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Bevacizumab in temozolomide refractory high-grade gliomas: single-centre experience and review of the literature

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Abstract

Background: Despite multidisciplinary treatment approaches, the prognosis for patients with high-grade glioma (HGG) is poor, with a median overall survival (OS) of 14.6 months for glioblastoma multiforme (GB). As high levels of vascular endothelial growth factor A (VEGF) are found in HGG, targeted anti-antiangiogenic therapy using the humanized monoclonal antibody bevacizumab (BEV) was studied in a series of clinical trials. Still, the discrepancy of BEV's efficacy with regard to initial clinical and radiological response and its reported failure to prolong survival remains to be explained. Here, we illustrate the effectiveness of BEV in recurrent HGG by summarizing our single-centre experience.

Methods: We have retrospectively investigated the effect of BEV in temozolomide refractory HGG in 39 patients treated at the University Hospital of Ulm, Germany.

Results: Median duration of BEV treatment was 12.5 weeks; 23% of patients received BEV for more than 6 months and 15% for more than 1 year, until clinical or radiological tumour progression led to discontinuation. Furthermore, Karnofsky performance status increased in 30.6% and steroid dose decreased in 39% of all patients.

Conclusions: The review of literature reveals that phase II and III studies support BEV as an effective therapy in recurrent HGG, at least with regard to progression-free survival (PFS), but landmark phase III trials failed to prove benefit concerning OS. Here, we discuss reasons that may account for this observation. We conclude that prolonging PFS with maintenance of neurological function and personal and economic independency justifies the off-label use of BEV.

Keywords: bevacizumab, glioblastoma, high-grade glioma, temozolomide, VEGF

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Introduction

High-grade gliomas (HGGs) account for approximately 25% of all central nervous system (CNS) tumours and have an annual incidence rate of 5–7 cases per 100,000 inhabitants. The most common HGG is the glioblastoma multiforme, World Health Organization (WHO) grade IV (GB), accounting for 16% of all primary brain and CNS tumours and 54% of all gliomas.[1] Despite multidisciplinary treatment approaches, the prognosis for patients with HGG is poor. With current standard of care (SOC), the median overall survival (OS) for GB is ~15 months and the 2-year survival rate is ~25%.[2]

Currently, SOC treatment of newly diagnosed GB is maximal surgical resection without risking neurological deficits, chemoradiotherapy with temozolomide (TMZ) followed by six cycles of TMZ monotherapy.[2] Adding TMZ to radiotherapy provided a significant survival benefit for patients with newly diagnosed GB, especially the ~40% with significant methylation of the methylguanine methyl transferase (MGMT) promoter, which by decreasing MGMT expression sensitizes GB cells to alkylating compounds.[3] The opposite applies to patients with MGMT promoter-unmethylated tumours, who hardly benefit from additional TMZ, have a worse prognosis[3]

and for whom effective second-line therapies are still pending.

In addition, with very rare exceptions, all HGG patients relapse after first- and further-line therapies with a median survival for recurrent grade III and IV HGG of ~10–12 months and ~6–8 months, respectively.[4,5] To date, there is no evidence-based and widely accepted SOC for patients with recurrent HGG. Treatment options include repeated resection, re-irradiation, re-exposure to TMZ or dose-dense TMZ, lomustine-containing regimens as well as mostly off-label systemic therapies.

GBs are characterized by increased microvascular proliferation, which is essential for tumour growth and invasion and which is mediated by vascular endothelial growth factor A (VEGF) signaling.[6,7] As VEGF expression increases concomitantly with glioma grade, higher VEGF levels are associated with poor outcome among GB patients[8,9] and are found increased in recurrent compared with treatment-naïve GB.[10] Clinical trials suggesting a substantial efficacy of the anti-angiogenic anti-VEGF humanized monoclonal antibody bevacizumab (BEV) in recurrent GB were reported as early as 2009.[11,12] Based on these studies, in May 2009 BEV was granted accelerated approval for treatment of recurrent GB by the United States (US) Food and Drug Administration (FDA) and Swissmedic in the US and Switzerland, respectively.[13] However, after the first enthusiasm subsequently performed rigorously designed placebo-controlled trials failed to unequivocally demonstrate an effect of BEV on OS in patients with newly diagnosed GB, while mostly confirming an effect on progression-free survival (PFS).[14–16] These results have hindered approval of BEV in primary as well as recurrent GB in the European Union, and, although frequently administered, it will most probably remain off-label also in the near future.

However, clinical experience strongly suggests that a subset of patients with recurrent HGG experience an impressive and long-lasting benefit in response to BEV treatment. Correspondingly, BEV remains a mainstay in the off-label third-line therapy of HGG. Here, we provide a summary of our single-centre experience with this targeted therapy in recurrent HGG, summarize the results of other reports and discuss the reasons that presumably led to the failure of BEV to prolong OS in clinical trial.

Methods

We retrospectively analysed the data of our patients with recurrent HGG treated with BEV over a period of 6.5 years. All patients provided written informed consent for inclusion in the data analysis according to institutional guidelines. The study was approved by the Ethical Committee of the University of Ulm, Germany (reference # 367/16).

We identified 39 patients, 35 patients with GB (90%) and 4 patients with other HGG (anaplastic gliomas of astrocytic, oligodendroglial or mixed phenotypes, 10%), Of note, the diagnoses were based on the last histological examination made before initiation of BEV therapy and most of the patients radiologically had progressed to grade IV tumours. Histological diagnosis was based on the 2007 WHO brain tumour classification.

All patients were previously treated with chemoradiotherapy followed by TMZ monotherapy according to the Stupp protocol.[2] Patient characteristics are shown in Table 1. Overall 74% (n = 29) of the patients received BEV monotherapy (10 mg/kg bodyweight BEV every 14 days). In 26% (n = 10), each BEV cycle was complemented by irinotecan (125 mg/m^2 or 340 mg/m^2) as reported by others.[14,15]

Results

The median time from initial diagnosis to BEV was 17.2 months. Radiological progression according to the RANO criteria[17] led to discontinuation of BEV in 73% of cases and clinical progression in 21%. Overall, 6% of the patients died during BEV therapy. This resulted in a median duration of BEV treatment of 12.5 weeks (range 2–69), corresponding to 2–35 cycles of BEV with a median of 7 cycles. However, almost one quarter of the patients (23%) were treated for more than 6 months (>26 weeks) and more than every eighth patient of the initial 39 patients (15%) received BEV for more than one year (>52 weeks). As a consequence, the median PFS after BEV therapy was 4.8 months (range 0.5–27.0) and the PFS at 6 months (PFS6) was 31.4%. Interestingly, Kaplan–Meier estimates for the median PFS of the chemotherapy directly preceding BEV were 4.5 months (range 1.5–73.0), similar to the PFS in response to BEV (p = 0.243) (Figure 1). In recurrent HGG, a low Karnofsky performance status (KPS) is associated with risk of early progression.[4] In addition,

Table 1. Patient characteristics ($n = 39$).

Characteristics	*n*	%
Sex		
Male	27	69
Female	12	31
Age (years)		
Median	51	
Range	(28;77)	
MGMT methylation ($n = 18$)		
Methylated	10	56
Unmethylated	8	44
Median time from initial diagnosis to start of BEV, days (months)	523 (17.2)	
Prior chemotherapy regimes ($n = 38$)		
Median	3.5	
Range	(1;7)	
1–3	8	21
>3	30	79

BEV, bevacizumab; MGMT, methyl-guanine methyl transferase.

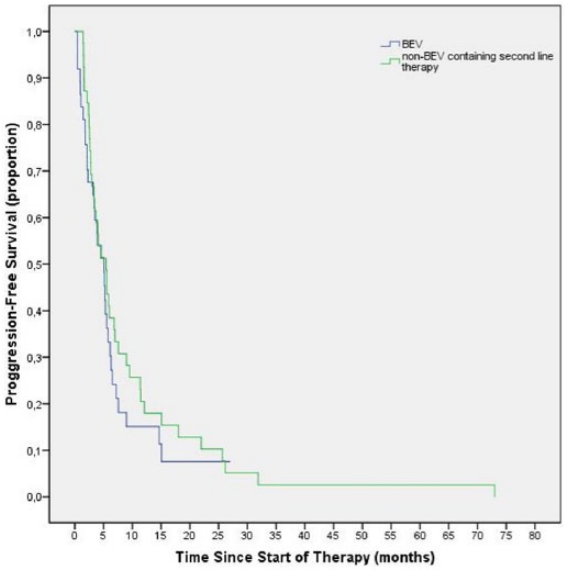

Figure 1. Paired comparison of PFS following BEV therapy versus PFS following the preceding non-BEV-containing therapy in individual patients.
BEV, bevacizumab; PFS, progression-free survival.

absence of significant methylation of the MGMT promoter is associated with a significantly shorter PFS under standard therapy for primary GB.[3] Therefore we also compared the PFS with BEV in dependence of the MGMT promotor methylation status. The median PFS in patients with a methylated MGMT promotor was 4.9 months, in patients with an unmethylated MGMT promotor 5.2 months, indicating that this high-risk group also benefits from this treatment approach, despite the fact that these patients entered BEV treatment at a significantly poorer KPS than methylated patients (60% *versus* 80%, $p = 0.046$).

In our cohort, concomitant irinotecan had no significant effect on median PFS (BEV + irinotecan 4.6 months, BEV mono 4.8 months, $p = 0.864$) or and OS (6.2 *versus* 8.4 months, $p = 0.265$) compared with BEV alone.

Aside from tumour response in form of absence of progression during BEV treatment, the KPS improved either from <60% to 60–80% or from 60–80% to 80–100% in 30.6% of patients regardless of MGMT promoter status. KPS remained stable in 56% of patients while in only 5% a KPS decline was noted. Correspondingly, steroid dose

Table 2. Bevacizumab-related adverse events.

Toxicity	Monotherapy BEV		BEV + irinotecan	
	n	%	*n*	%
Fatigue	9	31%	5	50%
Epistaxis	1	3%	0	0%
Diarrhoea	1	3%	4	40%
Hypertension	2	7%	1	10%
Headache	2	7%	0	0%
Proteinuria	0	0%	0	0%
Thromboembolism (venous)	0	0%	2	20%
Haematotoxicity				
Leukopaenia	0	0%	1	10%
Thrombopaenia	3	10%	1	10%
Neutropaenia	0	0%	2	20%

BEV, bevacizumab.

decreased in 39% of patients and did not increase in additional 51%.

In general, BEV was well tolerated. The most frequent drug-related adverse events were fatigue (36%) and diarrhoea (13%). In 10% of patients, thrombocytopenia was observed. None had intracranial haemorrhage or proteinuria (Table 2). Whereas in only 16 of 29 (55.2%) patients receiving single-agent BEV side effects were observed, all 10 patients with BEV in combination with irinotecan (100%) experienced side effects ($p = 0.016$). Diarrhoea, infections, and changes in blood count occurred significantly more often when BEV was combined with irinotecan ($p = 0.011$, $p = 0.004$ and $p = 0.032$, respectively).

Discussion and review of the literature

To date, the optimal management for patients with recurrent or progressive HGG is still ill-defined and there is no generally accepted SOC for second- or third-line therapies. However, it remains puzzling, although controlled clinical trials have not provided any evidence for an increased OS after BEV either in first-line or second-line therapy of HGG, it has maintained a role as mainstay of second- or third-line HGG therapy even in countries where there is no official approval but reimbursement of BEV therapy is possible.

Our single-centre data demonstrate that BEV as a single agent, less so in combination with irinotecan, is well tolerated and has positive effects on corticosteroid use, neurological status, and KPS. Within our patient population, only a few patients showed a decline in KPS during BEV treatment. While the median PFS of 4.8 months with a PFS6 of 31% in our study is in line with the response rates reported in other studies,[11,12,18–27] we showed that there was no significant difference in PFS following BEV therapy compared with the preceding therapy line in our paired intra-individual analysis (Figure 1). However, as BEV was given later in the course of disease, (e.g. in more heavily pretreated cases presenting with a lower KPS; a predictor for poor outcome),[4] this is possibly leading to an underestimation of the therapeutic efficacy of BEV.

In the following paragraphs, we will attempt to analyse the reasons for the broad acceptance of BEV in recurrent HGG. First of all, it is worth to remember that the initial studies that led to the accelerated approval of BEV in Switzerland and the US, were uncontrolled phase II trials that mainly reported that the PFS in response to BEV was highly favourable compared with historical controls along with good tolerability[11,12] (Table 3), corresponding to our data. However, in addition to the (at that time) valid MacDonald criteria both trials took the non-contrast-enhancing lesion for

Table 3. Synopsis of published response rates and survival in response to single-agent BEV in recurrent HGG.

Study	Type	*N*	Grade	Pretreat	Clinical status	OR (%)	PFS (months)	PFS6 (%)	OS (months)	Clinical improvement (%)
Friedman and colleagues[11]	Phase II	85	92% IV	1 (1–2)	50%: KPS 90–100	28.2[a]	4.2	42.6	9.2	n.r.
Kreisl and colleagues[12]	Phase II	38	100% IV	2 (1–7)	Median KPS 90%	35.0[a]	3.7	29.0	7.1	n.r.
Chamberlain and colleagues, 2010[23]	Retro.	50	100%IV	68% 2	n.r.	42.0	n.r.	42	8.5	n.r.
Raizer and colleagues[21]	Phase II	61	82% IV	2 (1–5)	Median KPS 80%	24.5	3.3	31	7.1	n.r.
Hofer and colleagues[18]	Retro.	225	78% IV	n.a.	40% KPS > 80%	n.r.	n.r.	n.r.	8.5	10 (ECOG >1)
Seystahl and colleagues, 2013[24]	Retro.	13	100% III	2 (2–9)	Median KPS 80%	31.0[b]	3.3	25.0	7.4	62 (KPS ⩾ 10% or steroids reduced)
Nagane and colleagues[25]	Phase II	31	93.5% IV	1–2	>60% KPS >80%	27.6[c]	3.3	33.9	10.5	
Taal and colleagues[26]	Phase II	50	100% IV	n.r.	90% ECOG 0–1	38.0b	3.0	16.0	8.0	n.r.
Hacibekiroglu and colleagues[20]	Retro.	24	92% IV	n.r.	Median KPS 70%	20.8[b]	4.1	37.5	6.4	70.8 (KPS ⩾ 10%)
Duerinck and colleagues[19]	Retro.	313	100% IV	Mostly 1	75% KPS 80–100%	35.5[b]	3.0	27.3	6.0	19 (ECOG >1)
Field and colleagues[29]	Phase II	62	84% IV	66% 1, 31% 2	80 % KPS 70–100	6.0[b]	3.5	18.0	7.5	n.r.
	Retro.	57	100% IV	1	34% ⩾ 70%	n.r.	5.0	n.r.	6.8	n.r.
Weathers and colleagues[27]	Phase II	36	100% IV	1 (1–2)	64% KPS 90–100%	19%[b]	4.1	23.6	8.3	n.r.

[a]Modified MacDonald criteria: increased T2/FLAIR regarded as progression.
[b]RANO criteria.
[c]MacDonald criteria.
PFS6, PFS at 6 months; BEV, bevacizumab; ECOG, Eastern Cooperative Oncology Group; HGG, high-grade glioma; KPS, Karnofsky performance score; n.r., not reported; OS, overall survival; PFS, progression-free survival; Retro., retrospective analysis.

assessment into account, thereby anticipating the RANO criteria of 2010.[17,28] These data were supported by additional observational studies that basically resulted in almost identical response rates and OS (Table 3).[18–21,23,25–27,29] In addition, these studies reported the rates of clinical improvement in response to BEV although the criteria for clinical improvement differed substantially. However, the two largest trials had comparable measures indicating that taken together 83 of 538 patients (15%) with recurrent HGG experienced a relevant clinical improvement [Eastern Cooperative Oncology Group (ECOG) decrease $\geqslant$1] in response to BEV.[18,19] Although, in their retrospective series of 62 patients receiving third-line BEV (37% single-agent BEV) after TMZ and CCNU (lomustine), Wenger and colleagues did not report overall response (OR) rates, PFS and OS separately for the single-agent BEV cohort, with an OR of 54.8%, a median PFS of 3.5 months and an OS of 7.5 months in the overall cohort the results matched the outcome reported by others.[30] In summary, the responses to BEV seem rather homogenous and show a good correspondence to our observations.

Several of the above mentioned trials also investigated the efficacy of BEV in combination with other systemic therapies.[11,12,18,24] Overall, the combination with irinotecan has not proven to provide any substantial anti-tumour efficacy compared with single-agent BEV in larger prospective trials.[11,12] However, the BELOB study resulted in improved 9 months OS (63%) in response to the combination of BEV and lomustine as compared with single-agent BEV (38%) or lomustine (43%) alone in patients with recurrent GB.[26] However, Wick and colleagues could not confirm a significant benefit in OS in a subsequent phase III trial, EORTC 26101, where 437 patients were randomized 2:1 for either combined treatment of BEV and lomustine or lomustine alone at first recurrence of GB,[31] despite the fact that PFS was significantly higher in the combination group (4.2 months *versus* 1.5 months). This might to some extent be explained by a crossover rate to BEV of 35.5% of the patients in the control cohort with single-agent lomustine. However, 19% of the BEV cohort received BEV beyond progression.

As the combination of BEV with irinotecan, the combination of BEV and carboplatin did not improve PFS or OS in a randomized phase II trial with 122 patients with recurrence after radiotherapy and TMZ.[29]

BEV-containing combination therapies were also tested in phase II and III trials as first-line therapy. BEV/irinotecan instead of TMZ in chemoradiotherapy and maintenance therapy in newly diagnosed GB did not show any improvement compared with the treatment according to Stupp with regard to both PFS and OS.[32] Thus, the unblinded phase II GLARIUS trial investigated the efficacy of irinotecan plus BEV compared with TMZ in addition to radiotherapy according to Stupp in newly diagnosed MGMT promoter-unmethylated GB 26976423.[32,33] Although the BEV-containing systemic anticancer therapy resulted in a superior median PFS of 9.7 months compared with 6.0 months, the OS was not different between the treatment groups, which was at least partially explained by the fact that 68.2% patients treated with BEV and irinotecan and 81.8% of the TMZ group received TMZ or BEV/irinotecan as second-line therapy, respectively. Gilbert and colleagues reported the well-powered placebo-controlled double-blinded phase III RTOG 0825 trial with 637 patients with newly diagnosed GB and ECOG 0–1. BEV (10 mg/kg bodyweight) or placebo every 14 days were administered starting in the fourth week of radiochemotherapy with TMZ according to Stupp until progression or up to 12 months.[14] TMZ was scheduled for 6 cycles or up to 12 when no or only mild adverse effect were noted. Although additional BEV treatment resulted in a significantly longer median PFS compared with placebo (10.7 *versus* 7.3 months), OS was not different (15.7 *versus* 16.1 months). Intriguingly, reportedly in only 56.1% of patients with disease progression when treated with BEV plus TMZ a salvage therapy was planned, which, although patients were unblinded upon progression, consisted of BEV in 45.4%, whereas for significantly more progressive patients treated with placebo plus TMZ (71.9%, $p < 0.001$) a salvage treatment was planned that in turn consisted of BEV in 68.0%. Taken together, while in patients that were progressive when treated with BEV plus TMZ as first-line therapy, an alternative (non-BEV) second-line therapy was planned in 31.0%; treatment with placebo plus TMZ led to planning an alternative second-line therapy, in this case BEV, in at least 48.3% of cases. Thus, different frequencies and activities of the second-line therapies administered to the two treatment groups might have influenced OS, favouring the placebo plus TMZ group. However, the AVAglio trial, a placebo-controlled double-blinded phase III trial with 921 patients with newly diagnosed GB and

ECOG 0–2, showed almost identical results although the treatment regimen was slightly different with BEV administered in parallel to radiochemotherapy with TMZ with 10 mg/kg bodyweight and then continued using the same dosing during six cycles of TMZ, followed by monotherapy with 15 mg/kg bodyweight every three weeks until progression. Again, BEV showed a significantly longer median PFS compared with placebo (10.6 months *versus* 6.2 months) but OS was not different (16.8 months *versus* 16.7 months).[15] In the BEV group, 57.4% received further anticancer therapy, 64.5% did so in the placebo group. In the BEV group, 23.4% received BEV, 35.6% TMZ, in the placebo group 48.2% BEV and 38.0% TMZ as salvage therapy. BEV as second-line therapy was administered significantly less often in the BEV plus TMZ arm (23.4%) compared with placebo plus TMZ arm (48.2%, $p < 0.0001$). Of the latter, 31.1% received BEV during the follow up. In contrast, significantly more patients within the intention-to-treat (ITT) population treated with BEV (299/465, 64.3%) completed all six cycles of TMZ, while only 165 of 446 in the placebo group did (37%, $p < 0.0001$), consistent with the shorter PFS in the placebo pus TMZ group. In contrast, Yonezawa and colleagues[34] reported a single-centre retrospective analysis of 88 cases with HGG, who over time received different primary adjuvant treatments, lomustine/procarbazine/vincristine from 2000 to 2006, TMZ from 2006 to 2013 and TMZ plus BEV from 2013 to 2016. Improvements in neurosurgical techniques were excluded as a confounder by choosing cases that received biopsies only. Although grade III tumours were more frequent in the non-BEV primary therapies, a BEV-containing first-line therapy was associated with a longer OS. A Cox proportional hazard model analysis led to BEV in addition with lower tumour grade and higher functional status as main predictor of prolonged survival.[34] In addition, a large retrospective study comprising 28.933 GB patients in the US prior TMZ approval, after TMZ approval and prior BEV approval for recurrent GB and after BEV approval showed an increasing OS over time due to administration of firstly TMZ concomitant with radiotherapy and adjuvant afterwards for newly diagnosed GB and then secondly due to the administration of BEV for recurrent GB.[35]

In summary, phase II trials and retrospective studies, like ours, support the idea of some activity of BEV in recurrent HGG. On the other hand, rigorously controlled phase III trials conducted to evaluate the activity of BEV in newly diagnosed GB did not support this view, at least with OS as most important endpoint. Although crossover effects might play some role, the lack of efficacy of BEV in combination with either TMZ or irinotecan on OS remains to be the major road block for its approval in most countries.

Of note, this lack of effect is observed in a compound that resulted in an objective response in imaging studies in more than one quarter of HGG patients and in substantial clinical improvement in 15% in further-line therapy. Overall, three reasons may account for this observation: (1) Either the proportion of patients responsive to BEV in a relevant manner is too small to lead to significant changes in median OS, (2) after initial response tumours acquire a BEV resistance that neutralizes the initial beneficial response that manifests itself as prolonged PFS[36] or (3) discontinuation of BEV upon radiological progression leads to rapidly fatal tumour growth or rapidly fatal development of blood–brain barrier dysfunction and subsequent oedema.

In our cohort, 15% received BEV more than 1 year. This corresponds to the 19% who received BEV for more than 1 year in the large 225 patient cohort reported by Hofer and colleagues, who additionally reported long-lasting BEV response of more than 2 years in 4.4%.[18] This confirms that a relevant proportion of patients show long-term response to BEV. As Wenger and colleagues, in their retrospective series of 62 patients receiving third-line BEV (37% single-agent BEV) after TMZ and CCNU, could show that OR in response to BEV translates to a significantly longer median OS of 8.6 months *versus* 6.4 months and OS rate at 12 months of 21.3% *versus* 0% in responders and nonresponders, respectively,[30] these long-term responders should also benefit from BEV with regard to survival. Similar observations were made in a post-hoc analysis of the BRAIN study published by Friedman and colleagues, again revealing a close relationship of maintained OR or PFS with OS.[37]

Several attempts have been made to identify these good responders to BEV that might also profit from BEV by means of prolonged survival. Ultra-early magnetic resonance imaging after a single dose of BEV when revealing a partial response, possibly representing the effect of BEV on the blood–brain barrier can identify patients having a

favourable response within the next 6 months.[12] A retrospective analysis of the AVAglio trial indicated that patients with the proneural GB subtype respond better to BEV as first-line therapy in combination with chemoradiotherapy than other GB subtypes.[38] High plasma levels of matrix metalloproteinase 2 might also predict a prolonged tumour control and survival in response to BEV.[39] In addition, an 8-microRNA profile generated from tumour tissue has shown to be able to identify responders to BEV.[40] However, so far no algorithm has been established that reliably identifies long-term BEV responders in clinical practice.

In summary despite the lack of improvement in OS in prospective controlled studies, prolonging PFS is a desirable and noteworthy achievement in patients with recurrent GB, as further progression leads to loss of personal and economic independency. Furthermore, the reported cases with long-term survival due to BEV after treatment failure of all established therapeutic strategies still lead physicians to decide on BEV in lack of alternative therapeutic options. As personalized medicine becomes increasingly essential in the treatment concept of cancer, predictive biomarkers for good response or resistance to BEV are needed. Understanding the mechanisms of BEV resistance might lead to rational combination therapies that boost BEV's long-term efficacy. Finally, continuation of BEV beyond progression, a concept embraced in other anticancer therapies, might preserve quality of life and lead to a prolonged survival. However, rigorously planned clinical trials that test these hypotheses still need to be done. Furthermore, there are promising ongoing studies on combining BEV with immunomodulatory agents, such as the both anti-PD-L1 antibodies pembrolizumab or durvalumab, which hopefully might provide more distinct results with respect to OS.

Implications for clinical care

BEV remains the best characterized drug that is available for third-line therapy in HGG. Although, prolonged OS has not been proven, clinical stabilization or improvement are frequently encountered upon treatment with BEV. Although, these remain short-lived in most patients also long-term responses to BEV are observed in a subgroup of patients.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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