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Patterns of bevacizumab use in patients with glioblastoma: an online survey among experts in neuro-oncology

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Abstract

Background. Bevacizumab (BEV) received accelerated FDA approval in 2009 for the treatment of recurrent glioblastoma (rGBM). Unfortunately, prospective randomized controlled phase 3 studies (AVAglio and Radiation Therapy Oncology Group 0825 in newly diagnosed, European Organisation for Research and Treatment of Cancer 26101 in rGBM) failed to show an overall survival benefit with BEV added to standard therapy. In light of these data, we aimed to capture current utilization patterns and perceived value of BEV in the treatment of GBM among experts in the field.

Methods. An online questionnaire comprising 14 multiple choice questions was sent out in spring 2017 to 207 oncologists/neuro-oncologists treating patients with GBM at all National Cancer Institute–designated cancer centers in the United States.

Results. Sixty-two of 207 (30%) invitees responded (by training, 70% neuro-oncologists, 20% medical oncologists, 10% pediatric oncologists/neuro-oncologists). Participants reported use of BEV most frequently in rGBM for control of edema (85% of respondents) and/or when no other treatment options were available (68%). BEV is rarely used in newly diagnosed GBM (<5% of cases by 78% respondents and in 5% to 10% cases by 15% respondents). Sixty-six percent of participants indicated that they thought BEV improved symptoms, 30% that it improved symptoms and survival, 3% that it had no benefit in GBM patients.

Conclusion. In this cross-sectional online survey we found that among neuro-oncology experts in the United States in 2017, BEV is predominantly utilized in select patients with rGBM, and is only rarely used in a small subgroup of patients with newly diagnosed GBM for control of edema. The low response rate may have introduced a nonresponse bias.

Keywords

bevacizumab | clinical practice | glioblastoma | recurrent | survey

Bevacizumab (BEV) is a monoclonal antibody that binds VEGF, preventing the interaction of VEGF with its receptors on the surface of endothelial cells.[1] Consequently, BEV is an angiogenesis inhibitor and is thought to alter metabolic activity of neoplasms, including glioblastomas.[2] Glioblastomas have a poor prognosis with standard therapy and most patients eventually have a recurrence and die of their disease.[3,4] Thus, many were hopeful for a breakthrough when the first preliminary reports of recurrent high-grade gliomas treated with BEV with or without

irinotecan showed radiographic response rates of 43% to 63%.[4–7] This led to subsequent accelerated FDA approval of BEV for the treatment of recurrent glioblastoma (rGBM) in 2009.[8] Unfortunately, the 2014 publications of 2 prospective, randomized, placebo-controlled phase 3 studies (AVAglio and Radiation Therapy Oncology Group (RTOG) 0825) in newly diagnosed GBM could not demonstrate an overall survival (OS) benefit attributable to the use of BEV.[9,10] Similarly, results from the European Organisation for Research and Treatment of Cancer (EORTC) 26101 phase 3 trial exploring the combination of BEV and lomustine vs lomustine alone in the treatment of rGBM failed to show improved OS with the combined regimen despite promising phase 2 data.[11,12] In contrast to the lack of evidence for OS benefit from BEV in GBM, progression-free survival (PFS) was improved.[9–12] However, it is debated whether the observed PFS benefit is purely radiographic. Thus, controversy continues regarding the clinical usefulness of BEV for GBM as it may potently reduce tumor-related edema, potentially decrease patients' steroid requirements and, in select cases, possibly improve quality of life.[12–15] In the United States, the current practice patterns of BEV use for the treatment of GBM are unclear. The goal of the present study is to gauge BEV usage among glioma experts in the United States in light of the available published data (Table 1).

Materials and Methods

This study was designed as a cross-sectional online survey investigating the current indications, patterns, and estimated percentage frequency of BEV use in the treatment of patients with GBM. As a study population, we chose to contact brain cancer experts (neuro-oncologists and medical oncologists) at the 70 National Cancer Center (NCI)-designated cancer centers in the United States. Experts at the respective institutions were identified through an online search of the institutional websites, as well as a search of emails listed on publications that are indexed in PubMed. An anonymous online questionnaire comprising 14 questions was sent to the identified experts. The survey was sent up to 2 additional times within 1 week from the initial email if addressees did not respond to the initial query. Data were received in a cumulative fashion through the online survey tool that was used for this study (Survey Monkey). There was no financial or other incentive provided to participate in this online survey. The study was approved by the Johns Hopkins Medical Institution's Investigational Review Board.

Statistical Considerations

The survey questionnaire was chosen specifically for oncologists who treat GBM patients in clinic. All questions were not necessarily mutually exclusive nor completely overlapping. The survey was designed for information gathering with restricted sampling among NCI-designated cancer centers. The survey results were presented with standard statistical descriptive summaries. All results should not be generalized outside this sampling perspective.

Results

A total of 62 out of 207 experts (30%) responded to this online survey. All respondents were providers who prescribe chemotherapy or make treatment recommendations for the management of brain cancers, with the majority being neuro-oncologists (71%), followed by medical oncologists (19%) and pediatric oncologists/neuro-oncologists (10%). Approximately half the respondents reported practicing for more than 10 years after fellowship (48%). Most of the respondents were men (71.7%). All respondents indicated they previously used BEV in the management of their patients with GBM. Details of survey response rates by subspecialty are shown in Table 2 and demographics of the study population in Table 3.

Responses to all other survey questions are summarized in Table 4.

Perceived Overall Benefit From BEV in GBM

Three of the 14 survey questions aimed at examining the perceived benefit from treatment with BEV in patients with GBM, as stated by the prescribing physician (Questions 3, 4, and 10). Based on submitted answers to these questions, it appeared the respondents considered BEV an antineoplastic agent, as well as a steroid-sparing medication to reduce vasogenic edema. Most respondents see the main benefit from BEV in symptom improvement, and about one-quarter of respondents felt BEV affects symptoms and survival alike. Participants stated in their response that BEV was overall either very or somewhat valuable in neuro-oncology practice; no respondent indicated that it was not valuable at all.

Use of BEV in rGBM or Newly Diagnosed GBM

Most respondents stated they utilized BEV in the recurrent setting for edema control and/or when no other treatment options were available (Question 2). Additionally, most providers marked using BEV in more than 25% of patients at some point during treatment (Question 5). In consideration of the question examining the most common use of BEV either alone or in combination with other agents, the most common response was that BEV was used as monotherapy (47% of respondents), followed by combination with a nitrosourea (37% of respondents; Question 9). Several questions aimed at appraising current use patterns of BEV in newly diagnosed GBM. Sixty-two percent of participants reported having used it in this setting with the goal of controlling edema, but only 3% of participants indicated they consider BEV a "standard of care" option in newly diagnosed GBM. Overall, only a small fraction of newly diagnosed GBM patients are reportedly receiving BEV under the care of most respondents (Question 5).

Dose and Frequency of BEV Infusions

Based on the survey responses, the most commonly used dose of BEV was 10 mg/kg (90% of respondents),

Table 1 Summary of Major Phase 2 and 3 Clinical Trials With Bevacizumab in Treatment of Glioblastoma

Authors, Year[Ref]	Treatment Groups	Type of Trial and Treatment Setting	Number of Patients	Endpoints	*P* value	Hazard Ratio for Death (95% CI)	Rates of Grade ≥3 Toxicity in BEV group
Wick et al, 2017[11]	CCNU + BEV vs CCNU alone	Phase 3 recurrent	437	mPFS (4.2 vs 1.5 months)	<.001	0.49 (0.39-0.61)	VTE: 4.9% HTN: 23.7% Hematologic: 53.7%
				mOS (9.1 vs 8.6 months)	.65	0.95 (0.74-1.21)	
Herrlinger et al, 2016[16]	RT+BEV, followed by BEV + irinotecan vs RT +TMZ, followed by TMZ	Phase 2 newly diagnosed, MGMT unmethylated	182	6-month PFS (79.3% vs 42.6%)	<.001	0.57 (0.41-0.80)	VTE + HTN: 11.8%
				mOS (16.6 vs 17.5 months)	N/A	1.02 (0.71-1.48)	
Taal et al, 2014[12]	CCNU vs BEV vs CCNU + BEV	Phase 2 recurrent	153	Nine-month OS (43%) vs 38% vs 63%	N/A	N/A	HTN: 26% Infection: 6%
Gilbert et al, 2014[10]	TMZ +RT + BEV vs TMZ + RT + placebo	Phase 3 newly diagnosed	637	mPFS (10.7 vs 7.3 months)	.007	0.79 (0.66-0.94)	HTN: 4.2% VTE: 7.7% Serious bleed: 1.5%
				mOS (15.7 vs 16.1 months)	.21	1.13 (0.93-1.30)	
Chinot et al, 2014[9]	TMZ + RT + BEV vs TMZ + RT + placebo	Phase 3 newly diagnosed	921	mPFS (10.6 vs 6.2 months)	<.001	0.64 (0.55-0.74)	HTN: 11.3% VTE: 7.6% CNS bleed: 2%
				mOS (16.8 vs 16.7 months)	.1	0.88 (0.76-1.02)	
Narayana et al, 2012[17]	RT/TMZ + BEV 10 mg/kg	Phase 2 newly diagnosed	51	mPFS 13 months mOS 23 months	N/A	N/A	Bleed: 9.8% DVT: 3.9%
Lai et al, 2011[15]	RT/TMZ + BEV 10 mg/kg	Phase 2 newly diagnosed	70	mPFS 13.6 months mOS 19.6 months	N/A	N/A	CVA: 9% CNS bleed: 3% HTN: 11%
Friedman et al, 2009[13]	Group 1: BEV	Phase 2 recurrent	85	Six-month PFS (42.6%) ORR (28.2%)	N/A	N/A	HTN: 8.3% Convulsion: 6%
	Group 2: BEV + irinotecan		82	Six-month PFS (50.3%) ORR (37.8%)	N/A	N/A	CNS bleed: 1% Convulsion: 13.9%
Kreisl et al, 2009[14]	BEV 10 mg/kg + irinotecan	Phase 2 recurrent	48	Six-month PFS (29%) 6-month OS (57%)	N/A	N/A	VTE: 12.5% HTN: 12.5%
Gutin et al, 2009[18]	BEV 10 mg/kg + RT	Phase 2 recurrent	25	Six-month PFS (65%) mOS 12.5 months	N/A	N/A	CNS bleed: 4%
Vredenburgh et al, 2007[6]	Cohort 1: BEV 10 mg/kg + irinotecan Cohort 2: BEV 15 mg/kg + irinotecan	Phase 2 recurrent	35	Six-month PFS (46%) 6-month OS (77%)	N/A	N/A	VTE: 11% CNS bleed: 2%

Abbreviations: BEV, bevacizumab; CVA, cerebral vascular accident; HTN, hypertension; MGMT, O(6)-methylguanine-DNA methyltransferase; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; RT, radiation therapy; TMZ, temozolomide; VTE, venous thromboembolism.

Table 2 Survey Response Rates by Subspecialty

Subspecialty of Experts	Total Number Invited to Participate (Percentage)	Total Responses (Subspecialty Response Rate[a])
Neuro-oncologists	144 (69.6%)	44 (30.6%)
Medical oncologists	37 (17.9%)	12 (32.4%)
Pediatric neuro-oncologists	22 (10.6%)	4 (18.1)
Pediatric oncologists	4 (1.9%)	2 (50%)
	Total = 207	Total = 62

[a]Subspecialty response rate = (total responses from a particular subspecialty / total number of subspecialists who received the survey) × 100%.

Table 3 Demographics of Survey Respondents

Demographics Questions	Responses	Total Responses
Training Background		62
Medical-oncology	12 (19.3%)	
Neuro-oncology	44 (71%)	
Pediatric oncology	2 (3.2%)	
Pediatric neuro-oncology	4 (6.5%)	
Other	0 (0%)	
Years of Practice After Fellowship		62
<5 years	16 (25.8%)	
5-10 years	16 (25.8%)	
>10 years	30 (48.4%)	
Gender of Responders		60
Male	43 (71.7%)	
Female	17 (28.3%)	

administered at 2-week intervals (85% of responses; Questions 7 and 8).

Discussion

Since the publication of the first clinical trials that were directed at examining the clinical benefit of BEV in the treatment of GBM (Table 1), and the drug's consequent accelerated approval by the FDA, BEV has been used commonly in neuro-oncology practice to treat GBM; however, recently conducted phase 3 trials have consistently shown BEV to have no positive effect on OS.[9–11] It is unknown whether these findings have had any impact on the use of BEV in the treatment of GBM; moreover, the current patterns of BEV use in the United States are not known. The purpose of this survey study was to capture current patterns of use and perception of the role of BEV in the treatment of GBM among experts in the field. The response rate to this survey was 30%, which may introduce a potential nonresponse bias; therefore, the results should be interpreted with caution.

We note several key findings in this study. First, BEV is still widely used. Second, although its use is prevalent, BEV is mostly used in recurrent disease and rarely in a newly diagnosed setting. Third, there are considerable differences regarding the perception of the drug's principal clinical benefit, ie, whether it improves survival, symptoms, both, or neither.

Over the past 10 years our understanding of the role of BEV in the treatment of GBM has evolved based on publication of major trials.[9–15] None of the trials proved any OS benefit of BEV. The benefit of BEV shown in these past trials, and in the phase 3 clinical trials since then, has been primarily improved PFS with or without symptomatic relief due to reduction of edema.[9–11] However, the FDA still gave the drug accelerated approval and since the completion of this study, on December 5, 2017, BEV received final FDA approval for the treatment of recurrent GBM.[8] This approval was granted on the basis of EORTC 260101, which showed that the addition of BEV to lomustine increased PFS and reduced corticosteroids use in patients with rGBM. The FDA acknowledged that these parameters have meaningful significance in patient care. However, reflecting on the clinical evidence collected on BEV thus far, questions arise as to whether reliance on purely radiographically defined PFS is an appropriate outcome measure for BEV for the treatment of rGBM, and whether the FDA indication should more clearly be labeled for edema control or aiding in reduction of corticosteroid use, instead of having a benefit on survival.

There is an ongoing challenge of standardizing neurologic functioning and quality of life outcomes and incorporating them into clinical trial design. For example, RTOG 0825 overall found adverse neurocognitive outcomes in the group with BEV added,[19] AVAglio detected favorable health-related quality of life measures for these patients, whereas EORTC 26101 detected no group differences in either of these. Thus, these studies provide no clear guidance regarding the clinical benefits of BEV for rGBM and leave abundant room for clinician judgment.[20]

Ultimately, there is a question of weighing the pros and cons of the use of BEV in treatment of rGBM by evaluating the potential clinical benefits of the drug vs the risk of possible complications. There are several positive features associated with use of this drug. There may be quick symptom relief in some patients with significant edema, or mass effect.[13,14] BEV is considered a steroid-sparing agent, allowing radiographic and sometimes clinical symptom control without some of the undesirable side effects of steroid therapy. This may be of relevance in light of recently described steroid-related gene expression changes that may promote a more aggressive GBM phenotype in a mouse model.[21] Although BEV is used primarily in recurrent GBM, it can also be used in select cases with newly diagnosed disease for which radiation therapy would otherwise not be tolerated. However, there are also some serious concerns identified with the use of BEV. The adverse events rising from complications associated with use of BEV (ie, increased risk for bleeding, including intracranial hemorrhage, pulmonary embolism

Table 4 Survey Questions and Responses

Question Number	Survey Question	Answer Choices	% of Responses (Number of Responses)	Total Number of Responses
1	Have you ever used bevacizumab for the management of glioblastoma?	Yes	100% (62)	62
		No	0% (0)	
2	In what setting do you use bevacizumab in patients with glioblastoma? (multiple answers were allowed)	Newly diagnosed glioblastoma as a standard of care	3.2% (2)	60
		Newly diagnosed glioblastoma for the control of edema	61.7% (37)	
		Recurrent glioblastoma as a standard of care	60% (36)	
		Recurrent glioblastoma for the control of edema	85% (51)	
		Recurrent glioblastoma when there are no other treatment options	68.3% (41)	
3	Why do you use bevacizumab in patients with glioblastoma?	As an antineoplastic agent	1.7% (1)	62
		As a steroid sparing agent/for control of edema	26.7% (16)	
		Both	71.7% (43)	
		None	0% (0)	
4	What is your opinion about the clinical benefit of bevacizumab in glioblastoma patients?	Improves survival	0% (0)	58
		Improves symptoms	67.2% (39)	
		Both	29.3% (17)	
		None	3.4% (2)	
5	What percentage of your patients with newly diagnosed glioblastoma gets treated with bevacizumab?	<5%	78.3% (47)	60
		5% to 10%	15% (9)	
		10% to 25%	5% (3)	
		>25%	1.7% (1)	
6	What percentage of your patients with recurrent glioblastoma gets treated with bevacizumab at some point in their disease course?	<5%	0% (0)	58
		5% to 10%	8.6% (5)	
		10% to 25%	6.9% (4)	
		>25%	84.5% (49)	
7	What dose of bevacizumab do you most commonly use in patients with glioblastoma?	10 mg/kg	90% (54)	60

Table 4 Continued

Question Number	Survey Question	Answer Choices	% of Responses (Number of Responses)	Total Number of Responses
		7.5 mg/kg	5% (3)	
		5 mg/kg	5% (3)	
8	What frequency of bevacizumab do you most commonly use in patients with glioblastoma?	Every 2 weeks	85% (51)	60
		Every 3 weeks	11.7% (7)	
		Every 4 weeks	3.3% (2)	
9	In which combination do you most commonly use bevacizumab for recurrent glioblastoma?	I do not use bevacizumab for recurrent glioblastoma	1.7% (1)	60
		Bevacizumab monotherapy	46.7% (28)	
		In combination with a nitrosourea (lomustine or carmustine)	36.7% (22)	
		In combination with temozolomide	5% (3)	
		In combination with irinotecan	1.7% (1)	
		In combination with carboplatin	3.3% (2)	
		In combination with radiation	1.7% (1)	
		In combination with NovoTTF	3.3% (2)	
10	How valuable is bevacizumab overall in the neuro-oncology practice?	Very valuable	51.7% (31)	60
		Somewhat valuable	48.3% (29)	
		Not valuable at all	0% (0)	

and deep venous thrombosis, bowel perforation, and others) are rare but severe. In addition, BEV needs to be discontinued prior to repeat surgery and even after stopping its use, surgery is often considered more difficult after prior BEV use. Furthermore, BEV use carries other potential disadvantages such as rendering response assessment difficult, and it often leads to ineligibility to participate in clinical trials.[22] There is also high cost associated with continuing treatment with BEV. The average wholesale price (AWP) of BEV for a dose of 400 mg/16 mL is $3732. Based on the stated AWP, the cost per dose for a 70 kg patient would be $6531 and because administration can be as frequent as every 2 weeks, 6 months of treatment would cost $78 372.[23] Overall, even if one is willing to start treatment with BEV after considering all the above factors, there is still no clinical evidence of survival benefit in patients with recurrent GBM.

The present survey aimed at examining current patterns of use of BEV and its perception as treatment for recurrent GBM among experts in the field, given the pros and cons associated with its treatment as well as the publicity surrounding it in recent years, attributed to the numerous publications of trials evaluating its use and consequent FDA approval. Nevertheless, this survey certainly had limitations. First, it was geographically limited to the United States. Practice patterns in other health care environments may significantly differ based on availability of BEV, insurance coverage, and regulatory decisions made by different governments. Second, there is the intrinsic limitation that participants' opinions captured using a multiple-choice format may not precisely reflect true practice patterns, which is present in any survey study such as this. Third, adult and pediatric oncologists and neuro-oncologists were included in this survey, which constitutes another limitation of this study as the practice patterns between adult and pediatric providers may differ. The proportion of pediatric providers in this survey though was only 10% and the impact of possible differences in BEV use on the overall outcome of this study is likely limited. Finally, all respondents reported having used BEV to treat GBM in the past, thus perceptions and practice patterns of providers who have never prescribed BEV were not captured by this survey.

Now that BEV is FDA approved for rGBM, it will be of interest to follow patterns of its use over time as more clinical

data from patients treated for rGBM with BEV become available. Future research could be directed toward formally assessing specific indications of BEV use in select patients with significant disease burden or unfavorable tumor locations who would otherwise not be able to complete their standard radiation and concurrent temozolomide, which is to date the most evidence-based treatment with a documented survival advantage in patients with this challenging disease.

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References

1. Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nat Rev Drug Discov.* 2004;3(5):391–400.
2. Fack F, Espedal H, Keunen O, et al. Bevacizumab treatment induces metabolic adaptation toward anaerobic metabolism in glioblastomas. *Acta Neuropathol.* 2015;129(1):115–131.
3. 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.
4. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol.* 1999;17(8):2572–2578.
5. Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. *Neuro Oncol.* 2005;369(7):abstract 342.
6. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res.* 2007;13(4):1253–1259.
7. Field KM, Jordan JT, Wen PY, Rosenthal MA, Reardon DA. Bevacizumab and glioblastoma: scientific review, newly reported updates, and ongoing controversies. *Cancer.* 2015;121(7):997–1007.
8. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist.* 2009;14(11):1131–1138.
9. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370(8):709–722.
10. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370(8):699–708.
11. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med.* 2017;377(20):1954–1963.
12. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *Lancet Oncol.* 2014;15(9):943–53.
13. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol.* 2009;27(28):4733–4740.
14. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol.* 2009;27(5):740–745.
15. 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.
16. Herrlinger U, Schäfer N, Steinbach JP, et al. Bevacizumab plus irinotecan versus temozolomide in newly diagnosed O6-Methylguanine-DNA methyltransferase nonmethylated glioblastoma: the randomized GLARIUS trial. *J Clin Oncol.* 2016;34(14):1611–1619.
17. Narayana A, Gruber D, Kunnakkat S, et al. A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma. *J Neurosurg.* 2012;116(2):341–345.
18. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75(1):156–163.
19. Armstrong TS, Won M, Wefel JS, et al. Comparative impact of treatment on patient reported outcomes (PROs) in patients with glioblastoma (GBM) enrolled in RTOG 0825. *J Clin Oncol.* 2003;31(15 suppl):abstract 2003.
20. Sandmann T, Bourgon R, Garcia J, et al. Patients with proneural glioblastoma may derive overall survival benefit from the addition of bevacizumab to first-line radiotherapy and temozolomide: retrospective analysis of the AVAglio trial. *J Clin Oncol.* 2015;33(25):2735–2744.
21. Pitter KL, Tamagno I, Alikhanyan K, et al. Corticosteroids compromise survival in glioblastoma. *Brain.* 2016;139(pt 5):1458–1471.
22. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963–1972.
23. Bevacizumab. In: *Lexi-Drugs Online.* Hudson (OH): Lexicomp, Inc; 2018. [updated 11 May 2018; cited 14 May 2018]. Available at http://online.lexi.com.