survival; KPS, Karnofsky performance status; BVZ, Bevacizumab; Iri, Irinotecan; RT, radiotherapy; TMZ, Temozolomide; CI, confidence interval; HR, hazard ratio; NA, not available; RPA, recursive partitioning analysis; MGMT, 06-methylguanine-DNA methyltransferase; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme.

difference in median OS was seen as compared to the OS observed following standard treatment, as originally published by Stupp et al.¹ This indicates that BVZ in general does not influence OS in patients with GBM. Whether subgroup analysis may define patients more sensitive to BVZ treatment still remains to be examined.

In contrast to comparable results for the effects of BVZ on PFS and OS, the AVAGlio and RTOG 0825 studies found contradicting results when evaluating QOL. The AVAGlio study¹⁸ showed that increased PFS in the BVZ arm was accompanied by a better QOL, while the opposite if any change in QOL was found in the RTOG 0825 study.¹⁹

In addition to the above, a third Phase III randomized study, GLARIUS, has been published, in which standard treatment was compared to RT combined with concomitant and adjuvant BVZ, plus irinotecan.²⁰ The study included non-methylated MGMT GBMs only, who are patients with supposedly worse prognoses as compared to patients with methylated MGMT. The data showed increased median OS in both arms as compared to published data from non-methylated groups,³⁵ which indicates that some sort of selection other than MGMT methylation status might have occurred. Nevertheless, RT and concomitant and adjuvant BVZ plus irinotecan increased PFS, but not median OS, as compared to standard treatment. In addition, the QOL study did not show any difference.²⁰ In conclusion, three well conducted, randomized Phase III studies^{18–20} could not demonstrate any survival benefit of adding BVZ to standard treatment in patients with newly diagnosed GBM.

Safety of BVZ in the first line setting

The Phase II studies^{11–17} and the three randomized studies^{18–20} were comparable in terms of safety and toxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (Table 2). In general, concomitant RT and TMZ with and without BVZ was well tolerated, with hematotoxicity being the most common toxicity in both treatment groups.^{11–20} The rates of serious adverse events were higher in the BVZ group than in the control group in the three randomized studies.^{18–20} Notably, it was observed in the randomized studies that grade >3 hypertension and thromboembolic events were significantly more frequent in patients treated with BVZ, as compared to standard treatment.^{18–20} In addition, in some studies, gastrointestinal perforation, cerebral bleeding, fatigue, wound healing complications, and proteinuria appeared more frequently in patients treated with BVZ, as compared to patients not receiving the drug.^{11,18–20}

Recurrence pattern

The recurrence pattern is shown in Table 3. The data available are very heterogeneous and in general, the major studies^{18,36–38} do not uniformly support the assumption that BVZ treatment induces migratory growth at time of recurrence, resulting in more diffuse tumors.^{39,40}

Discussion

Only a subset or approximately one third of patients with newly diagnosed or recurrent GBM respond to BVZ treatment, and some studies report a better QOL while others do not.^{9,18–20} Several factors could be responsible for this, including molecular, cellular, and phenotypic resistance; problems in evaluating clinical and preclinical response; and nonstandard procedure of reporting QOL data. Some important issues will be discussed in the following sections.

Resistance to BVZ

Multiple mechanisms of resistance to anti-angiogenic therapy have been described, and modes of resistance to anti-angiogenic therapy can be classified into intrinsic resistance (where tumors fail to respond from the onset of treatment) and adaptive resistance (where tumors initially respond, and then progress whilst still on treatment).²³ The molecular, cellular, and phenotypic bases of these two modes of resistance are still not well understood, and no molecular features have been identified which in clinical practice can predict which patient should be treated with anti-angiogenic therapy.^{41–43}

Although increased blood flow might occur during a short normalization window,⁵ several studies have described hypoxia due to vascular pruning as being a central hallmark in resistance to long-term, anti-angiogenic therapy.^{24,40,44,45} Among other mechanisms, hypoxia induces upregulation of alternative angiogenic growth factors such as fibroblast growth factor 2, delta-like ligand 4, stromal cell-derived factor 1, platelet-derived growth factor alpha, angiopoietins, and placental growth factor. These and other angiogenic factors interact between tumor cells, endothelial cells, and stromal cells (eg, inflammatory cells and pericytes) in a complex network in order to adapt to anti-angiogenic therapy. Some factors, such as fibroblast growth factor 2, directly interact with receptors on endothelial cells to stimulate angiogenesis while others, such as stromal cell-derived factor 1, indirectly stimulate angiogenesis by recruiting pro-angiogenic, bone marrow-derived cells (BMDCs).^{23,24,46}

Also, myeloid BMDCs may be involved in the resistant phenotype. Preclinical studies have shown an increase in the number of tumor-infiltrating, pro-angiogenic BMDCs

Table 2 Toxicity of bevacizumab in newly diagnosed GBM

Reference	Regimen	Toxicity (NCI-CTCAE)	Grade ≥3, %		
			Treatment arm A	Treatment arm B	
Neoadjuvant BVZ					
Hofland et al ¹²	A: Neoadjuvant BVZ and Iri for 8 weeks	Hematotoxicity			
		Leukopenia	3.2	9.4	
	Concomitant standard RT, BVZ, and Iri	Lymphopenia	6.5	6.3	
		Thrombocytopenia	0.0	9.4	
	Adjuvant BVZ and Iri for 8 weeks.	Bleeding			
		Cerebral hemorrhage	0.0	0.0	
		Mucocutaneous bleeding	NA	NA	
	B: Neoadjuvant BVZ and TMZ for 8 weeks	Other	NA	NA	
		Wound dehiscence	0.0	0.0	
	Concomitant RT, BVZ, and TMZ Adjuvant BVZ and TMZ for 8 weeks.	Arterial thromboembolic events	0.0	0.0	
		Venous thromboembolic events (DVT/PE)	3.2	0.0	
		Hypertension	0.0	9.4	
		Proteinuria	NA	NA	
		GI perforation (including GI fistula/abscess)	0.0	0.0	
		Abscesses and fistulae	0.0	0.0	
		Congestive heart failure	0.0	0.0	
		Posterior reversible encephalopathy syndrome	0.0	0.0	
Chauffert et al ¹¹		A: Neoadjuvant BVZ and Iri for 8 weeks	Hematotoxicity		
			Neutropenia	7.0	8.9
	Concomitant RT, BVZ, and TMZ Adjuvant BVZ and Iri.	Lymphopenia	12.3	12.5	
		Thrombocytopenia	3.5	14.2	
	B: Standard treatment: concomitant RT and TMZ + adjuvant TMZ.	Bleeding			
		Cerebral hemorrhage	5.3 (3 patients grade 5)	1.8 (1 patient grade 5)	
		Mucocutaneous bleeding	NA	NA	
		Other	NA	NA	
		Wound dehiscence	NA	NA	
		Arterial thromboembolic events	1.8	1.8	
		Venous thromboembolic events (DVT/PE)	8.8	0.0	
		Hypertension	0.0	0.0	
		Proteinuria	NA	NA	
		GI perforation/infection	5.3 (1 patient grade 5)	3.6 (1 patient grade 5)	
		Abscesses and fistulae	NA	NA	
		Congestive heart failure	NA	NA	
		Posterior reversible encephalopathy syndrome	NA	NA	
Lou et al ¹⁴	Neoadjuvant BVZ + TMZ for 16 weeks.	Hematotoxicity			
		Neutropenia	4.9		
	Standard treatment: Concomitant RT and TMZ + adjuvant TMZ.	Thrombocytopenia	7.3		
		Bleeding			
	Cerebral hemorrhage	0.0			
	Mucocutaneous bleeding	NA			
	Other	NA			
	Wound-healing complications	2.4			
	Arterial thromboembolic events	2.4 (1 patient grade 5)			
	Venous thromboembolic events (DVT/PE)	9.8			
	Hypertension	NA			
	Proteinuria	NA			
	GI perforation	2.4			
	Abscesses and fistulae	NA			
	Congestive heart failure	2.4			
	Posterior reversible encephalopathy syndrome	NA			
	First line treatment				
Vredenburg et al ¹⁷	Concomitant RT, BVZ, and TMZ Adjuvant TMZ, BVZ, and Iri for 6–12 cycles.	1.3% (1 patient) grade 5 neutropenic sepsis;			
		1.3% (1 patient) grade 5 PE;			
		1.3% (1 patient) GI perforation.			

(Continued)

Table 2 (Continued)

Reference	Regimen	Toxicity	Grade ≥ 3 , %	
			Treatment arm A	Treatment arm B
Lai et al ¹³	Concomitant RT, BVZ, and TMZ Adjuvant TMZ and BVZ until progression or for a maximum of 24 cycles.	Hematotoxicity	NA	
		Bleeding		
		Cerebral hemorrhage	2.9	
		GI bleeding	2.9	
		Other	1.4	
		Wound-healing complications	NA	
		Arterial thromboembolic events	NA	
		Venous thromboembolic events (DVT/PE)	18.6	
		Hypertension	11.4	
		Proteinuria	11.4	
		GI perforation	2.9	
		Abscesses and fistulae	NA	
		Congestive heart failure	NA	
Posterior reversible encephalopathy syndrome	NA			
Narayana et al ¹⁵	Concomitant RT, TMZ, and BVZ Adjuvant TMZ 150 mg/m ² days 1–7, and BVZ on days 8 and 22.	Hematotoxicity	NA	
		Bleeding		
		Cerebral hemorrhage	0.0	
		Mucocutaneous bleeding	0.0	
		Other	0.0	
		Wound-healing complications	NA	
		Arterial thromboembolic events	NA	
		Venous thromboembolic events (DVT/PE)	5.9	
		Hypertension	NA	
		Proteinuria	NA	
		GI perforation (including GI fistula/abscess)	NA	
		Abscesses and fistulae	NA	
		Congestive heart failure	NA	
Posterior reversible encephalopathy syndrome	NA			
Omuro et al ¹⁶	Hypofractionated stereotactic RT (6*6 Gy to contrast- enhancing tumor and 6*4 Gy to FLAIR) was administered concomitant with BVZ and TMZ Adjuvant BVZ and TMZ.	Hematotoxicity	NA	
		Bleeding	NA	
		Cerebral hemorrhage		
		GI bleeding		
		Other		
		Wound-healing complications	NA	
		Arterial thromboembolic events	NA	
		PE	5.0	
		Hypertension	NA	
		Proteinuria	NA	
		GI perforation	NA	
		Abscesses and fistulae	NA	
		Congestive heart failure	NA	
Posterior reversible encephalopathy syndrome	NA			
Chinot et al (AVAGlio) ¹⁸	A: Concomitant RT, TMZ, and BVZ Adjuvant BVZ and TMZ for 6 cycles followed by BVZ monotherapy (15 mg/kg) every 3 weeks until progression. B: Concomitant RT, TMZ, and placebo Adjuvant placebo and TMZ for 6 cycles followed by placebo monotherapy every 3 weeks until progression.	Hematotoxicity		
		Thrombocytopenia	15.0	9.8
		Bleeding		
		Cerebral hemorrhage	2.0	0.9
		Other, including mucocutaneous bleeding	1.3	0.9
		Wound-healing complications	3.3	1.6
		Arterial thromboembolic events	5.0	1.3
		Venous thromboembolic events (DVT/PE)	7.6	8.0
		Hypertension	11.3	2.2
		Proteinuria	5.4	0.0
		GI perforation (including GI fistula/abscess)	1.1	0.2
		Abscesses and fistulae	0.4	0.7
		Congestive heart failure	0.4	0.0

(Continued)

Table 2 (Continued)

Reference	Regimen	Toxicity	Grade ≥ 3 , %	
			Treatment arm A	Treatment arm B
Gilbert et al (RTOG 0825) ¹⁹	A: 3 weeks' concomitant RT and TMZ followed by 3 weeks' concomitant RT, TMZ, and BVZ Adjuvant TMZ and BVZ for a maximum of 12 cycles. B: 3 weeks' concomitant RT and TMZ followed by 3 weeks' concomitant RT, TMZ, and placebo Adjuvant TMZ and placebo for a maximum of 12 cycles.	Posterior reversible encephalopathy syndrome	0.0	0.0
		Fatigue	7.4	4.7
		Hematotoxicity		
		Anemia	2.6	1.6
		Leukopenia	13.8	8.3
		Neutropenia	17.2	9.3
		Lymphopenia	23.7	22.3
		Thrombocytopenia	21.4	19.3
		Bleeding	1.5 (1 patient grade 5)	1.3
		Cerebral hemorrhage	NA	NA
		Mucocutaneous bleeding	NA	NA
		Other	NA	NA
		Wound-healing complications	2.5	1.1
		Thromboembolic events (arterial/venous)	11.9 (1 patient grade 5)	8.4
		Hypertension	5.5	1.2
		Proteinuria	NA	NA
		GI perforation	1.5	0.7
Abscesses and fistulae	NA	NA		
Congestive heart failure	NA	NA		
Posterior reversible encephalopathy syndrome	NA	NA		
Fatigue	15.4	11.7		
Herrlinger (GLARIUS) ²⁰	A: Concomitant RT, BVZ, and Iri Adjuvant BVZ and Iri until progression. B: Standard treatment: concomitant RT and TMZ + adjuvant TMZ for 6 months.	Hematotoxicity	1.7	14.6
		Bleeding		
		Cerebral hemorrhage	0.8	0.0
		Subdural hematoma	0.0	3.6
		Mucocutaneous bleeding	NA	NA
		Other	NA	NA
		Wound-healing complications	0.8	0.0
		Arterial thromboembolic events	NA	NA
		Venous thromboembolic events (DVT/PE)	5.9	1.8
		Hypertension	8.4	1.8
		Proteinuria	2.7	0.0
		GI perforation (including GI fistula/abscess)	0.8	0.0
		Abscesses and fistulae	NA	NA
		Congestive heart failure	NA	NA
		Posterior reversible encephalopathy syndrome	0.8	0.0

Notes: Other bleeding refers to bleeding from other organs.

Abbreviations: BVZ, Bevacizumab; Iri, Irinotecan; RT, radiotherapy; TMZ, Temozolomide; DVT, deep vein thrombosis; PE, pulmonary embolism; GI, gastrointestinal; NA, not available; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme.

during tumor progression while on anti-angiogenic therapy.^{23,25,47} Myeloid BMDCs consist of a variety of cell subpopulations including tumor-associated macrophages, which appear to constitute the largest subpopulation in GBM patient tumors after progression on anti-angiogenic therapy.⁴⁷ Tumor-associated macrophages are believed to induce resistance by the release of potent pro-angiogenic factors, a variety of cytokines, growth factors, and vascular-modulating enzymes.⁴⁸ Similarly, other subpopulations of BMDCs have been described as being involved in

mechanisms of resistance to anti-angiogenic therapy in GBM.^{49–51} A common feature of most studies describing BMDCs in GBM is the use of xenograft models, which are characterized by the lack of a normal immune system,^{25,50–52} and this may have influenced the observations of these studies. Future studies on BMDCs and other immune cells from patient GBM tissue or preclinical models other than the xenograft model might provide new knowledge of the immune system's role in resistance to anti-angiogenic therapy in GBM patients.

Table 3 Patterns of recurrence in bevacizumab treated GBM patients

Reference and evaluation criteria	Regimen	n	Pattern at baseline (n)	Local or non-diffuse recurrences, % (n)	Diffuse or multifocal recurrences, % (n)
First line treatment					
Narayana et al ¹⁵ Evaluation criteria: ^a	Concomitant RT, TMZ, and BVZ Adjuvant TMZ 150 mg/m ² days 1–7, and BVZ on days 8 and 22.	35	NA (35)	43 (15)	57 (20)
Chinot et al (AVAGlio) ¹⁸ Evaluation criteria: ^a	A: Standard treatment + concomitant, adjuvant, and maintenance BVZ. B: Standard treatment + concomitant, adjuvant, and maintenance placebo.	294 314	Local (218) Multifocal (75) Non-diffuse (89) Diffuse (205) Local (241) Multifocal (73) Non-diffuse (127) Diffuse (187)	89 (194) 12 (9) 75 (67) 2 (4) 89 (214) 8 (6) 77 (98) 2 (3)	11 (24) 88 (66) 25 (22) 98 (201) 11 (27) 92 (67) 23 (29) 98 (184)
Second or third line treatment					
Norden et al ¹⁰¹ Evaluation criteria: ^b	BVZ in combination.	26	NA (26)	62 (16)	31 (8)
Iwamoto et al ¹⁰⁶ Evaluation criteria: ^b	BVZ alone or in combination.	37	NA (37)	46 (17)	54 (19)
Narayana et al ¹⁰⁷ Evaluation criteria: ^b	BVZ in combination with Iri or carboplatin.	50	NA (50)	70 (35)	30 (15)
Pope et al ³⁸ Evaluation criteria: ^c	A: BVZ alone. B: BVZ + Iri.	124	Local (88) Multifocal or distant (10) Diffuse (26)	63 (55) 0 (0) 0 (0)	37 (33) 100 (10) 100 (26)
Chamberlain et al ³⁷ Evaluation criteria: ^c	BVZ alone.	80	Local (65)	88 (57)	12 (8)
Wick et al ¹⁰⁸ Evaluation criteria: ^d	BVZ alone or in combination with multiple agents.	44	NA (44)	77 (34)	23 (10)
Bloch et al ³⁶ Evaluation criteria: ^d	BVZ alone or in combination.	71	Local (71)	83 (59)	17 (12)
Soffietti et al ¹⁰⁹ Evaluation criteria: ^d	BVZ + Fotemustine.	50	Local (42) Multifocal (8)	76 (32) 0 (0)	24 (10) 100 (8)
Desjardins et al ¹¹⁰ Evaluation criteria: ^a	BVZ + TMZ.	21	NA (21)	52 (11)	48 (10)

Notes: Tumor progression patterns at baseline and time of on-study progression were evaluated according to different criteria: ^athe modified MacDonald Response Criteria;⁸⁰ ^bthe MacDonald Response Criteria;⁶⁴ ^cthe Pope Criteria;³⁸ and ^dthe Radiologic Assessment in Neuro-Oncology (RANO) criteria.⁶⁶

Abbreviations: BVZ, Bevacizumab; Iri, Irinotecan; RT, radiotherapy; TMZ, Temozolomide; NA, not available; GBM, glioblastoma multiforme; n, number of patients in the whole table.

Several studies have reported tumor invasion as being an important resistance mechanism to BVZ.^{24,40,44,45} Among the theories for development of an invasive BVZ-resistant tumor phenotype is the involvement of the tyrosine kinase c-mesenchymal-epithelial transition factor (c-Met), which in both preclinical animal studies and in patient GBM tumors has been shown to be upregulated during progression on anti-angiogenic therapy.^{25,53,54} c-Met seems to be involved in resistance to anti-angiogenic therapy by promoting tumor invasion and importantly, this resistance mechanism was blocked by inhibiting c-Met in combination with anti-angiogenic therapy.⁵³ Although the recurrence patterns from the clinical studies described in Table 3 do not support increased migratory growth during anti-angiogenic therapy,^{18,36–38} these findings suggest that the combination of anti-angiogenic therapy and a c-Met inhibitor may produce a more efficacious therapeutic effect in GBM.

Moreover, the expression of VEGF receptor 2 on GBM cells has been suggested as a resistance mechanism to BVZ.³¹ In some GBM cells, the receptor is believed to be activated in an autocrine manner by VEGF, and has been linked to promotion of cell proliferation and tumor growth, in addition to the formation of vessel-like structures from the tumor cells themselves, thereby making the tumors independent of the normal endothelial cell-derived vasculature.^{31,55,56} As BVZ can only cross the BBB in areas where the BBB is disrupted, and BVZ has to diffuse against a high intratumoral pressure gradient, autocrine VEGF stimulation will probably not be targeted.⁵⁷ In addition, new data from our laboratory suggest that the receptors in GBM are not solely dependent on VEGF, but are additionally activated by the growth factor vascular endothelial growth factor C (Michaelsen et al, unpublished data, 2014), which also could explain resistance to BVZ.

Additionally, recent data presented at the American Society of Clinical Oncology (ASCO) indicate that different molecular subtypes of GBM may represent tumor phenotypes with different resistance profiles to BVZ. This study performed subgroup analysis on GBM tissue taken from the AVAGlio study.⁵⁸ A total of 99 patients (56 receiving placebo treatment and 43 BVZ treatment) were classified into four subtypes by gene expression analysis: proneural, mesenchymal, proliferative, and unclassified.^{59,60} In addition, *IDH1* mutation status analysis was performed. It was demonstrated that patients with proneural tumors without *IDH1* mutation had a significantly longer median OS in the BVZ treatment group compared to the control treatment group (17.1 and 12.1 months, respectively; hazard ratio 0.63, 95% confidence interval: 0.4–0.99; $P=0.043$). Although this potential predictor needs validation in an independent dataset, it could potentially be used for patient and therapy stratification in the future, and it provides more information on BVZ resistance and mode of action.

In conclusion, many mechanisms have been suggested as responsible for BVZ resistance. However, no clear molecular or adaptive data definitively explain why only some GBM patients respond to BVZ.

Dosing and scheduling

Different dosing and scheduling strategies of BVZ were used in the three randomized phase III trials (Table 1). In all three studies, BVZ was administered concomitant and adjuvant at a dose of 10 mg/kg every 2 weeks, starting at week 4 of RT in the RTOG 0825¹⁹ and day 1 of RT in the AVAGlio¹⁸ and GLARIUS²⁰ trials. The adjuvant treatment phase in the three studies varied in length, dosing, and scheduling. The dosing and scheduling were based on previously reported trials on recurrent GBM and other non-GBM malignancies.^{32,61} Although BVZ is most often used at a dose of 10 mg/kg administered every 2 weeks in recurrent GBM until toxicity or progression occurs, its optimal dose has not been established yet. A meta-analysis of BVZ for recurrent GBM in 548 patients from 15 phase II studies reported no difference in efficacy between BVZ at 5 mg/kg and higher doses (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks), and this inconsistent dose–response relationship has also been reported in other non-GBM malignancies.⁶¹ Nevertheless, the efficacy and toxicity of these different doses warrants further investigation in prospective clinical trials.

The GLARIUS²⁰ and the AVAGlio¹⁸ trials continued treatment until progression. Recent retrospective data on recurrent GBM have shown that BVZ discontinuation

unrelated to disease progression does not appear to cause rebound recurrence or shorten PFS in patients who benefit from BVZ.⁶² However, the optimal duration of BVZ treatment and the impact of discontinuation requires prospective evaluation in clinical trials.

Safety

Regardless of the potential benefits of BVZ in combination with standard therapy, BVZ is associated with higher risk of several potential toxicities when combined with standard radiotherapy. The most frequent toxicity was hypertension, and BVZ was also associated with an increased risk of arterial and venous thromboembolic events.^{18–20} Other observed BVZ toxicities were gastrointestinal perforation, cerebral bleeding, fatigue, wound healing complications, and proteinuria.^{11,18–20} Evaluation for these toxicities is important in BVZ-treated patients, because early intervention may decrease morbidity and mortality risk if this treatment moves into first line treatment in the future. Additionally, treatment with BVZ can significantly alter a patient's treatment planning, as it can require treatment cessation to avoid exacerbation of an adverse event. However, the data on the optimal toxicity management guidelines are currently limited, and are based on the experiences in recurrent GBM and a variety of non-GBM cancers.⁶³

Clinical endpoints of GBM treatment

When assessing clinical efficacy, different endpoints are used in various malignant diseases. Interpreting endpoints in GBM presents several hurdles, especially when treating with anti-angiogenic drugs. These problems are discussed in the following section.

Response evaluation

Tumor response is normally evaluated by the MacDonald Criteria and/or the Radiologic Assessment in Neuro-Oncology (RANO) criteria, which are based on a combination of tumor measurements, or estimates based on contrast- and non-enhancing tumor images and utilizing magnetic resonance imaging (MRI) scan techniques, including MRI T2-weighted and fluid-attenuated inversion recovery image sequences. In addition, corticosteroid dose and neurological status are evaluated.^{64–66}

Response evaluation has some inherent difficulties. Tumor enhancement can be non-specific, as it also partly represents peritumoral edema due to the leakiness of tumor vessels. Moreover, enhancement can be influenced by changes in corticosteroid dose and radiologic technique. In addition,

increased enhancement can be caused by other processes that are not related to tumor progression such as treatment-related inflammation, seizure activity, post-surgical changes, ischemia, and radiation effects.^{67–70}

Pseudo-progression is an increase in contrast enhancement unrelated to tumor progression. Pseudo-progression is seen in 20%–30% of patients receiving RT and temozolomide, is a result of increased permeability of vasculature after RT, and can be accompanied by progressive neurological symptoms.^{71–74}

Other limitations include difficulty in measuring irregular-shaped tumors, inter-observer variability, lack of assessment of the non-enhancing tumor component, and limitations when assessing multifocal tumors and walls of cystic or surgical cavities.^{75–77}

Anti-angiogenic treatment raises new challenges, as MRI scans can sometimes show signs of response to such treatment due to normalization of tumor vasculature, not necessarily antitumor activity, and therefore represent a so-called pseudo-response. As a consequence, it is postulated that anti-angiogenic treatment might control contrast-enhancing tumors more effectively than non-enhancing tumors, which can cause problems when interpreting MRI scans.²⁴ As anti-angiogenic treatment seems to control tumor enhancement as early as 1–2 days after initiation of treatment,^{32,78} non-enhancing tumors may continue to grow and therefore, measuring only the enhancing lesion fails to correctly estimate tumor growth.^{75,76,79}

Difficulties assessing non-enhancing tumors using MRI can arise from the fact that increases in T2 and fluid-attenuated inversion recovery signal can arise from post-irradiation damage, decreased glucocorticoid dosage, postoperative changes, seizure activity, demyelination, and ischemic injury, and can mistakenly be interpreted as tumor progression.⁹

In recognition of the potential challenges with response assessment, the AVAGlio study¹⁸ used the modified response criteria,⁸⁰ while both the RTOG 0825¹⁹ and the GLARIUS²⁰ studies used the MacDonald Criteria.⁶⁴ In these studies, there seems to be a strong concordance in determining response and progression by different “standardized criteria”,⁸¹ but it cannot be excluded that variation in the estimate of PFS in the three randomized studies might be due to differences in interpretation of response.

Recently, baseline ¹⁸F-fluoro-D-glucose (FDG)-PET (positron emission tomography) imaging has been suggested as a feasible biomarker in recurrent GBM patients for predicting tumor control and survival following anti-angiogenic therapy with BVZ.⁸² However, due to the high rate of glucose

metabolism in normal brain tissue and in inflammatory cells, FDG has shown diagnostic limitations when used for brain tumor imaging.⁸³ In contrast, radiolabeled amino acids have a relatively low uptake in normal brain tissue and usually accumulate intensely in tumor cells. Preclinical and clinical studies have shown that ¹⁸F amino acid and nucleic analog PET tracers, eg, O-(2-¹⁸F-fluoroethyl)-L-tyrosine and [¹⁸F]-fluoro-L-thymidine, are superior to the FDG-PET in predicting treatment efficacy, and that predictability is enhanced by a combination of both PET and MRI.^{84–86} Although these techniques still need to be validated, non-invasive PET tracers, in addition to MRI, may add information in response assessment, which could be useful for clinical decision making, eg, discontinuation of BVZ.

PFS and OS

When assessing the efficacy of drugs in clinical trials, PFS and OS have been the most commonly used primary endpoints.^{1,18–20,32} OS is a straightforward endpoint that apparently offers a simple interpretation.⁸⁷ However, OS is likely to be influenced by the subsequent anticancer treatments the patients receive after going off-study for any reason (eg, due to disease progression or intolerable toxicities).

Treatment with BVZ in patients with GBM seems to increase median PFS, but not OS. However, evaluating PFS depends on accurate and objective means to detect progression. Further, it is influenced by pseudo-progression and pseudo-response (see the “Response evaluation” section), especially in patients receiving temozolomide in combination with radiation and anti-angiogenic treatment, and these problems may lead to inaccurate estimation of PFS.⁸⁸

QOL

Maintenance or increase of QOL is an important endpoint in the treatment of GBM. GBM is accompanied by neurological and cognitive impairments in almost all patients.⁸⁹ These impairments are related to the tumor and its position in the central nervous system, tumor-related epilepsy, and treatment related factors.^{9,89,91} When treating GBM patients with targeted therapies such as anti-angiogenic agents, QOL should be taken into consideration, since treatment could delay deterioration of neurological and cognitive functions and thereby improve QOL. Although still controversial, especially in newly diagnosed GBMs, some evidence suggest that BVZ produces an improvement or preservation of neurocognitive function.⁸

Headache, nausea, and vomiting are frequent symptoms seen in patients with GBM, which are due to increased intracranial pressure caused by peritumoral edema. Administering corticosteroids can diminish peritumoral edema, thereby

alleviating the symptoms associated with increased intracranial pressure. On the other hand, corticosteroids may induce negative effects on neurocognitive function and/or QOL,^{92–94} and it has been documented that corticosteroid use in primary brain tumors and metastases can lead to increases in blood glucose levels, peripheral edema, psychiatric disorders, and Cushing's syndrome.^{95,96} However, the reduced intracranial pressure associated with corticosteroid treatment improves neurocognitive functions and QOL, despite other corticosteroid-induced adverse effects.

Studies, including the AVAGlio study, have shown that BVZ has a steroid-sparing effect, which may be a consequence of improved tumor control as well as alleviation of vasogenic brain edema. This would be expected to positively impact QOL due to lower corticosteroid dose and, therefore, less corticosteroid-related toxicity.^{9,18,63,81–85} Moreover, the steroid-sparing effect of BVZ is associated with clinical response and improved neurological symptoms in high-grade glioma, or GBM.^{84,86–88}

It is still unclear whether BVZ given as part of primary treatment in patients with newly diagnosed GBM in fact influences QOL positively, and further evaluation of the AVAGlio,¹⁸ RTOG 0825,¹⁹ and the GLARIUS²⁰ studies is therefore needed.

Conclusion

BVZ given as part of primary treatment in newly diagnosed GBM patients is feasible and safe. It does prolong PFS, but not OS. It might influence QOL, but we still await critical evaluation of published data. No molecular or clinical data are available that can predict which subpopulation of patients might benefit from BVZ treatment.

Disclosure

The authors report no conflicts of interest in this work.

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