Am J Cancer Res 2025;15(4):1874-1901
www.ajcr.us /ISSN:2156-6976/ajcr0163324

Review Article

Treatment mechanism and research progress of bevacizumab for glioblastoma

Xinliang Liu[1,2*], Zhigang Chen[3*], Pengwei Yan[2], Tao Yang[4], Dan Zong[2], Wenjie Guo[2], Xia He[2,5]

[1]Department of Radiotherapy, Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, The Third Affiliated Hospital of Nanjing Medical University, Changzhou Medical Center, Nanjing Medical University, Changzhou 213000, Jiangsu, China; [2]Department of Radiotherapy, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, and Jiangsu Institute of Cancer Research, Nanjing 210009, Jiangsu, China; [3]Department of Gastrointestinal Surgery, Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, The Third Affiliated Hospital of Nanjing Medical University, Changzhou Medical Center, Nanjing Medical University, Changzhou 213000, Jiangsu, China; [4]Department of Radiation Oncology, The Affiliated Lianyungang Hospital of Xuzhou Medical University (The First People's Hospital of Lianyungang), Lianyungang 222023, Jiangsu, China; [5]Collaborative Innovation Center for Cancer Personalized Medicine, Nanjing Medical University, Nanjing 210000, Jiangsu, China. [*]Equal contributors.

Received January 14, 2025; Accepted April 17, 2025; Epub April 25, 2025; Published April 30, 2025

Abstract: Hypervascularization is a notable pathological hallmark of glioblastoma (GBM). Bevacizumab (Bev) remains the sole antiangiogenic agent approved by the U.S. Food and Drug Administration (FDA) for GBM treatment. The approval for this indication was supported by several phase II studies demonstrating that Bev significantly improved progression-free survival and the best imaging response in patients with recurrent GBM. Three large phase III randomized controlled trials reported that Bev did not significantly extend overall survival (OS). Nevertheless, Bev has been shown to delay the deterioration of patients' quality of life by postponing tumor progression. This review synthesizes findings from recent investigations exploring Bev in combination with targeted therapies, immunotherapy, or reirradiation. Additionally, this review discusses dosing regimens, administration, treatment failure patterns, third-line therapeutic applications, and prognostic markers of Bev. By synthesizing current evidence, this review aims to inform clinical decision-making for neuro-oncology clinicians.

Keywords: Bevacizumab, glioblastoma, chemoradiotherapy, targeted therapy, immunotherapy, dosage and route of administration, patterns of treatment failure, third-line therapy, prognostic markers

Introduction

Glioblastoma (GBM) is characterized by elevated incidence and recurrence rates alongside substantial mortality. GBM accounts for 50.9% of adult malignant central nervous system tumors, exhibiting an increasing prevalence with a 6-month progression-free survival (PFS) rate of 15% and a 5-year survival rate of 6.7% [1]. Furthermore, GBM patients demonstrate severe deterioration in health-related quality of life (QoL), characterized by progressive neurocognitive decline attributed to advanced age (median age: 65), rapid disease progression, or toxicity from treatment drugs. These factors underscore critical unmet therapeutic demands for GBM.

Bevacizumab (Bev; Avastin®), a monoclonal IgG1 antibody that targets vascular endothelial growth factor (VEGF), has opened a new chapter in GBM therapeutics. Building on efficacy observed in metastatic colorectal cancer, Stark-Vance et al. pioneered the application of Bev for glioma therapy in 2005 [2, 3]. A study enrolling 21 patients with recurrent malignant glioma (10/21 with high-grade glioma) demonstrated a 42.9% objective response rate (ORR) with Bev-irinotecan (Iri) combination therapy [2]. Phase II clinical studies subsequently validated Bev's efficacy as monotherapy for recurrent GBM (rGBM), yielding ORR and 6-month progression-free survival (PFS6) rates of 28.2%-57% and 29%-46%, respectively [4-6]. This evi-

https://doi.org/10.62347/RNUE7193

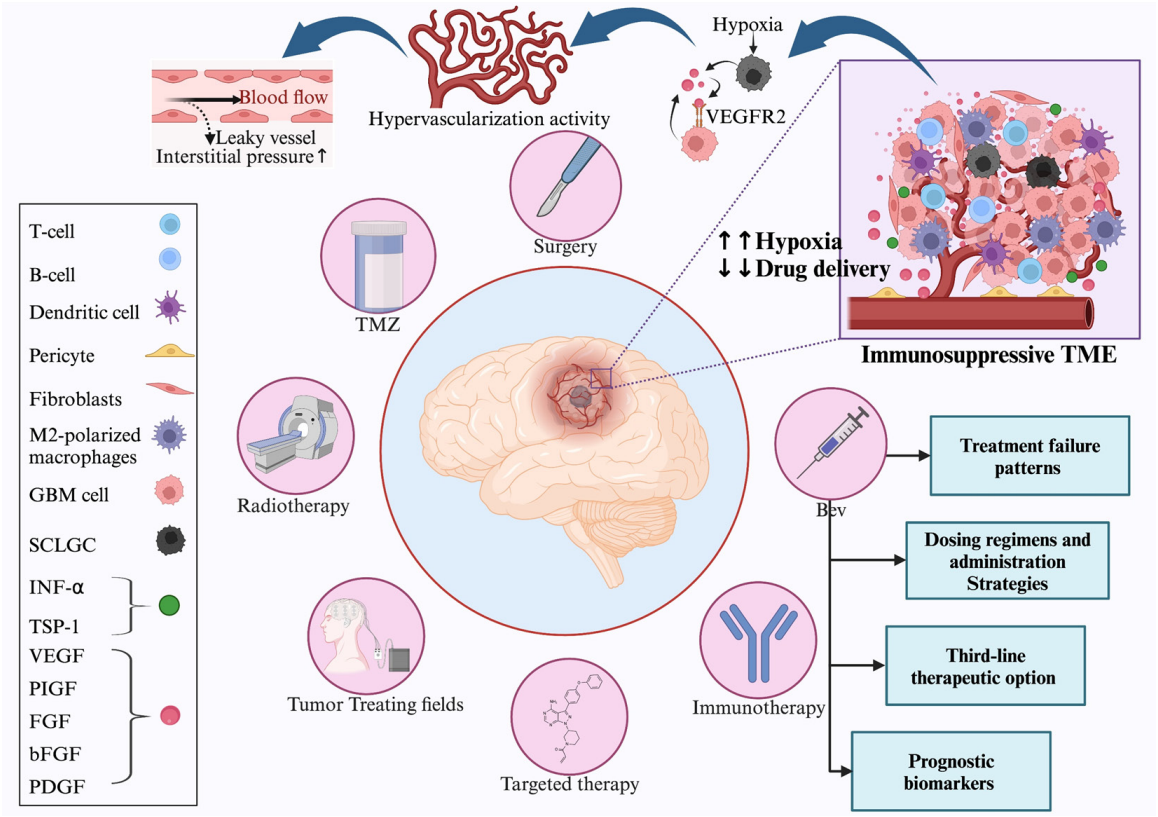

Figure 1. Graphical abstract of the review article. Hypoxia-induced dysregulation of angiogenic factors promotes pathological vascular remodeling and the formation of an immunosuppressive TME in GBM. Bev, a VEGF-A-targeting monoclonal antibody, is utilized in clinical practice as part of combination therapies to disrupt these pathways. This review further examines four critical dimensions of Bev in clinical practice. SCLGC, stem cell-like glioma cell; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TSP-1, thrombin-sensitive protein-1; INF-alpha, interferon-alpha; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; PlGF, placental growth factor; VEGFR, VEGF receptor. Created in BioRender. Yang, T. (2025) https://BioRender.com/avq3e42.

dence led to the U.S. FDA's accelerated approval of Bev for rGBM in 2009 [7].

The dual objectives of GBM therapy are survival prolongation and preservation or enhancement of QoL. GBM management has transitioned from traditional surgical resection combined with the Stupp protocol to multimodal approaches incorporating tumor-treating fields, targeted agents, and immunotherapies. Bev-based clinical strategies for rGBM initially focused on monotherapy and chemotherapeutic combinations (e.g., alkylating agents, Iri, and carboplatin), whereas recent investigations explore its integration into frontline settings, including administration during or prior to concurrent chemoradiotherapy or as a presurgical intervention. Three pivotal phase III randomized controlled trials (RCTs) failed to establish significant overall survival (OS) benefits with Bev [8-10]. However, Bev may mitigate QoL deterioration through delayed tumor progression [5, 11, 12]. This review critically evaluates emerging combinatorial strategies integrating Bev with targeted therapies, immunotherapies, or reirradiation. Furthermore, this review discusses dosing regimens, administration routes, failure patterns, third-line applications, and prognostic markers of bev, which have great value in clinical practice (**Figure 1**).

This synthesis of pivotal Bev-associated clinical trials in GBM seeks to inform evidence-based decision-making for neuro-oncology practitioners.

Mechanism

Hypervascularization activity, characterized by irregular vascular morphology, inefficient trans-

port, and pericyte deficiency, represents a critical pathological hallmark of GBM [13]. Hypoxia-induced dysregulation of angiogenesis-related factors in the tumor microenvironment (TME) manifests as upregulated pro-angiogenic factors - including vascular endothelial growth factors [VEGFs], basic fibroblast growth factors [bFGFs], and transforming growth factor-β [TGF-β]) - coupled with diminished expression of anti-angiogenic factors such as thrombin-sensitive protein-1 (TSP-1) and interferon (INF)-alpha, thereby perpetuating the activation of the tumor angiogenesis switch [14].

VEGF plays a pivotal role in both physiological and pathophysiological processes: it maintains endothelial cell survival, proliferation, and migration; promotes glioma cell growth via autocrine signaling; enhances vascular permeability, also known as vascular permeability factor; and contributes to the immunosuppressive TME [15, 16].

Bev exerts therapeutic effects by neutralizing VEGFs (primarily VEGF-A), thereby blocking its interaction with receptors (Flt-1 and KDR) and inhibiting downstream signaling [17]. Bev mainly targets genomically stable endothelial cells, indirectly suppressing tumor progression rather than directly killing tumor cells, which confers a lower propensity for drug resistance. Furthermore, Bev disrupts the proangiogenic effect of stem cell-like glioma cells (SCLGCs), inhibiting transplanted tumor growth in experimental models [18].

Both endothelial cells and glioma cells can express VEGF and its receptors. In GBM, VEGF expression is regulated by two primary pathways: hypoxia-dependent mechanisms mediated by hypoxia-inducible factor-1 (HIF-1) [19] and hypoxia-independent mechanisms involving epidermal growth factor receptor (EGFR) activation [20, 21]. SCLGCs continuously secrete substantial VEGF in vitro, amplifying the proangiogenic function of endothelial cells - a process exacerbated by hypoxia [18, 22]. Notably, VEGFR expression has been detected in GBM cells. Joensuu et al. reported that 39% of GBM patients exhibit amplification of VEGFR2 [23]. Quantitative analyses across 12 brain tumor types revealed significantly elevated VEGFR levels in GBM [24]. Preclinical studies confirm that VEGF-VEGFR pathway blockade suppresses glioma cell growth in immunodeficient rat models [25].

Progressive and recurrent glioblastoma (rGBM)

Bev monotherapy

Bev has been recommended as the preferred treatment for rGBM by the National Comprehensive Cancer Network (NCCN) guidelines in the U.S. [26]. **Table 1** summarizes key clinical trial outcomes. The noncomparative phase II AVAREG trial evaluated Bev against fotemustine (FTM) in rGBM patients, randomizing participants at a 2:1 ratio (Bev *vs*. FTM), with the primary endpoint being the 6-month OS rate [12]. No significant differences were observed in the 6-month OS rate or median OS (mOS) between the two groups [12]. A similar conclusion was reached in the Japanese JO22506 study [27].

However, the use of Bev in rGBM remains contentious. Unlike the FDA, the European Medicines Agency has not approved Bev for rGBM treatment [28].

First, although Bev improves the ORR and median PFS (mPFS) in rGBM patients, it fails to extend OS [4-6]. This discrepancy suggests that surrogate endpoint improvements do not translate into an OS benefit. Ballman et al. reported a 90% concordance between PFS6 and 12-month OS in their analysis of phase II trials [29]. However, their analysis did not include clinical trials related to Bev, leaving its generalizability to Bev-treated cohorts uncertain.

Second, Bev complicates neuro-oncological response assessment. Traditional imaging assessments rely mainly on contrast-enhanced MRI based on the MacDonald criteria, but these can be influenced by various factors, such as radiation damage, MRI equipment parameters, and steroid use [30]. Bev's ability to stabilize the blood-brain barrier (BBB) and reduce contrast leakage may interfere with comparisons of pre- and posttreatment enhanced MR images. As a result, a reduction in contrast enhancement may mask an actual increase in tumor burden, inducing "pseudoresponse". To address this issue, the Response Assessment in Neuro-Oncology (RANO) criteria

Table 1. Bev alone or in combination with cytotoxic chemotherapy for the treatment of rGBM

Ref.	Study Design	No. of patients	Study arms	Bev Dose (mg/kg)	ORR (%)	mOS (months)	mPFS (months)	PFS6 (%)
Stark-Vance 2005 [2]	NA	GBM: 11 Other: 10	Bev + Iri	5	43	NA	NA	NA
Vredenburgh 2007 [6]	II	35	Bev + Iri Bev + Iri	10 15	57	9.2	4.2	46
Bokstein 2008 [97]	NA 2005-2007	GBM: 17 AO: 2 AOA: 1	Bev + Iri	5	47.3	7	4.2	25
Kreisl 2009 NCI 06-C-0064E [5]	II, comparative 2006-2007	48	Bev→Bev + Iri	10	Levin: 71 Macdonald: 35	7.75	4	29
Friedman 2009 BRAIN [4]	II, multicenter, open-label, randomized, noncomparative 2006-2007	167	Bev + Iri Bev	10	28.2	8.7 9.2	5.6 4.2	NA
Nghiemphu 2009 [11]	Retrospective 2005-2006	44 79	Bev Other	5	NA	9.01* 6.11	4.25* 1.82	41 18
Raizer 2010 [96]	II	GBM: 50	Bev	15	24.5	6.5	NA	25
Taal 2014 BELOB [36]	II, multicenter, randomized 2009-2011	47 51 47	LOM LOM90 + Bev Bev	10	5 34 38	8.0 12.0 8.0	1.0 4.0 3.0	13 41 16
Field 2015 CABARET [38]	II, multicenter, randomized, open-label 2010-2012	60 62	Bev + Carboplatin Bev	10	14 6	6.9 7.5	3.5 3.5	15 18
Brandes 2016 AVAREG [12]	II, Noncomparative, multicenter, randomized 2011-2012	91	Bev FTM	10	29 9	7.3 8.7	3.38 3.45	19.6 10.7
Wick 2017 EORTC 26101 [10]	III 2011-2014	288 149	LOM + Bev LOM	10	13.9 41.5	9.1 8.6	4.2 1.5	28.4 16.8
Gilbert 2017 RTOG 0625 [146]	II, randomized 2007	60 57	Bev + dose-dense TMZ Bev + Iri	10	19 28	9.4 7.7	4.7 4.1	39 38.6
Desjardins 2019 [147]	Retrospective, single-institution, real-world study 2009-2012	74	Bev	10	NA	11.1	6.4	24.3▼
Cloughesy 2020 TOCA 5 [148]	II/III, open-label, multicenter, randomized rHGG 2015-2018	201 202	Toca 511 + Toca FC SOC (Bev/TMZ/LOM)	10	NA	11.10 12.22	NA	NA
Detti 2021 [149]	Retrospective, rHGG 2009-2019	92 (GBM: 71)	Bev	10/15	36.1	9	6.9	58
Friedman 2023 [33]	II, multicenter, open-label, Noncomparative		Bev Bev + Iri	10	28.2 37.8	9.2 8.7	4.2 5.6	42.6 50.3
Smolenschi 2023 [150]	Retrospective, real-world study, single-institution rGBM 2006-2016	202	Bev	10/15	42	23.7	6.8	NA
Witte 2024 [151]	Retrospective, rGBM 2006-2016	134	HCQ + BEV + aRCT BEV + aRCT	NA	NA	23.92 9.63*	NA	NA
Lee 2024 [152]	Nationwide population-based study rGBM 2008-2021	450 396	Bev Bev + Iri	NA	NA	22.60 20.44	NA	NA

Note: ▼, PFS12; AOA, Anaplastic oligoastrocytoma; AO, Anaplastic oligodendroglioma; PFS6, 6-month progression-free survival; PFS, progression-free survival; OS, overall survival; GBM, glioblastoma multiforme; q, every; TMZ, temozolomide; Carbo, carboplatin; LOM/CNNU, carmustine; FTM, fotemustine; NA, not available; SOC, standard of care; Toca 511, vocimagene amiretrorepvec; Toca FC, flucytosine; HCQ, chloroquine; aRCT, adjuvant-radiochemotherapy; *, $P < 0.05$.

were developed, which incorporate T2-weighted imaging/fluid-attenuated inversion recovery (T2/FLAIR) to evaluate nonenhancing lesions for a more accurate and comprehensive evaluation of patient efficacy [31]. Additionally, the timing of assessments is crucial. Early MRI scans post-Bev initiation (e.g., within 24 hours) often show reduced enhancement unrelated to antitumor efficacy [5]. Interestingly, patients with "partial response" on day 4 or 28 scans exhibit prolonged PFS [5]. These patients may have greater sensitivity to Bev treatment.

Finally, several clinical trials have design flaws. The NCI 06-C-0064E study relied on historical controls for their interpretation [5], while the AVF3708g study employed a noncomparative design despite randomization [4].

In conclusion, despite the aforementioned controversies, two points are clear: First, owing to differing mechanisms of action, the two drugs exhibit different toxicity profiles, with Bev primarily causing adverse events such as bleeding, thrombosis, hypertension, and proteinuria, whereas alkylating agents (such as FTM, lomustine [LOM], and TMZ) mainly lead to hematological toxicity, such as thrombocytopenia and neutropenia [12, 32]. A recent study showed that thrombocytopenia can lead to dose adjustments or discontinuation of CCNU, thereby decreasing survival in rGBM patients [32]. Second, Bev can significantly improve QoL and effectively decrease the use of corticosteroids by reducing BBB permeability and alleviating cerebral edema [5, 11, 12, 33]. Therefore, in a context where treatment options are limited, Bev may provide an alternative treatment option for rGBM patients.

With chemotherapy (CT)

Theoretically, Bev combined with CT may exhibit a synergistic effect [34]. Bev induces vascular normalization, which enhances drug distribution uniformity and increases intratumoral drug perfusion. Furthermore, unlike TMZ, the first-line CT agent for GBM, CT agents such as Iri and carboplatin, do not have cross-resistance and demonstrate proven antitumor efficacy in other malignancies [35].

Main clinical trial outcomes are summarized in **Table 1**. In 2014, the first randomized controlled trial of Bev for rGBM - the phase II BELOB study - was conducted by Taal et al., in which 145 rGBM patients were randomized to three arms: CCNU monotherapy, Bev monotherapy, or CCNU+Bev combination therapy [36]. The 9-month OS rates were reported as 43%, 38%, and 59%, respectively, with the combination group showing superior survival compared to the Bev alone group [36]. However, Bev monotherapy achieved a higher ORR (38% *vs*. 5%) and longer mPFS (3 *vs*. 1 month) than CCNU monotherapy. No crossover Bev administration occurred among the 3 groups [36].

To validate the BELOB findings, the phase III EORTC 26101 trial, led by Wick et al., enrolled 437 rGBM patients randomized 2:1 to receive Bev+CCNU or CCNU alone [10]. Although combination therapy significantly prolonged PFS (4.2 *vs*. 1.5 months), no mOS benefit was observed. The addition of Bev exhibited higher rates of grade 3-5 adverse events (AEs) (63.6% *vs*. 38.1%), and it did not improve patients' neurocognitive function; in fact, their overall health status scores were worse [10]. Consequently, the BELOB results were not replicated in this larger trial. Furthermore, a cost-utility analysis by Chen et al. further concluded that the Bev+CCNU combination regimen lacked cost effectiveness in the EORTC 26101 study [37].

The randomized phase II CABARET study compared Bev+carboplatin to Bev monotherapy in rGBM, revealing no significant differences in mPFS, mOS, or ORR [38]. Notably, the ORR (6%-14%) was markedly lower than historical controls, potentially attributable to the mRANO criteria (incorporating T2/FLAIR assessments) and approximately one-third of the enrolled patients with ≥2 prior recurrences [38].

In summary, while Bev+CT combinations prolong PFS, they concurrently increase toxicity without conferring OS benefits. Large phase III trials remain scarce due to the low incidence of GBM. Additionally, heterogeneity in trial design, eligibility criteria, prior therapies, and response assessment protocols limits cross-trial comparability.

With targeted therapy

The limited efficacy of Bev monotherapy in rGBM may be attributed to redundant angiogenesis signaling pathways or compensatory dysregulation of downstream signaling mole-

cules of VEGF/VEGFR signaling molecules, such as epidermal growth factor receptor (EGFR) overexpression or gene amplification (observed in ~50% of cases), platelet-derived growth factor receptor (PDGFR) overexpression (75%), and aberrant mesenchymal-epithelial transition factor pathways activity [39, 40]. Consequently, recent therapeutic strategies have focused on combining Bev with multiple targeted agents to overcome resistance.

Several phase I/II trials have explored the effects of Bev combined with targeted therapies for rGBM, including three randomized controlled phase II studies (see **Table 2**). Among these studies, only one study demonstrated a survival benefit [41]. This single-arm phase II study reported that TVB-2640 (a fatty acid synthase inhibitor) combined with Bev significantly improved mPFS (4.6 *vs*. 3 months) and PFS6 (31.4% *vs*. 16%) compared to Bev monotherapy in the historical BELOB cohort [41]. However, no significant OS advantage was observed.

Additionally, a phase II trial involving 25 recurrent high-grade glioma (rHGG) patients evaluated anlotinib (a multitarget tyrosine kinase inhibitor targeting VEGFR and PDGFR, etc.) alone or combined with Bev (initiated upon peritumoral edema occurred) [42]. The combination failed to enhance efficacy but significantly increased treatment-related adverse events (TRAEs) [42].

In summary, as molecular profiling of GBM advances, targeted therapy has emerged as a hot topic of intensive research. While double-blind phase II RCTs provide level II evidence [43], no published phase III studies have yet validated the effectiveness of Bev-targeted therapy combinations. Thus, the use of Bev combined with targeted agents for rGBM remains investigational and is not recommended outside clinical trials.

With immunotherapy (IT)

Patients with rGBM often derive limited benefit from IT alone, partially due in part to the VEGF-driven immunosuppressive TME [44]. Bev can reduce the use of corticosteroids, which decrease effector immune cell levels [45]. In addition, Bev synergistically enhances the antitumor activity of IT, as evidenced by preclinical and clinical data from other cancer types [46].

Currently, the application of Bev-IT combinations in rGBM remains exploratory. The findings from the main studies are compiled in **Table 3**. The phase III CheckMate 143 study compared nivolumab (Nivo, a PD-1 monoclonal antibody) monotherapy to Bev monotherapy in rGBM, revealing superior PFS and ORR for Bev, though OS and serious adverse events rates did not differ significantly [47]. In a phase II study Nayak et al., 80 rGBM patients randomized to pembrolizumab (Pemb, a PD-1 monoclonal antibody) ± Bev demonstrated improved mPFS (4.1 *vs*. 1.4 months) and ORR (20% *vs*. 0%) with combination therapy, yet no OS advantage (8.8 *vs*. 10.3 months) [48]. Similarly, durvalumab (anti-PD-L1) ± Bev failed to meet efficacy expectations in another phase II trial (mOS: 6.7-9.3 months) [45].

Contrastingly, recent phase I/II studies have indicated that Bev combined with avelumab (a PD-L1 monoclonal antibody) or toripalimab (a PD-1 monoclonal antibody) can improve survival, with a median OS of 13-22.3 months [49-51]. Meanwhile, Yang et al. reported a case of rGBM with lung metastasis achieving 11-month PFS and 27-month OS. This patient received Bev combined with Pemb due to PD-L1 overexpression [52]. In addition to the limited number of case reports and differences in local drug penetration concentrations, further research is warranted to investigate whether extracranial metastatic sites and intracranial recurrence sites exhibit distinct TMEs and tumor cell biological characteristics [52].

Novel approaches, such as viruses or vaccines, have also been explored. The phase III GLOBE trial evaluated VB-111 (an anticancer viral therapy that induces endothelial cell apoptosis and activates antitumor immunity) ± Bev, showing no mOS improvement but increased grade 3-5 adverse events with combination therapy (67% *vs*. 40%) [53]. A study by Brenner et al. yielded similar results in the same year [54]. Additionally, Brenner et al. found a significant prolongation of survival in the subgroup of VB-111 monotherapy upon continued in combination with Bev after recurrence [54], suggesting timing-dependent immune activation. Similarly, neoadjuvant/adjuvant Pemb improves survival versus adjuvant-only regimens, potentially via enhanced tumor-specific T cell priming [55]. Reardon et al.'s phase II trial of rindopepimut (a vaccine targeting *EGFRvIII*) ± Bev reported

Table 2. Bev in combination with targeted therapy for the treatment of rGBM

Ref.	Study Design	NO. patients	Study arms	ORR (%)	mOS (months)	mPFS (months)	PFS6 (%)
Puduvalli 2020 [153]	II, multicenter, randomized, bayesian adaptiv	49	Vorinostat + Bev	NA	7.8	3.7	25
		41	Bev		9.3	3.9	28
Lee 2020 NRG/RTOG 1122 [154]	II, randomized, double-blinded, placebo-controlled study	57	Trebananib + Bev	4.2	7.5	4.8	22.6
		58	Trebananib + Pla	5.9	11.5	4.2*	41.4
Kelly 2023 [41]	II, single-institution, open-label	25	TVB-2640 + Bev	56	8.9	4.6	31.4►►,*
McCrea 2021 [155]	I 2013-2018	13	Cetuximab + Bev	30	7.2	NA	NA
Brenner 2021 [136]	II, open-label, Single group 2015-2017	33	Evofosfamide + Bev	9	4.6	53 days	31‡
Galanis 2022 N1174 [156]	I/II	52	TRC105 + Bev	13	9.7	2.9	25
		49	Bev	16	7.4	3.2	30
Zhao 2024 [42]	II, Single group, rHGG 2020-2022	18	Anlotinib	28	15	4.2	NA
		7	Anlotinib + Bev†	43	9.8	8	
Cloughesy 2017 GO27819 [39]	II, double-blinded, randomized controlled, multicenter	64	Onartuzumab + Bev	22.2	8.8	3.9	29.7
		65	Pla + Bev	23.7	12.6	2.9	26.2
Cardona 2021 [157]	Retrospective, *EGFR amplification and EGFRvIII mutation* rGBM	15	osimertinib + Bev	13.3	9.0	5.1	46.7

Note: Pla, placebo; ‡, 4-month PFS rate; ►►, control from the Bev monotherapy group in the BELOB study; †, When peritumoral edema develops, patients will receive interim treatment with Bev; TRC105, anti-CD105 antibody; *, $P < 0.05$.

Table 3. Summary of published clinical studies of Bev in combination with immunotherapy for the treatment of rGBM

Ref.	Study Design	NO. patients	Study arms	ORR (%)	mOS (mos)	mPFS (mos)	PFS6 (%)
Wang 2024 [51]	IIa, single center, single-arm, open-label 2021-2023	32	Tislelizumab + low-dose Bev	25	22.3	4.0	NA
Guo 2024 [50]	II, single center, open-label 2022-2023	32	Tislelizumab + low-dose Bev	56.3	14.3	8.2	NA
Chiu 2023 [49]	I, open-label, nonrandomized 2018-2019	5 7	Avelumab + Bev LITT + avelumab + Bev	NA	13 13.5	3 2.5	16.5
Bota 2022 [158]	Prospective 2018-2021	21	SITOIGANAP + GM-CSF + cyclophosphamide + Bev + Nivo or Pemb	NA	19.63	9.14	76.19
Sahebjam 2021 [72]	I, single-arm, open-label 2015-2019	24 (Bev-naïve cohort) 8 (Bev-resistant cohort)	HFSRT + Pemb + Bev	83 62	13.4 9.3	7.92 6.54	66.67
Nayak 2021 [48]	II, randomized, multicenter, open-label, Bev-naïve 2015-2016	50 30	Pemb + Bev Pemb	20 0	8.8 10.3	4.1 1.43	26.0 6.7
Ahluwalia 2021 [159]	II, randomized 2018-2020	90	Nivo + standard-dose Bev (10 mg/kg) Nivo + low-dose Bev (3 mg/kg)	NA	41.1 37.7▼	NA	NA
Brenner 2020 [54]	I/II, rGBM 2011-2015	72 (all)	VB-111 dose escalation VB-111 monotherapy VB-111→(VB-111 + Bev) VB-111 + Bev	63 53 21 20	315 days 223 days* 414 days 141.5 days**	55 60* 90 63	NA
Cloughesy 2020 (GLOBE) [53]	III, randomized 1:1 2015-2017	128 128	VB-111 + Bev Bev	27.3 21.9	6.8 7.9	3.4 3.7	22.7 28.9
Reardon 2020 (CheckMate 143) [47]	III, randomized 1:1 2014-2015	184 185	Nivo *vs.* Bev	7.8 23.1	9.8 10.0	1.5 3.5**	15.7 29.6
Nayak 2022 [45]	II, multicenter, nonrandomized 2015-2017	A: 40 (unmethylated *MGMT* promotor) B: 31 (bevacizumab naïve) B2: 33 (bevacizumab naïve) B3: 33 (bevacizumab naïve) C: 22 (bevacizumab refractory)	Durvalumab + standard RT Durvalumab Durvalumab + t standard-dose Bev Durvalumab + low-dose Bev Durvalumab + t standard-dose Bev	10.3 12.9 9.1 9.1 0	15.1 6.7 8.7 9.3 4.5	4.6 3.0 3.7 3.7 1.9	41.1 19.4 15.2 17.2 0
Wang 2024 [51]	IIa, single center rGBM 2021-2023	32	Tislelizumab + Bev	25	22.3	4	NA

Note: LITT, laser interstitial thermal therapy; Nivo, nivolumab; Pemb, pembrolizumab; SITOIGANAP, tumor cells and lysates; RT, radiation therapy; ▼, 1-year OS rate; *, $P < 0.05$, **, $P < 0.001$; Tislelizumab, an anti-PD-1 antibody.

comparable PFS6 but a higher 24-month OS rate than the control group did (20% *vs*. 3%) and corticosteroids discontinued rates (33% *vs*. 0%) in the combination arm [56].

In summary, the conclusions drawn from various studies differ, which may be related to the characteristics of the drugs studied, the baseline characteristics of the enrolled patients, and so on. Currently, there is no conclusive high-level evidence supporting the use of Bev combined with IT drugs in the treatment of rGBM patients. However, this combination therapy shows great promise and has become a hot area of current research (see **Table 4**).

With reirradiation

Reirradiation (re-RT) is an important therapeutic modality for rGBM. The mechanisms underlying the combination of Bev with re-RT are multifactorial. Preclinical studies have demonstrated that ionizing radiation markedly elevates VEGF levels in tumors, while Bev enhances intratumoral oxygenation and disrupts the vascular niche harboring cancer stem cells (CSCs) [57]. Clinical evidence further indicates that Bev mitigates the risk of radiation necrosis (RN) and cerebral edema [58].

When Bev is combined with re-RT techniques - including HSRT, SRS, and GK - mOS ranges from 10.1 to 13.9 months, and mPFS spans 5-11 months (**Table 5**). The NRG Oncology/RTOG1205 trial, the first multicenter phase II study to utilize modern RT techniques in rGBM, evaluated the efficacy of integrating re-RT with Bev [59]. Between 2012 and 2016, 170 patients were randomized 1:1 to Bev+re-RT or Bev monotherapy. No significant difference in mOS was observed (10.1 *vs*. 9.7 months); however, the combination group exhibited superior mPFS (7.1 *vs*. 3.8 months) and PFS6 rates (54.3% *vs*. 29.1%) [59]. Acute grade 3+ TRAEs occurred in only 4.8% of the combination group [59]. Notably, baseline imbalances were observed: the combination group included more patients with ≥2 more recurrences (25.6% *vs*. 13.1%), a poor prognostic factor, but also a higher proportion with O6-methylguanine DNA methyltransferase (MGMT) promoter methylation (20.9% *vs*. 14.3%), a favorable prognostic factor [59]. Prolonged PFS may delay declines in QoL and neurocognitive function [59]. Multivariate analysis identified Karnofsky performance status (KPS) - not age - as a significant OS prognosticator, supporting this regimen's applicability to elderly patients with KPS scores ≥ 70%. A retrospective study also reported that SRS+Bev is a positive prognostic marker for HGG [60]. The ongoing phase II HSCK-005 trial (NCT05611645) is investigating whether HFSRT combined with Bev enhances PFS6 in rGBM.

Bev administration timing relative to re-RT - neoadjuvant (neoBev), concurrent (concBev), or adjuvant (adjBev) - has been explored. A large retrospective study by Palmer et al. found no survival difference in rHGG patients receiving Bev before or after re-RT [61]. Conversely, Cuneo et al. reported that adjBev post-SRS significantly improved mOS (5.2 *vs*. 2.1 months) and 1-year OS compared to no Bev [62]. A retrospective multicenter study of 482 rHGG patients (1997-2023), presented at the 2024 American Society of Clinical Oncology annual meeting, found adjBev unrelated to survival outcomes, whereas concBev correlated with poorer OS but lower neurotoxicity [63]. Thus, optimal Bev-re-RT sequencing remains undefined.

Consensus is similarly lacking on optimal re-RT target volume and dosing with Bev. In re-RT monotherapy, comparable survival was observed with 25 Gy/5 f and 35 Gy/5 f [64]. There was no difference in OS or PFS when comparing local re-RT to systemic treatment with Bev [65]. However, Kulinich et al. identified Bev as a survival enhancer in HFSRT-treated patients [66]. Recently, the GLIAA study prospectively compared 18F-fluoroethyltyrosine (FET) positron emission tomography (PET) and T1Gd MRI-guided re-RT in rGBM, revealing no differences in survival, local control rates, or RN rates [67]. Additionally, a large-scale retrospective study reported that large-volume re-RT (median PTV: 135 cm^3) has been deemed feasible for refractory rGBM [68].

Radiation-related toxicity remains a key concern. As GBM typically recurs near surgical margins, re-RT target often overlap initial RT fields. RN - the most severe late radiation complication - is pathologically characterized by brain tissue necrosis. The exact mechanisms underlying RN are still unclear, but they may be related to the loss of pericytes and vascular smooth muscle cells [69]. Clinically, RN usually

Table 4. Summary of ongoing clinical studies of Bev in combination with immunotherapy for the treatment of rGBM (data from https://clinicaltrials.gov)

NCT	Study Start	Enrollment	Immunological drug	Phase	Interventions	Primary endpoint
NCT04116658	2020-07-13	100	EO2401, Nivo	I/II	EO240 EO2401 + Nivo EO2401 + Nivo + Bev	OS
NCT06061809	2024-08-07	20	N-803, PD-L1 t-haNK	II	N-803 + PD-L1 t-haNK + Bev	TEAEs, SAEs
NCT04277221	2019-09-19	118	ADCTA	III	ADCTA *vs*. Bev	OS
NCT06047379	2023-11-01	134	Ipi, Pemb and Nivo	I/II	NEO212 + Ipi NEO212 + Pemb NEO212 + Nivo NEO212 + regorafenib NEO212 + carboplatin + paclitaxel NEO212+ FOLFIRI + Bev NEO212	MTD, PFS6
NCT05502991	2022-12-11	60	Sintilimab	II	Sintilimab + Bev	12/18-month OS rate

Note: TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; ADCTA, autologous dendritic cell/tumor antigen; NEO212, TMZ + perillyl alcohol; Ipi, ipilimumab; FOLFIRI, 5-fluorouracil + leucovorin + Iri.

Table 5. Bev in combination with re-RT for the treatment of rGBM

Ref.	Study design	No. patients	Treatment	mOS (months)	mPFS (months)	PFS6 (%)	Median GTV (cc) (Range)	RT dose (Gy/Fractions)
Tsien 2023 [59]	II, andomized 2012-2016	170	BEV + re-RT BEV	10.1 9.7	7.1 3.8*	54.3 29.1*	18 (0.5-208)	35 Gy/10 f
She 2022 [160]	Retrospective 2019-2021	26	Bev + re-RT	13.6	8.0	65.4	Median PTV size (ml) (range): 114.8 (11.9-360.1)	30-35 Gy/10 f (for the small GTV) 40-45 Gy/20-27 f (for the large GTV)
Arvold 2017 [65]	Retrospective 2010-2014	67 117	re-RT Bev	10.7 NA	4.8 NA	NA	NA	30 Gy/5 f (36%), 35 Gy/10 f (21%), 40 Gy/15 f (15%), 18-20 Gy/1 f (15%)
Palmer 2018 [61]	Retrospective 2006-2013	118 (GBM: 87; AA: 31): 50 68	Bev → HFSRT FSRT → Bev	13.3 13.9	NA	NA	44.8 cm^3 17.04 cm^3	35 Gy/10 f
Zhang 2024 [161]	Retrospective 2012-2022	19 57 19	Bev Bev + GK GK	6.5 11.5 7.9*	5.0 7.7 4.9*	NA	15.9 ± 11.5 7.6 ± 11.6 13.2 ± 16.1	NA
Mantica 2023 [162]	II 2015-2017	16	Bev + SRS SRS	11.73 8.74*	NA	65.2 33.2*	NA	NA
Morris 2019 [163]	Retrospective 2009-2015	45	Bev + GK	13.3	5.2	NA	2.2 cm^3 (0.1-25.2 cm^3)	17.0 Gy
Abbassy 2018 [164]	I	9	Bev + SRS	13	7.5	NA	4.4 cm^3 (2.1-8.8) 5.13 cm^3 (4.38-6.47) 4.64 cm^3 (2.54-6.62)	18 Gy 20 Gy 22 Gy

Note: HFSRT, hypofractionated stereotactic radiotherapy; SRS, stereotactic radiosurgery; GK, Gamma Knife; *, $P < 0.05$.

presents with the re-emergence of symptoms and a decline in neurological function, while imaging reveals enhancing lesions indistinguishable from tumor progression. A recent retrospective analysis revealed that apparent diffusion coefficient values exhibit significant discriminative capability [70]. Additionally, most clinical studies do not report the incidence of RN. The phase II CHROME trial protocol recently proposed chlorophyllin for RN management in diffuse gliomas [71], though its efficacy versus corticosteroids, Bev, or surgery warrants validation.

In summary, the ideal Bev-re-RT regimen remains uncertain, with most evidence derived from retrospective studies prone to selection bias. Incorporating IT into the Bev-re-RT strategies represents a promising frontier. A phase I trial of HFSRT combined with pembrolizumab (Pemb) and Bev in 32 rHGG patients demonstrated safety profile but no survival benefits [72]. Ongoing trials (e.g., NCT03743662, NCT06160206) aim to address these gaps.

Newly diagnosed glioblastoma (nGBM)

In rGBM, Bev demonstrates potent tumor-shrinking activity and significantly prolongs PFS, while its combination with RT or TMZ has been demonstrated to be safe. However, the inclusion of Bev in standard first-line therapy for nGBM remains controversial.

With the Stupp regimen

Several phase II studies have reported that the mOS for standard therapy combined with Bev is approximately 19.6-23 months, with a mPFS of approximately 13-14.2 months (**Table 6**). While PFS was significantly prolonged compared to historical or contemporary controls, OS improvements were observed only relative to historical controls [73]. These findings suggest the survival status of nGBM patients treated with the same first-line regimen has improved compared with that in the EORTC-NCIC era, potentially attributable to advancements in patient management [9, 74]. However, cross-trial comparisons are confounded by variability in OS definitions - for instance, Vredenburgh et al. calculated OS from enrollment [73], whereas Lai et al. used the date of diagnosis as the starting point [74].

Two phase III studies (AVAglio [8], RTOG 0825 [9]) subsequently evaluated Bev's addition to first-line standard therapy, yielding divergent outcomes. Although both studies failed to demonstrate OS benefits, AVAglio reported prolonged PFS (3-4 months) and delayed deterioration in health-related QoL, neurocognitive function, and corticosteroid dependence [8, 9]. Conversely, the RTOG 0825 study found accelerated QoL and neurocognitive decline in the Bev arm [75], a trend echoed in the ARTE trial [76]. These discrepancies may reflect differences in response criteria (e.g., the AVAglio study's modified MacDonald criteria [8]), crossover effects (48% of control-group patients received post-progression Bev), or imbalances in treatment cycles (17-27% higher 6-cycles TMZ completion rates in Bev arms) [8, 9]. The incidence of adverse events was similar in both studies, but the percentage of patients who discontinued treatment due to toxicity or complications was approximately 15% greater in the experimental group than in the control group [8, 9]. Notably, subgroup analysis from the AVAglio study hinted at OS/PFS benefits in patients not receiving post-progression therapy [77], though clinical implementation remains impractical due to challenges in pretreatment identification.

On the basis of the results of the AVAglio study, Japan approved the use of Bev for treating nGBM in 2013 [78]. Motoo et al. subsequently conducted postmarketing surveillance of Bev in the Japanese GBM population [8, 78]. The analysis replicated the AVAglio trial's safety profile (≥ grade 3 AE rates: 15.1%) and reported a 1-year OS rate of 78% at 18-month follow-up, while the mOS had not yet been reached [78]. However, can the reported survival improvement be entirely attributed to Bev? Can the results from this population be effectively extrapolated to other ethnicities?

Recently, some researchers have suggested the use of Bev before chemoradiotherapy or even before surgery (**Table 7**). The theoretical basis is that Bev can shrink tumors and prune blood vessels, thereby reducing surgical difficulty and improving the R0 resection rate; Bev can alleviate patients' brain edema, improve their physical condition, and enhance surgical tolerance [79]. Several small-sample phase II studies have shown that this approach has no

Table 6. Bev in combination with chemoradiotherapy for the treatment of nGBM

Ref.	Study design	No. of patients	Study arms	mOS (months)	mPFS (months)
Vredenburgh 2011 [73]	II, single group 2006-2008	75	BEV + RT + TMZ→TMZ + Bev + Iri	21.2	14.2
Lai 2011 [74]	II, single group 2006-2008	70	I: BEV + RT + TMZ→TMZ + Bev C1 (UCLA): RT + TMZ→TMZ C2 (EORTC-NCIC): RT + TMZ→TMZ	19.6 21.1 14.6	13.6 7.6 6.9
Chinot 2014 AVAglio [8]	III, randomized 2009-2011	921	I: Bev + RT + TMZ→TMZ + Bev C: RT + TMZ→TMZ	16.8 16.7	10.6 6.2*
Gilbert 2014 RTOG 0825 [9]	III, randomized 2009-2011	637	I: BEV + RT + TMZ→TMZ + Bev C: RT + TMZ + placebo→TMZ	15.7 16.1	10.7 7.3
Herrlinger 2016 GLARIUS [165]	II, open-label, randomized, *MGMT*met	122 60	I: BEV + RT→Bev + Iri C: RT + TMZ→TMZ	16.6 17.5	5.99 9.7*
Reyes-Botero 2018 ATAG [85]	II, single group, older than 70 years, KPS < 70%	66	BEV + TMZ	5.98	3.83
Nagane 2022 [166]	II, multicenter	90	BEV + RT + TMZ→TMZ + Bev→Bev	25	14.9
Omuro 2014 MSKCC 08-126 [90]	II,	40	HFSRT (36 Gy/6 f) + TMZ + Bev→TMZ + Bev	19	10
Ney 2015 [89]	II, 2010-2013	30	Hypo-IMRT (60 Gy/10 f) + Bev + TMZ	16.3	14.3
Carlson 2015 [93]	II, comparative	26 30	Hypo-IMRT (60 Gy/10 f) + TMZ Hypo-IMRT (60 Gy/10 f) + TMZ + Bev	16.3 16.3	9.4 12.8
Wirsching 2018 ARTE [76]	II, noncomparative, multicenter, older than 65 years 2013-2015	50 25	Arm A: Hypo-IMRT (40 Gy/15 f) + Bev Arm B: Hypo-IMRT (40 Gy/15)	12.1 12.2	7.4 4.8*
Matsuda 2018 [167]	Retrospective, older than 75 years 2014-2017	18	HFRT (45 Gy/15 f) + TMZ/Bev	20	2.5
Ohno 2019 [88]	Retrospective, older than 75 years 2007-2018	20 10	HFRT (45 Gy/15 f) + TMZ HFRT (45 Gy/15 f) + TMZ/Bev	12.9 14.6	8.5 10.4
Kanamori 2025 [168]	II, 2015-2018	49	CNNU + RT + TMZ + Bec	24.8	11.8

Note: UCLA, University of California, Los Angeles; HFSRT, hypofractionated stereotactic radiotherapy; hypo-IMRT, hypofractionated-intensity modulated radiotherapy; HFRT, hypofractionated radiotherapy; *, $P < 0.05$.

Table 7. Bev before chemoradiotherapy for the treatment of nGBM

Ref.	Study design	No. of patients	Study arms	ORR (%)	mOS (months)	mPFS (months)
Chauffert 2014 TEMAVIR [81]	II, noncomparative, randomized, unresectable 2009-2011	60 60	BEV + Iri→RT + TMZ + Bev→Bev + Iri RT + TMZ→TMZ	NA	11.1 11.1	7.1 5.2
van Linde 2015 [79]	Single group	19	BEV + RT + TMZ→TMZ	NA	16	9.6
Balana 2016 GENOM 009 [80]	II, randomized, unresectable 2009-2013	44 43	BEV + TMZ→RT + TMZ + Bev→TMZ TMZ→RT + TMZ→TMZ	22.9 6.7*	10.6 7.7	4.8 2.2
Tanaka 2024 [169]	I/II 2017-2021	15	Bev + TMZ→Surgery→RT + TMZ→TMZ	NA	16.5	9.5

Note: *, $P < 0.05$; NA, not available.

advantage in terms of ORR, PFS, or OS and may negatively affect the completion of subsequent treatments due to toxicity [79-81]. The TEMAVIR study further revealed lower concurrent chemoradiation completion rates in the Bev group (58% *vs*. 82%) [81]. Thus, for large, unresectable nGBM, the benefits of neoadjuvant Bev are limited.

In conclusion, the use of Bev in nGBM patients is not recommended due to its high incremental cost-utility ratio. One of the future strategies is to identify a beneficial population, such as the proneuronal subtype linked to OS benefits in AVAglio post hoc analyses [82].

With hypofractionated radiotherapy (HFRT)

HFRT represents a viable therapeutic option for elderly or frail nGBM patients [83]. A systematic review indicates comparable OS between HFRT and standard fractionated in HGG, particularly for GBM patients aged ≥60 years [84]. Bev has also demonstrated potential survival benefits in this population [5, 11, 74, 85]. Notably, TMZ monotherapy or TMZ+HFRT remains preferred for elderly GBM patients with MGMT promoter methylation [86, 87].

Compared with conventional fractionation, HFRT offers advantages such as shortened treatment duration, improved patient compliance, and mitigation of tumor cell repopulation via reducing the repair of sublethal damage. However, its application is limited by the elevated risk of RN and delayed neurotoxicity. Bev may theoretically reduce RN and brain edema. Therefore, Bev is expected to improve the tolerance of nGBM patients to hypofractionated radiotherapy while increasing the biological effective dose (BED).

Clinical investigations of HFRT+Bev in elderly GBM patients are summarized in **Table 6**. A phase II ARTE study compared the HFST ± Bev in elderly or frail nGBM patients with unmethylated MGMT promoter [76]. The results indicated that the addition of Bev extended PFS by approximately 3 months but did not improve OS, a finding similar to that in younger adult nGBM patient populations [76]. Additionally, a retrospective study compared HFRT combined with TMZ or TMZ+Bev in nGBM patients aged ≥75 years and reported that adding Bev increased a nonsignificant 2-month OS [88]. Interestingly, subgroup analysis in this study showed MGMT status showed no prognostic impact [88], contradicting the conclusions of the CAN-NCIC-CE6 study [87]. However, all three studies included surgically treated patients with acceptable tolerance, leaving the utility of these regimens in inoperable elderly GBM patients unclear.

In younger adult patients with nGBM, several studies have investigated Bev+HFRT (**Table 6**). This section focuses on RN and recurrence patterns reported in these studies. First, higher PTV volumes and escalated radiation doses in HFRT are associated with an increased risk of RN. A phase II study with a median PTV1 volume of 131.1 cm^3 (BED = 96) reported RN in 50% of patients, prompting early study termination [89]. Conversely, the MSKCC 08-126 study, which restricted tumor volume to ≤60 cc (BED = 57.6), observed no RN cases [90]. Second, RN has been linked to extended survival outcomes, with patients experiencing RN demonstrating a median OS advantage of approximately 3 months compared to non-RN cohorts [89, 91, 92]. However, long-term survivors with RN exhibited diminished QoL. Third, Bev seems to have a limited role in RN prevention [89, 93], and its use correlates with a shift in failure patterns from local to distant intracranial recurrence (see below) [91-93].

In summary, Bev+HFST did not achieve the expected survival outcomes, and its efficacy in elderly GBM patients is similar to that in younger adult patients. Prospective studies contradict retrospective analyses, as the former do not support Bev's clinical utility. Current evidence remains confined to phase II studies.

Optimization of Bev dosing regimens and administration strategies

The optimal dosing regimen for Bev in GBM remains undefined. Preclinical glioma mouse models demonstrate that both low and high Bev doses induce vascular regression, with the latter also inhibiting the activity and growth of glioma cells [22]. However, high doses of Bev may exacerbate hypoxia and promote immunosuppressive myeloid cell infiltration.

Interestingly, clinical studies suggest no dose-dependent antitumor efficacy for Bev [94, 95]. Most trials have adopted regimens of 5-15 mg/kg every 2-3 weeks. A phase II single-arm study first explored 15 mg/kg Bev every 3 weeks,

achieving a PFS6 rate of 25% and mOS of 25.6 weeks [96]. Bokstein et al. reported comparable efficacy with reduced toxicity using low-dose Bev (5 mg/kg biweekly) in HGG patients with poor performance status (mean KPS = 65%) [97]. An early meta-analysis of rGBM studies found no dose-response effect, with similar outcomes between high- (10-15 mg/kg) and low-dose (5 mg/kg) regimens [97, 98]. However, it remains unclear whether higher doses lead to a faster onset of action [98]. The phase II VAMANA study recently reported an mOS of 6.1 months for ultralow-dose Bev (1.5 mg/kg triweekly) combined with CCNU in rGBM [99]. In fact, nonrandomized controlled phase II trials were classified as Class III evidence [43].

Enhancing Bev's intracranial delivery is critical. Rubenstein et al. proposed that antiangiogenic drugs target abnormal blood vessels and are therefore not limited by the blood-brain barrier (BBB) [100]. Indeed, intravenous administration often fails to achieve therapeutic intracranial concentrations in GBM patients due to the BBB and systemic dose-limiting toxicity. Selective intra-arterial drug infusion - direct drug delivery to tumor-feeding arteries - elevates local drug exposure by 3-5.5-fold [101, 102]. Patel et al. combined hyperosmotic BBB disruption with superselective intra-arterial brain infusion (SIACI)-administered Bev in nGBM patients, achieving a mPFS of 11.5 months (95% CI 7.7-25.9 months) and mOS of 23.1 months, with no Grade ≥3 TRAEs [103]. Admittedly, this new treatment technique is more precise and shows improved efficacy [103]. However, the study has several limitations, including the absence of a control group and a small sample size (n = 31) [103]. SIACI faces challenges related to complex hemodynamics and transient drug retention [104], and the technique relies on the operator's skill level, which has a long training period, making widespread adoption difficult.

Notably, the application of novel nanotechnology-based carriers in in vitro models has been reported to suppress angiogenesis and reduce tumor volume, demonstrating promising therapeutic efficacy [105, 106]. Moreover, the nanocapsules can be administered intranasally [107]. Recently, an exosome-based Bev delivery platform engineered by Chu et al. demonstrated enhanced BBB penetrability [108].

In conclusion, the distinct pharmacokinetic and pharmacodynamic profiles of targeted therapies compared to traditional chemotherapy necessitate comprehensive dose-response studies for Bev in GBM, providing important evidence for the use of low-dose Bev in patients with poor performance status or in cost-constrained therapeutic settings. The development of advanced drug delivery systems specifically targeting GBM remains insufficient, whereas novel biomimetic materials persist as a focal point in current research efforts.

Treatment failure patterns associated with Bev

The duration of response to Bev in GBM is short, with 40-60% of patients experiencing recurrence within six months, predominantly exhibiting local progression [109, 110]. Treatment failure may be driven by phosphofructokinase-1, muscle isoform, mesenchymal transition, and aberrant activation of the cell adhesion molecule pathway [111-113]. Through microarray analysis, DeLay et al. classified Bev-resistant GBM (BRG) MRI enhancement patterns into two subtypes: enhanced (62%) and nonenhanced type (34.2%) [114, 115]. BRG patients have an mOS of 2.5 months (range: 1-4.5 months) [96, 116].

The impact of Bev on recurrence patterns - specifically, diffuse *vs*. nondiffuse invasion and multifocal *vs*. focal growth - remains controversial. Lucio and Rubenstein reported that long-term use of Bev enhances GBM invasiveness, characterized by multifocal satellite lesions and finger-like tumor cell formations [100, 117]. The formation of these structures helps hijack existing host blood vessels [100]. Norden et al. observed higher rates of diffuse and metastatic progression in the Bev-treated patients compared to controls (30% *vs*. 21%) [109, 110], potentially mediated by CXCL12/CXCR4 axis activation and MET/VEGFR2 complex formation [118, 119]. Conversely, post hoc analyses of the GLARIUS and AVAglio trials found no association between Bev and multifocal or diffuse recurrence [120, 121]. Furthermore, the prognostic significance of diffuse progression is unclear. Pope et al. reported similar survival outcomes for patients with local-to-diffuse versus local-to-local progression [122]. Another study indicated that T2 diffuse progression is associated with prolonged survival [123].

Table 8. Prognostic biomarkers of BEV

Ref.	Prognostic factors	Positive/Negative
Fu 2021 [82, 112]	Low ITGAM expression, proneural subtype	Positive
Takei 2022 [139]	FOXM1 low-expression	Positive
Scheer 2023 [140] Strauss 2025 [170]	Hypertension	Positive
Kessler 2023 [171]	Neurofibromin 1 mutations	Positive
Kim and Breda-Yepes 2023 [172, 173]	vessel size index and relative cerebral blood volume↑	Negative
Hiller-Vallina 2024 [141]	Sexual-biased necroinflammation	Positive
Joshkon 2022 [142]	high soluble CD146 secretion	Negative
Lallemand 2020 [143]	ADCC activity↑	Negative
Carvalho 2021 [144]	c-Met/VEGFR2 overexpression	Negative
Ellingson 2023 [174]	time to tumor regrowth, depth of response	Positive
Nagane 2022 [166]	macrophage or microglia activation	Positive
Jiguet-Jiglaire 2022 [175]	matrix metalloproteinase 9	Negative

Prognostic factors in Bev-treated GBM will be discussed in detail later.

Bev as a third-line therapeutic option for Bev-naïve or resistant rGBM

Currently, there is no standard third-line therapy established for rGBM. Given the limited treatment options, whether Bev can be used to delay or continue treatment for secondary or later relapses remains exploratory. Franceschi et al. retrospectively analyzed 168 GBM patients receiving third-line treatment, revealing a 2-month survival benefit with Bev compared to chemotherapy (P = 0.014) [124]. In most third-line Bev studies, first recurrence (second-line) treatments primarily include CT (such as nitrosoureas) or Bev.

Post-progression options after second-line Bev include continued Bev, CT, and re-RT. First, two randomized phase II trials - CABARET and TAMIGA - evaluated whether Bev continuation after progression during Bev treatment improved outcomes, with no significant survival or QoL benefits compared to non-Bev therapies [116, 125]. Schaub et al. reported similar PFS between third- and second-line Bev treatment [126]. Second, retrospective studies noted that Bev combined with nitrosourea increased toxicity without survival benefits [127]. Finally, re-RT combined with Bev demonstrated good tolerability and superior survival (mOS: 4.8-8.8 months) compared to historical controls in rHGG after second-line Bev failure [128-132]. These findings suggest that Bev+re-RT may outperform BEV-based CT in survival and toxicity. Can the addition of IT to re-RT combined with Bev further reverse Bev resistance? A recent phase II study reported improved survival with re-RT plus Pemb and Bev in Bev-refractory patients [133].

On the other hand, two retrospective studies support single-agent Bev feasibility in GBM patients progressing after second-line nitrosoureas (such as CCNU or FTM), with mOS of 6-7.5 months and PFS6 rates of 13-21.5% [134, 135].

In summary, for patients progressing after second-line CT or Bev treatment, single-agent Bev or Bev plus re-RT may be viable options. However, due to short survival, many patients only receive first- or second-line treatments, driving current research to optimize interventions for newly diagnosed patients or first recurrence GBM. As OS improves, identifying an optimal subsequent therapy plan will become increasingly important. Recent efforts explore novel agents, such as evofosfamide [136], carotuximab [137], and base excision repair inhibitor TRC102 [138], for Bev-refractory GBM.

Prognostic markers for Bev

In the context of limited survival benefits in the general GBM population, the identification of patient subgroups likely to benefit from Bev is critical.

Genetic, molecular, imaging, and clinical markers associated with Bev response in GBM have been identified in recent studies (**Table 8**). For

instance, Takei et al. demonstrated that reduced *FOXM1* expression predicts prolonged survival in Bev-treated GBM patients [139]. Clinical factors such as hypertension have also been linked to favorable responses [140], while Hiller-Vallina et al. identified sexual-biased necroinflammation as a novel positive predictor [141]. Conversely, negative correlations have been reported with soluble CD146 secretion [142], elevated antibody-dependent cellular cytotoxicity (ADCC) activity [143], and c-Met/VEGFR2 overexpression [144], underscoring the multifactorial nature of resistance mechanisms in Bev-treated GBM.

However, the clinical translation of predictive biomarkers is hindered by several challenges. First, study design biases, high examination costs, invasive sample collection, and stringent regulatory approvals limit their practical application [145]. Second, the extent to which predictive biomarkers demonstrate reproducible and independent predictive utility across diverse cohorts and clinical contexts represents a pivotal consideration. Finally, future research should prioritize the integration of technological advancements, including multi-omics approaches and artificial intelligence, alongside fostering interdisciplinary collaborations and standardized protocols to expedite the translation of biomarkers from experimental research to clinical practice.

In brief, the development of personalized treatment paradigms guided by prognostic markers is recognized as an inevitable trajectory in the era of precision medicine.

Summary and outlook

GBM is the most common primary malignant brain tumor, known for its rapid progression and poor prognosis, with limited effective treatment options. Bev is one of only three options approved by the FDA for GBM treatment in the past two decades, leading to a rapid increase in related research. This paper provides a comprehensive review of recent advancements in BEV research, with a focused discussion on topics pertinent to clinical decision-making.

However, the clinical outcomes of Bev in GBM have been disappointing, with several unresolved challenges. First, the mechanisms underlying Bev's limited efficacy are not fully understood. Second, improvements in short-term efficacy metrics - such as the ORR, PFS6 rates, and PFS - have not translated into OS benefits. Additionally, the optimal sequencing or combination of Bev with other therapies for second- or third-line therapy remains unclear. Finally, clinically applicable prognostic markers to guide Bev use in GBM are still lacking.

Recent advances, such as regorafenib's survival benefits in rGBM, highlight the potential of antiangiogenic therapies. The exploration of novel agents or multimodal treatment approaches, such as multitarget antiangiogenic agents, phytochemicals, or combination strategies, warrants further investigation. Given the constraints imposed by BBB, enhancing drug delivery efficiency to the brain tumor has emerged as a critical focus in advancing GBM therapeutics development. Concurrently, the identification of patient subgroups likely to benefit from Bev through prognostic biomarker-driven stratification has emerged as a key area of investigation in current research. The Global Brain Tumor Adaptive Clinical Trial System (GBM AGILE, NCT03970447) has pioneered an innovative framework for clinical trial design, significantly streamlining the assessment of emerging therapies.

Acknowledgements

The Graphical Abstract in this review was created with Biorender (https://www.biorender.com/). This paper was supported by [National Natural Science Foundation of China] under Grant [number: 82172804].

Disclosure of conflict of interest

None.

Address correspondence to: Xia He, Department of Radiotherapy, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, and Jiangsu Institute of Cancer Research, No. 42 Baiziting, Xuanwu District, Nanjing 210009, Jiangsu, China. E-mail: hexia2021@njmu.edu.cn

References

[1] Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C and Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. Neuro Oncol 2023; 25: iv1-iv99.

[2] Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. Neuro Oncology 2005; 7: 369.
[3] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-2342.
[4] Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WKA, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M and Cloughesy T. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009; 27: 4733-4740.
[5] Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS and Fine HA. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. JCO 2009; 27: 740-745.
[6] Vredenburgh JJ, Desjardins A, Herndon JE, Marcello J, Reardon DA, Quinn JA, Rich JN, Sathornsumetee S, Gururangan S, Sampson J, Wagner M, Bailey L, Bigner DD, Friedman AH and Friedman HS. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007; 25: 4722-4729.
[7] Cohen MH, Shen YL, Keegan P and Pazdur R. FDA drug approval summary: bevacizumab (Avastin®) as treatment of recurrent glioblastoma multiforme. Oncologist 2009; 14: 1131-1138.
[8] Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, Carpentier AF, Hoang-Xuan K, Kavan P, Cernea D, Brandes AA, Hilton M, Abrey L and Cloughesy T. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 2014; 370: 709-722.
[9] Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ and Mehta MP. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014; 370: 699-708.
[10] Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, Brandes AA, Taal W, Domont J, Idbaih A, Campone M, Clement PM, Stupp R, Fabbro M, Le Rhun E, Dubois F, Weller M, Von Deimling A, Golfinopoulos V, Bromberg JC, Platten M, Klein M and Van Den Bent MJ. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017; 377: 1954-1963.
[11] Nghiemphu PL, Liu W, Lee Y, Than T, Graham C, Lai A, Green RM, Pope WB, Liau LM, Mischel PS, Nelson SF, Elashoff R and Cloughesy TF. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. Neurology 2009; 72: 1217-1222.
[12] Brandes AA, Finocchiaro G, Zagonel V, Reni M, Caserta C, Fabi A, Clavarezza M, Maiello E, Eoli M, Lombardi G, Monteforte M, Proietti E, Agati R, Eusebi V and Franceschi E. AVAREG: a phase II, randomized, noncomparative study of fotemustine or bevacizumab for patients with recurrent glioblastoma. NEUONC 2016; 18: 1304-1312.
[13] Tamma R, Ingravallo G, Annese T, d'Amati A, Lorusso L and Ribatti D. Tumor microenvironment and microvascular density in human glioblastoma. Cells 2022; 12: 11.
[14] Groblewska M and Mroczko B. Pro- and antiangiogenic factors in gliomas: implications for novel therapeutic possibilities. IJMS 2021; 22: 6126.
[15] Michaelsen SR, Staberg M, Pedersen H, Jensen KE, Majewski W, Broholm H, Nedergaard MK, Meulengracht C, Urup T, Villingshøj M, Lukacova S, Skjøth-Rasmussen J, Brennum J, Kjær A, Lassen U, Stockhausen MT, Poulsen HS and Hamerlik P. VEGF-C sustains VEGFR2 activation under bevacizumab therapy and promotes glioblastoma maintenance. Neuro Oncol 2018; 20: 1462-1474.
[16] Tamura R, Tanaka T, Akasaki Y, Murayama Y, Yoshida K and Sasaki H. The role of vascular endothelial growth factor in the hypoxic and immunosuppressive tumor microenvironment: perspectives for therapeutic implications. Med Oncol 2019; 37: 2.
[17] Gerber HP and Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. Cancer Res 2005; 65: 671-680.
[18] Bao S, Wu Q, Sathornsumetee S, Hao Y, Li Z, Hjelmeland AB, Shi Q, McLendon RE, Bigner DD and Rich JN. Stem cell-like glioma cells promote tumor angiogenesis through vascular endothelial growth factor. Cancer Res 2006; 66: 7843-7848.
[19] Kaur B, Khwaja FW, Severson EA, Matheny SL, Brat DJ and Van Meir EG. Hypoxia and the hypoxia-inducible-factor pathway in glioma growth and angiogenesis. Neuro Oncol 2005; 7: 134-153.
[20] Pore N, Liu S, Haas-Kogan DA, O'Rourke DM and Maity A. PTEN mutation and epidermal growth factor receptor activation regulate vascular endothelial growth factor (VEGF) mRNA

expression in human glioblastoma cells by transactivating the proximal VEGF promoter. Cancer Res 2003; 63: 236-241.
[21] Reardon DA, Turner S, Peters KB, Desjardins A, Gururangan S, Sampson JH, McLendon RE, Herndon JE, Jones LW, Kirkpatrick JP, Friedman AH, Vredenburgh JJ, Bigner DD and Friedman HS. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. J Natl Compr Canc Netw 2011; 9: 414-427.
[22] García-Romero N, Palacín-Aliana I, Madurga R, Carrión-Navarro J, Esteban-Rubio S, Jiménez B, Collazo A, Pérez-Rodríguez F, Ortiz de Mendivil A, Fernández-Carballal C, García-Duque S, Diamantopoulos-Fernández J, Belda-Iniesta C, Prat-Acín R, Sánchez-Gómez P, Calvo E and Ayuso-Sacido A. Bevacizumab dose adjustment to improve clinical outcomes of glioblastoma. BMC Med 2020; 18: 142.
[23] Joensuu H, Puputti M, Sihto H, Tynninen O and Nupponen NN. Amplification of genes encoding KIT, PDGFRalpha and VEGFR2 receptor tyrosine kinases is frequent in glioblastoma multiforme. J Pathol 2005; 207: 224-231.
[24] Huang H, Held-Feindt J, Buhl R, Mehdorn HM and Mentlein R. Expression of VEGF and its receptors in different brain tumors. Neurol Res 2005; 27: 371-377.
[25] Stefanik DF, Fellows WK, Rizkalla LR, Rizkalla WM, Stefanik PP, Deleo AB and Welch WC. Monoclonal antibodies to vascular endothelial growth factor (VEGF) and the VEGF receptor, FLT-1, inhibit the growth of C6 glioma in a mouse xenograft. J Neurooncol 2001; 55: 91-100.
[26] Horbinski C, Nabors LB, Portnow J, Baehring J, Bhatia A, Bloch O, Brem S, Butowski N, Cannon DM, Chao S, Chheda MG, Fabiano AJ, Forsyth P, Gigilio P, Hattangadi-Gluth J, Holdhoff M, Junck L, Kaley T, Merrell R, Mrugala MM, Nagpal S, Nedzi LA, Nevel K, Nghiemphu PL, Parney I, Patel TR, Peters K, Puduvalli VK, Rockhill J, Rusthoven C, Shonka N, Swinnen LJ, Weiss S, Wen PY, Willmarth NE, Bergman MA and Darlow S. NCCN guidelines® insights: central nervous system cancers, version 2.2022. J Natl Compr Canc Netw 2023; 21: 12-20.
[27] Nagane M, Nishikawa R, Narita Y, Kobayashi H, Takano S, Shinoura N, Aoki T, Sugiyama K, Kuratsu J, Muragaki Y, Sawamura Y and Matsutani M. Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. Jpn J Clin Oncol 2012; 42: 887-895.
[28] Weller M, Van Den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, Bendszus M, Balana C, Chinot O, Dirven L, French P, Hegi ME, Jakola AS, Platten M, Roth P, Rudà R, Short S, Smits M, Taphoorn MJB, Von Deimling A, Westphal M, Soffietti R, Reifenberger G and Wick W. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol 2021; 18: 170-186.
[29] Ballman KV, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR and Jaeckle KA. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. Neuro Oncol 2007; 9: 29-38.
[30] Jaspan T, Morgan PS, Warmuth-Metz M, Sanchez Aliaga E, Warren D, Calmon R, Grill J, Hargrave D, Garcia J and Zahlmann G. Response assessment in pediatric neuro-oncology: implementation and expansion of the RANO criteria in a randomized phase II trial of pediatric patients with newly diagnosed high-grade gliomas. AJNR Am J Neuroradiol 2016; 37: 1581-1587.
[31] Wen PY, van den Bent M, Youssef G, Cloughesy TF, Ellingson BM, Weller M, Galanis E, Barboriak DP, de Groot J, Gilbert MR, Huang R, Lassman AB, Mehta M, Molinaro AM, Preusser M, Rahman R, Shankar LK, Stupp R, Villanueva-Meyer JE, Wick W, Macdonald DR, Reardon DA, Vogelbaum MA and Chang SM. RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. J Clin Oncol 2023; 41: 5187-5199.
[32] Le Rhun E, Oppong FB, van den Bent M, Wick W, Brandes AA, Taphoorn MJ, Platten M, Idbaih A, Clement PM, Preusser M, Golfinopoulos V, Gorlia T and Weller M. Thrombocytopenia limits the feasibility of salvage lomustine chemotherapy in recurrent glioblastoma: a secondary analysis of EORTC 26101. Eur J Cancer 2023; 178: 13-22.
[33] Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WKA, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M and Cloughesy T. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2023; 41: 4945-4952.
[34] Dickson PV, Hamner JB, Sims TL, Fraga CH, Ng CYC, Rajasekeran S, Hagedorn NL, McCarville MB, Stewart CF and Davidoff AM. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. Clin Cancer Res 2007; 13: 3942-3950.
[35] Chamberlain MC. Bevacizumab plus irinotecan in recurrent glioblastoma. J Clin Oncol 2008; 26: 1012-1013; author reply 1013.
[36] Taal W, Oosterkamp HM, Walenkamp AME, Dubbink HJ, Beerepoot LV, Hanse MCJ, Buter J,

Honkoop AH, Boerman D, De Vos FYF, Dinjens WNM, Enting RH, Taphoorn MJB, Van Den Berkmortel FWPJ, Jansen RLH, Brandsma D, Bromberg JEC, Van Heuvel I, Vernhout RM, Van Der Holt B and Van Den Bent MJ. 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: 943-953.

[37] Chen Z, Tian F and Zhang Y. Cost-effectiveness analysis of bevacizumab combined with lomustine in the treatment of progressive glioblastoma using a Markov model simulation analysis. Front Public Health 2024; 12: 1410355.

[38] Field KM, Simes J, Nowak AK, Cher L, Wheeler H, Hovey EJ, Brown CS, Barnes EH, Sawkins K, Livingstone A, Freilich R, Phal PM, Fitt G; CABARET/COGNO investigators; Rosenthal MA. Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. Neuro-Oncology 2015; 17: 1504-1513.

[39] Cloughesy T, Finocchiaro G, Belda-Iniesta C, Recht L, Brandes AA, Pineda E, Mikkelsen T, Chinot OL, Balana C, Macdonald DR, Westphal M, Hopkins K, Weller M, Bais C, Sandmann T, Bruey JM, Koeppen H, Liu B, Verret W, Phan SC and Shames DS. Randomized, double-blind, placebo-controlled, multicenter phase II study of onartuzumab plus bevacizumab versus placebo plus bevacizumab in patients with recurrent glioblastoma: efficacy, safety, and hepatocyte growth factor and O6-methylguanine-DNA methyltransferase biomarker analyses. J Clin Oncol 2017; 35: 343-351.

[40] Cruz Da Silva E, Mercier MC, Etienne-Selloum N, Dontenwill M and Choulier L. A systematic review of glioblastoma-targeted therapies in phases II, III, IV clinical trials. Cancers (Basel) 2021; 13: 1795.

[41] Kelly W, Diaz Duque AE, Michalek J, Konkel B, Caflisch L, Chen Y, Pathuri SC, Madhusudanannair-Kunnuparampil V, Floyd J and Brenner A. Phase II investigation of TVB-2640 (Denifanstat) with bevacizumab in patients with first relapse high-grade astrocytoma. Clin Cancer Res 2023; 29: 2419-2425.

[42] Zhao S, Zhang M, Zhang Q, Wu J and Dai H. Anlotinib alone or in combination with bevacizumab in the treatment of recurrent high-grade glioma: a prospective single-arm, open-label phase II trial. BMC Cancer 2024; 24: 6.

[43] Winograd E, Germano I, Wen P, Olson JJ and Ormond DR. Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of targeted therapies and immunotherapies in the management of progressive glioblastoma. J Neurooncol 2022; 158: 265-321.

[44] Motz GT, Santoro SP, Wang LP, Garrabrant T, Lastra RR, Hagemann IS, Lal P, Feldman MD, Benencia F and Coukos G. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med 2014; 20: 607-615.

[45] Nayak L, Standifer N, Dietrich J, Clarke JL, Dunn GP, Lim M, Cloughesy T, Gan HK, Flagg E, George E, Gaffey S, Hayden J, Holcroft C, Wen PY, Macri M, Park AJ, Ricciardi T, Ryan A, Schwarzenberger P, Venhaus R, Reyes M de L, Durham NM, Creasy T, Huang RY, Kaley T and Reardon DA. Circulating immune cell and outcome analysis from the phase II study of PD-L1 blockade with durvalumab for newly diagnosed and recurrent glioblastoma. Clin Cancer Res 2022; 28: 2567-2578.

[46] Wang F, Jin Y, Wang M, Luo HY, Fang WJ, Wang YN, Chen YX, Huang RJ, Guan WL, Li JB, Li YH, Wang FH, Hu XH, Zhang YQ, Qiu MZ, Liu LL, Wang ZX, Ren C, Wang DS, Zhang DS, Wang ZQ, Liao WT, Tian L, Zhao Q and Xu RH. Combined anti-PD-1, HDAC inhibitor and anti-VEGF for MSS/pMMR colorectal cancer: a randomized phase 2 trial. Nat Med 2024; 30: 1035-1043.

[47] Reardon DA, Brandes AA, Omuro A, Mulholland P, Lim M, Wick A, Baehring J, Ahluwalia MS, Roth P, Bähr O, Phuphanich S, Sepulveda JM, De Souza P, Sahebjam S, Carleton M, Tatsuoka K, Taitt C, Zwirtes R, Sampson J and Weller M. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol 2020; 6: 1003-1010.

[48] Nayak L, Molinaro AM, Peters K, Clarke JL, Jordan JT, de Groot J, Nghiemphu L, Kaley T, Colman H, McCluskey C, Gaffey S, Smith TR, Cote DJ, Severgnini M, Yearley JH, Zhao Q, Blumenschein WM, Duda DG, Muzikansky A, Jain RK, Wen PY and Reardon DA. Randomized phase II and biomarker study of pembrolizumab plus bevacizumab versus pembrolizumab alone for patients with recurrent glioblastoma. Clin Cancer Res 2021; 27: 1048-1057.

[49] Chiu D, Qi J, Thin TH, Garcia-Barros M, Lee B, Hahn M, Mandeli J, Belani P, Nael K, Rashidipour O, Ghatan S, Hadjipanayis CG, Yong RL, Germano IM, Brody R, Tsankova NM, Gnjatic S, Kim-Schulze S and Hormigo A. A phase I trial of VEGF-A inhibition combined with PD-L1 blockade for recurrent glioblastoma. Cancer Res Commun 2023; 3: 130-139.

[50] Guo G, Zhang Z, Zhang J, Wang D, Xu S, Liu G, Gao Y, Mei J, Yan Z, Zhao R, Wang M, Li T and Bu X. Predicting recurrent glioblastoma clinical outcome to immune checkpoint inhibition and

low-dose bevacizumab with tumor in situ fluid circulating tumor DNA analysis. Cancer Immunol Immunother 2024; 73: 193.
[51] Wang D, Zhang J, Bu C, Liu G, Guo G, Zhang Z, Lv G, Sheng Z, Yan Z, Gao Y, Wang M, Liu G, Zhao R, Li T, Ma C and Bu X. Dynamics of tumor in situ fluid circulating tumor DNA in recurrent glioblastomas forecasts treatment efficacy of immune checkpoint blockade coupled with low-dose bevacizumab. J Cancer Res Clin Oncol 2024; 150: 466.
[52] Yang G, Fang Y, Zhou M, Li W, Dong D, Chen J, Da Y, Wang K, Li X, Zhang X, Ma T and Shen G. Case report: the effective response to pembrolizumab in combination with bevacizumab in the treatment of a recurrent glioblastoma with multiple extracranial metastases. Front Oncol 2022; 12: 948933.
[53] Cloughesy TF, Brenner A, de Groot JF, Butowski NA, Zach L, Campian JL, Ellingson BM, Freedman LS, Cohen YC, Lowenton-Spier N, Rachmilewitz Minei T, Fain Shmueli S; GLOBE Study Investigators; Wen PY. A randomized controlled phase III study of VB-111 combined with bevacizumab vs bevacizumab monotherapy in patients with recurrent glioblastoma (GLOBE). Neuro Oncol 2020; 22: 705-717.
[54] Brenner AJ, Peters KB, Vredenburgh J, Bokstein F, Blumenthal DT, Yust-Katz S, Peretz I, Oberman B, Freedman LS, Ellingson BM, Cloughesy TF, Sher N, Cohen YC, Lowenton-Spier N, Rachmilewitz Minei T, Yakov N, Mendel I, Breitbart E and Wen PY. Safety and efficacy of VB-111, an anticancer gene therapy, in patients with recurrent glioblastoma: results of a phase I/II study. Neuro Oncol 2020; 22: 694-704.
[55] Cloughesy TF, Mochizuki AY, Orpilla JR, Hugo W, Lee AH, Davidson TB, Wang AC, Ellingson BM, Rytlewski JA, Sanders CM, Kawaguchi ES, Du L, Li G, Yong WH, Gaffey SC, Cohen AL, Mellinghoff IK, Lee EQ, Reardon DA, O'Brien BJ, Butowski NA, Nghiemphu PL, Clarke JL, Arrillaga-Romany IC, Colman H, Kaley TJ, de Groot JF, Liau LM, Wen PY and Prins RM. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. Nat Med 2019; 25: 477-486.
[56] Reardon DA, Desjardins A, Vredenburgh JJ, O'Rourke DM, Tran DD, Fink KL, Nabors LB, Li G, Bota DA, Lukas RV, Ashby LS, Duic JP, Mrugala MM, Cruickshank S, Vitale L, He Y, Green JA, Yellin MJ, Turner CD, Keler T, Davis TA and Sampson JH; ReACT trial investigators. Rindopepimut with bevacizumab for patients with relapsed EGFRvIII-expressing glioblastoma (ReACT): Results of a double-blind randomized phase II trial. Clin Cancer Res 2020; 26: 1586-1594.
[57] Fu M, Zhou Z, Huang X, Chen Z, Zhang L, Zhang J, Hua W and Mao Y. Use of bevacizumab in recurrent glioblastoma: a scoping review and evidence map. BMC Cancer 2023; 23: 544.
[58] Fleischmann DF, Gajdi L, Corradini S, Schönecker S, Marschner S, Bodensohn R, Hofmaier J, Garny S, Forbrig R, Thon N, Belka C and Niyazi M. Re-irradiation treatment regimens for patients with recurrent glioma - evaluation of the optimal dose and best concurrent therapy. Radiother Oncol 2024; 199: 110437.
[59] Tsien CI, Pugh SL, Dicker AP, Raizer JJ, Matuszak MM, Lallana EC, Huang J, Algan O, Deb N, Portelance L, Villano JL, Hamm JT, Oh KS, Ali AN, Kim MM, Lindhorst SM and Mehta MP. NRG oncology/RTOG1205: a randomized phase II trial of concurrent bevacizumab and reirradiation versus bevacizumab alone as treatment for recurrent glioblastoma. J Clin Oncol 2023; 41: 1285-1295.
[60] Guan Y, Xiong J, Pan M, Shi W, Li J, Zhu H, Gong X, Li C, Mei G, Liu X, Pan L, Dai J, Wang Y, Wang E and Wang X. Safety and efficacy of Hypofractionated stereotactic radiosurgery for high-grade Gliomas at first recurrence: a single-center experience. BMC cancer 2021; 21: 123.
[61] Palmer JD, Bhamidipati D, Song A, Eldredge-Hindy HB, Siglin J, Dan TD, Champ CE, Zhang I, Bar-Ad V, Kim L, Glass J, Evans JJ, Andrews DW, Werner-Wasik M and Shi W. Bevacizumab and re-irradiation for recurrent high grade gliomas: does sequence matter? J Neurooncol 2018; 140: 623-628.
[62] Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, Friedman HS, Willett CG and Kirkpatrick JP. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 2012; 82: 2018-2024.
[63] Helis CA, Zarabi H, Russell G, LeCompte M, Liu W, Hattangadi-Gluth J, Halasz LM, Soltys SG, Braunstein SE, Wang TJC, Shi W, Shen C, Mignano J, Masters A, Kleinberg L, Huang J, Hopper A, Barbour AB, Jeyapalan SA and Chan MD. Multi-institutional study of reirradiation for recurrent high grade glioma. J Clin Oncol 2024; 2063-2063.
[64] Chen ATC, Serante AR, Ayres AS, Tonaki JO, Moreno RA, Shih H, Gattás GS, Lopez RVM, Dos Santos de Jesus GR, de Carvalho IT, Marotta RC, Marta GN, Feher O, Neto HS, Ribeiro ISN, Vasconcelos KGMDC, Figueiredo EG and Weltman E. Prospective randomized phase 2 trial of hypofractionated stereotactic radiation therapy of 25 gy in 5 fractions compared with 35 gy in 5 fractions in the reirradiation of re-

current glioblastoma. Int J Radiat Oncol Biol Phys 2024; 119: 1122-1132.
[65] Arvold ND, Shi DD, Aizer AA, Norden AD, Reardon DA, Lee EQ, Nayak L, Dunn IF, Golby AJ, Johnson MD, Claus EB, Chiocca EA, Ligon KL, Wen PY and Alexander BM. Salvage re-irradiation for recurrent high-grade glioma and comparison to bevacizumab alone. J Neurooncol 2017; 135: 581-591.
[66] Kulinich DP, Sheppard JP, Nguyen T, Kondajji AM, Unterberger A, Duong C, Enomoto A, Patel K and Yang I. Radiotherapy versus combination radiotherapy-bevacizumab for the treatment of recurrent high-grade glioma: a systematic review. Acta Neurochir (Wien) 2021; 163: 1921-1934.
[67] Popp I, Weber WA, Graf E, Mix M, Wiehle R, Nestle U, Schimek-Jasch T, Niyazi M, Belka C, Paulsen F, Eckert F, Eble MJ, König L, Giordano FA, Sperk E, Momm F, Spehl I, Combs SE, Bernhardt D and Grosu AL. Re-irradiation in recurrent glioblastoma: PET- or MRI-based? Results of a prospective randomized clinical trial. J Clin Oncol 2024; 42: 2021-2021.
[68] Tong E, Horsley P, Wheeler H, Wong M, Venkatesha V, Chan J, Kastelan M and Back M. Hypofractionated re-irradiation with bevacizumab for relapsed chemorefractory glioblastoma after prior high dose radiotherapy: a feasible option for patients with large-volume relapse. J Neurooncol 2024; 168: 69-76.
[69] Lee ST, Seo Y, Bae JY, Chu K, Kim JW, Choi SH, Kim TM, Kim IH, Park SH and Park CK. Loss of pericytes in radiation necrosis after glioblastoma treatments. Mol Neurobiol 2018; 55: 4918-4926.
[70] Khalaj K, Jacobs MA, Zhu JJ, Esquenazi Y, Hsu S, Tandon N, Akhbardeh A, Zhang X, Riascos R and Kamali A. The use of apparent diffusion coefficient values for differentiating bevacizumab-related cytotoxicity from tumor recurrence and radiation necrosis in glioblastoma. Cancers (Basel) 2024; 16: 2440.
[71] Dasgupta A, Sawant S, Chatterjee A, Gota V, Sahu A, Choudhari A, Bhattacharya K, Puranik A, Dev I, Moiyadi A, Shetty P, Singh V, Menon N, Epari S, Sahay A, Shah A, Bano N, Shaikh F, Jirage A and Gupta T. Study protocol of a prospective phase 2 study of chlorophyllin for the management of brain radionecrosis in patients with diffuse glioma (CHROME). Cancer Med 2025; 14: e70657.
[72] Sahebjam S, Forsyth PA, Tran ND, Arrington JA, Macaulay R, Etame AB, Walko CM, Boyle T, Peguero EN, Jaglal M, Mokhtari S, Enderling H, Raghunand N, Gatewood T, Long W, Dzierzeski JL, Evernden B, Robinson T, Wicklund MC, Kim S, Thompson ZJ, Chen DT, Chinnaiyan P and Yu HM. Hypofractionated stereotactic re-irradiation with pembrolizumab and bevacizumab in patients with recurrent high-grade gliomas: results from a phase I study. Neuro Oncol 2021; 23: 677-686.
[73] Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE, Marcello J, Kirkpatrick JP, Sampson JH, Bailey L, Threatt S, Friedman AH, Bigner DD and Friedman HS. The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res 2011; 17: 4119-4124.
[74] Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, Filka E, Yong WH, Mischel PS, Liau LM, Phuphanich S, Black K, Peak S, Green RM, Spier CE, Kolevska T, Polikoff J, Fehrenbacher L, Elashoff R and Cloughesy T. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 2011; 29: 142-148.
[75] Wefel JS, Armstrong TS, Pugh SL, Gilbert MR, Wendland MM, Brachman DG, Roof KS, Brown PD, Crocker IR, Robins HI, Hunter G, Won M and Mehta MP. Neurocognitive, symptom, and health-related quality of life outcomes of a randomized trial of bevacizumab for newly diagnosed glioblastoma (NRG/RTOG 0825). Neuro Oncol 2021; 23: 1125-1138.
[76] Wirsching HG, Tabatabai G, Roelcke U, Hottinger AF, Jörger F, Schmid A, Plasswilm L, Schrimpf D, Mancao C, Capper D, Conen K, Hundsberger T, Caparrotti F, von Moos R, Riklin C, Felsberg J, Roth P, Jones DTW, Pfister S, Rushing EJ, Abrey L, Reifenberger G, Held L, von Deimling A, Ochsenbein A and Weller M. Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial. Ann Oncol 2018; 29: 1423-1430.
[77] Chinot OL, Nishikawa R, Mason W, Henriksson R, Saran F, Cloughesy T, Garcia J, Revil C, Abrey L and Wick W. Upfront bevacizumab may extend survival for glioblastoma patients who do not receive second-line therapy: an exploratory analysis of AVAglio. Neuro Oncol 2016; 18: 1313-1318.
[78] Motoo N, Hayashi Y, Shimizu A, Ura M and Nishikawa R. Safety and effectiveness of bevacizumab in Japanese patients with malignant glioma: a post-marketing surveillance study. Jpn J Clin Oncol 2019; 49: 1016-1023.
[79] van Linde ME, Verhoeff JJC, Richel DJ, van Furth WR, Reijneveld JC, Verheul HMW and Stalpers LJA. Bevacizumab in combination with radiotherapy and temozolomide for pa-

tients with newly diagnosed glioblastoma multiforme. Oncologist 2015; 20: 107-108.
[80] Balana C, De Las Penas R, Sepúlveda JM, Gil-Gil MJ, Luque R, Gallego O, Carrato C, Sanz C, Reynes G, Herrero A, Ramirez JL, Pérez-Segura P, Berrocal A, Vieitez JM, Garcia A, Vazquez-Estevez S, Peralta S, Fernandez I, Henriquez I, Martinez-Garcia M, De la Cruz JJ, Capellades J, Giner P and Villà S. Bevacizumab and temozolomide versus temozolomide alone as neoadjuvant treatment in unresected glioblastoma: the GENOM 009 randomized phase II trial. J Neurooncol 2016; 127: 569-579.
[81] Chauffert B, Feuvret L, Bonnetain F, Taillandier L, Frappaz D, Taillia H, Schott R, Honnorat J, Fabbro M, Tennevet I, Ghiringhelli F, Guillamo JS, Durando X, Castera D, Frenay M, Campello C, Dalban C, Skrzypski J and Chinot O. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMAVIR study from ANOCEF†. Ann Oncol 2014; 25: 1442-1447.
[82] Sandmann T, Bourgon R, Garcia J, Li C, Cloughesy T, Chinot OL, Wick W, Nishikawa R, Mason W, Henriksson R, Saran F, Lai A, Moore N, Kharbanda S, Peale F, Hegde P, Abrey LE, Phillips HS and Bais C. 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. JCO 2015; 33: 2735-2744.
[83] Chang EL, Yi W, Allen PK, Levin VA, Sawaya RE and Maor MH. Hypofractionated radiotherapy for elderly or younger low-performance status glioblastoma patients: outcome and prognostic factors. Int J Radiat Oncol Biol Phys 2003; 56: 519-28.
[84] Khan L, Soliman H, Sahgal A, Perry J, Xu W and Tsao MN. External beam radiation dose escalation for high grade glioma. Cochrane Database Syst Rev 2020; 5: CD011475.
[85] Reyes-Botero G, Cartalat-Carel S, Chinot OL, Barrie M, Taillandier L, Beauchesne P, Catry-Thomas I, Barrière J, Guillamo JS, Fabbro M, Frappaz D, Benouaich-Amiel A, Le Rhun E, Campello C, Tennevet I, Ghiringhelli F, Tanguy ML, Mokhtari K, Honnorat J and Delattre JY. Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial (ATAG). Oncologist 2018; 23: 524-e44.
[86] Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, Nikkhah G, Papsdorf K, Steinbach JP, Sabel M, Combs SE, Vesper J, Braun C, Meixensberger J, Ketter R, Mayer-Steinacker R, Reifenberger G and Weller M; NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012; 13: 707-15.
[87] Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, Nishikawa R, Cairncross JG, Roa W, Osoba D, Rossiter JP, Sahgal A, Hirte H, Laigle-Donadey F, Franceschi E, Chinot O, Golfinopoulos V, Fariselli L, Wick A, Feuvret L, Back M, Tills M, Winch C, Baumert BG, Wick W, Ding K and Mason WP; Trial Investigators. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med 2017; 376: 1027-1037.
[88] Ohno M, Miyakita Y, Takahashi M, Igaki H, Matsushita Y, Ichimura K and Narita Y. Survival benefits of hypofractionated radiotherapy combined with temozolomide or temozolomide plus bevacizumab in elderly patients with glioblastoma aged ≥ 75 years. Radiat Oncol 2019; 14: 200.
[89] Ney DE, Carlson JA, Damek DM, Gaspar LE, Kavanagh BD, Kleinschmidt-DeMasters BK, Waziri AE, Lillehei KO, Reddy K and Chen C. Phase II trial of hypofractionated intensity-modulated radiation therapy combined with temozolomide and bevacizumab for patients with newly diagnosed glioblastoma. J Neurooncol 2015; 122: 135-143.
[90] Omuro A, Beal K, Gutin P, Karimi S, Correa DD, Kaley TJ, DeAngelis LM, Chan TA, Gavrilovic IT, Nolan C, Hormigo A, Lassman AB, Mellinghoff I, Grommes C, Reiner AS, Panageas KS, Baser RE, Tabar V, Pentsova E, Sanchez J, Barradas-Panchal R, Zhang J, Faivre G, Brennan CW, Abrey LE and Huse JT. Phase II study of bevacizumab, temozolomide, and hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma. Clin Cancer Res 2014; 20: 5023-5031.
[91] Iuchi T, Hatano K, Kodama T, Sakaida T, Yokoi S, Kawasaki K, Hasegawa Y and Hara R. Phase 2 trial of hypofractionated high-dose intensity modulated radiation therapy with concurrent and adjuvant temozolomide for newly diagnosed glioblastoma. Int J Radiat Oncol Biol Phys 2014; 88: 793-800.
[92] Reddy K, Gaspar LE, Kavanagh BD and Chen C. Hypofractionated intensity-modulated radiotherapy with temozolomide chemotherapy may alter the patterns of failure in patients with glioblastoma multiforme. J Med Imaging Radiat Oncol 2014; 58: 714-21.
[93] Carlson JA, Reddy K, Gaspar LE, Ney D, Kavanagh BD, Damek D, Lillehei K and Chen C. Hy-

pofractionated-intensity modulated radiotherapy (hypo-IMRT) and temozolomide (TMZ) with or without bevacizumab (BEV) for newly diagnosed glioblastoma multiforme (GBM): a comparison of two prospective phase II trials. J Neurooncol 2015; 123: 251-257.
[94] Gleeson JP, Keane F, Keegan NM, Mammadov E, Harrold E, Alhusaini A, Harte J, Eakin-Love A, O'Halloran PJ, MacNally S, Hennessy BT, Breathnach OS, Grogan L and Morris PG. Similar overall survival with reduced vs. standard dose bevacizumab monotherapy in progressive glioblastoma. Cancer Med 2020; 9: 469-475.
[95] Levin VA, Mendelssohn ND, Chan J, Stovall MC, Peak SJ, Yee JL, Hui RL and Chen DM. Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma. J Neurooncol 2015; 122: 145-150.
[96] Raizer JJ, Grimm S, Chamberlain MC, Nicholas MK, Chandler JP, Muro K, Dubner S, Rademaker AW, Renfrow J and Bredel M. A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. Cancer 2010; 116: 5297-5305.
[97] Bokstein F, Shpigel S and Blumenthal DT. Treatment with bevacizumab and irinotecan for recurrent high-grade glial tumors. Cancer 2008; 112: 2267-2273.
[98] Wong ET, Gautam S, Malchow C, Lun M, Pan E and Brem S. Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. J Natl Compr Canc Netw 2011; 9: 403-407.
[99] Menon NS, Shah MJ, Gupta T, Sridhar E, Chatterjee A, Dasgupta A, Sahu A, Sawant R, Kapu V, Trikha M, Shah A, Peelay ZR, Puranik A, Dev I, Jadhav M, Moiyadi A, Shetty P, Sahay A, Singh VK and Patil VM. VAMANA: a phase 2 study of low-dose bevacizumab plus CCNU in relapsed/recurrent glioblastoma. JCO 2024; 42: LBA2064.
[100] Rubenstein JL, Kim J, Ozawa T, Zhang M, Westphal M, Deen DF and Shuman MA. Anti-VEGF antibody treatment of glioblastoma prolongs survival but results in increased vascular cooption. Neoplasia 2000; 2: 306-314.
[101] Fortin D, Morin PA, Belzile F, Mathieu D and Paré FM. Intra-arterial carboplatin as a salvage strategy in the treatment of recurrent glioblastoma multiforme. J Neurooncol 2014; 119: 397-403.
[102] Lim J, Santo BA, Baig AA, Ciecierska SK, Donnelly B, Balghonaim S, Levy BR, Jaikumar V, Levy EI, Tutino VM and Siddiqui AH. Efficacy of intra-arterial carboplatin and bevacizumab in the C6 rat glioma model of glioblastoma multiforme. J Neurointerv Surg 2025; jnis-2024-021789.
[103] Patel NV, Wong T, Fralin SR, Li M, McKeown A, Gruber D, D'Amico RS, Patsalides A, Tsiouris A, Stefanov DG, Flores O, Zlochower A, Filippi CG, Ortiz R, Langer DJ and Boockvar JA. Repeated superselective intraarterial bevacizumab after blood brain barrier disruption for newly diagnosed glioblastoma: a phase I/II clinical trial. J Neurooncol 2021; 155: 117-124.
[104] Kappel AD, Jha R, Guggilapu S, Smith WJ, Feroze AH, Dmytriw AA, Vicenty-Padilla J, Alcedo Guardia RE, Gessler FA, Patel NJ, Du R, See AP, Peruzzi PP, Aziz-Sultan MA and Bernstock JD. Endovascular applications for the management of high-grade gliomas in the modern era. cancers (Basel) 2024; 16: 1594.
[105] Di Filippo LD, Lobato Duarte J, Hofstätter Azambuja J, Isler Mancuso R, Tavares Luiz M, Hugo Sousa Araújo V, Delbone Figueiredo I, Barretto-de-Souza L, Miguel Sábio R, Sasso-Cerri E, Martins Baviera A, Crestani CC, Teresinha Ollala Saad S and Chorilli M. Glioblastoma multiforme targeted delivery of docetaxel using bevacizumab-modified nanostructured lipid carriers impair in vitro cell growth and in vivo tumor progression. Int J Pharm 2022; 618: 121682.
[106] Sousa F, Costa-Pereira AI, Cruz A, Ferreira FJ, Gouveia M, Bessa J, Sarmento B, Travasso RDM and Mendes Pinto I. Intratumoral VEGF nanotrapper reduces gliobastoma vascularization and tumor cell mass. J Control Release 2021; 339: 381-390.
[107] de Cristo Soares Alves A, Lavayen V, de Fraga Dias A, Bruinsmann FA, Scholl JN, Cé R, Visioli F, Oliveira Battastini AM, Stanisçuaski Guterres S, Figueiró F and Raffin Pohlmann A. EGFRvIII peptide nanocapsules and bevacizumab nanocapsules: a nose-to-brain multitarget approach against glioblastoma. Nanomedicine (Lond) 2021; 16: 1775-1790.
[108] Chu L, Sun Y, Tang X, Duan X, Zhao Y, Xia H, Xu L, Zhang P, Sun K, Yang G and Wang A. The tumor-derived exosomes enhanced bevacizumab across the blood-brain barrier for antiangiogenesis therapy against glioblastoma. Mol Pharm 2025; 22: 972-983.
[109] Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, Ciampa AS, Ebbeling LG, Levy B, Drappatz J, Kesari S and Wen PY. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 2008; 70: 779-787.
[110] Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, Saran F, Le Deley MC, Varlet P, Morgan PS, Jaspan T, Jones C, Giangaspero F, Smith H, Garcia J, Elze MC, Rousseau RF, Abrey L, Hargrave D and Vassal G. Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediat-

ric patients with newly diagnosed high-grade glioma. J Clin Oncol 2018; 36: 951-958.
[111] Chandra A, Jahangiri A, Chen W, Nguyen AT, Yagnik G, Pereira MP, Jain S, Garcia JH, Shah SS, Wadhwa H, Joshi RS, Weiss J, Wolf KJ, Lin JG, Müller S, Rick JW, Diaz AA, Gilbert LA, Kumar S and Aghi MK. Clonal ZEB1-driven mesenchymal transition promotes targetable oncologic antiangiogenic therapy resistance. Cancer Res 2020; 80: 1498-1511.
[112] Fu M, Hussain A, Dong Y and Fei Y. A retrospective analysis of GSE84010: cell adhesion molecules might contribute to bevacizumab resistance in glioblastoma. J Clin Neurosci 2021; 86: 110-115.
[113] Lim YC, Jensen KE, Aguilar-Morante D, Vardouli L, Vitting-Seerup K, Gimple RC, Wu Q, Pedersen H, Elbaek KJ, Gromova I, Ihnatko R, Kristensen BW, Petersen JK, Skjoth-Rasmussen J, Flavahan W, Rich JN and Hamerlik P. Non-metabolic functions of phosphofructokinase-1 orchestrate tumor cellular invasion and genome maintenance under bevacizumab therapy. Neuro Oncol 2023; 25: 248-260.
[114] DeLay M, Jahangiri A, Carbonell WS, Hu YL, Tsao S, Tom MW, Paquette J, Tokuyasu TA and Aghi MK. Microarray analysis verifies two distinct phenotypes of glioblastomas resistant to antiangiogenic therapy. Clin Cancer Res 2012; 18: 2930-2942.
[115] Cho SJ, Kim HS, Suh CH and Park JE. Radiological recurrence patterns after bevacizumab treatment of recurrent high-grade glioma: a systematic review and meta-analysis. Korean J Radiol 2020; 21: 908-918.
[116] Hovey EJ, Field KM, Rosenthal MA, Barnes EH, Cher L, Nowak AK, Wheeler H, Sawkins K, Livingstone A, Phal P, Goh C and Simes J; CABARET/COGNO investigators. Continuing or ceasing bevacizumab beyond progression in recurrent glioblastoma: an exploratory randomized phase II trial. Neurooncol Pract 2017; 4: 171-181.
[117] Lucio-Eterovic AK, Piao Y and de Groot JF. Mediators of glioblastoma resistance and invasion during antivascular endothelial growth factor therapy. Clin Cancer Res 2009; 15: 4589-4599.
[118] Pham K, Luo D, Siemann DW, Law BK, Reynolds BA, Hothi P, Foltz G and Harrison JK. VEGFR inhibitors upregulate CXCR4 in VEGF receptor-expressing glioblastoma in a TGFβR signaling-dependent manner. Cancer Lett 2015; 360: 60-67.
[119] Lu KV, Chang JP, Parachoniak CA, Pandika MM, Aghi MK, Meyronet D, Isachenko N, Fouse SD, Phillips JJ, Cheresh DA, Park M and Bergers G. VEGF inhibits tumor cell invasion and mesenchymal transition through a MET/VEGFR2 complex. Cancer Cell 2012; 22: 21-35.
[120] Schaub C, Kebir S, Junold N, Hattingen E, Schäfer N, Steinbach JP, Weyerbrock A, Hau P, Goldbrunner R, Niessen M, Mack F, Stuplich M, Tzaridis T, Bähr O, Kortmann RD, Schlegel U, Schmidt-Graf F, Rohde V, Braun C, Hänel M, Sabel M, Gerlach R, Krex D, Belka C, Vatter H, Proescholdt M, Herrlinger U and Glas M. Tumor growth patterns of MGMT-non-methylated glioblastoma in the randomized GLARIUS trial. J Cancer Res Clin Oncol 2018; 144: 1581-1589.
[121] Wick W, Chinot OL, Bendszus M, Mason W, Henriksson R, Saran F, Nishikawa R, Revil C, Kerloeguen Y and Cloughesy T. Evaluation of pseudoprogression rates and tumor progression patterns in a phase III trial of bevacizumab plus radiotherapy/temozolomide for newly diagnosed glioblastoma. Neuro Oncol 2016; 18: 1434-1441.
[122] Pope WB, Xia Q, Paton VE, Das A, Hambleton J, Kim HJ, Huo J, Brown MS, Goldin J and Cloughesy T. Patterns of progression in patients with recurrent glioblastoma treated with bevacizumab. Neurology 2011; 76: 432-437.
[123] Nowosielski M, Ellingson BM, Chinot OL, Garcia J, Revil C, Radbruch A, Nishikawa R, Mason WP, Henriksson R, Saran F, Kickingereder P, Platten M, Sandmann T, Abrey LE, Cloughesy TF, Bendszus M and Wick W. Radiologic progression of glioblastoma under therapy-an exploratory analysis of AVAglio. Neuro Oncol 2018; 20: 557-566.
[124] Franceschi E, Lamberti G, Paccapelo A, Di Battista M, Genestreti G, Minichillo S, Mura A, Bartolini S, Agati R and Brandes AA. Third-line therapy in recurrent glioblastoma: is it another chance for bevacizumab? J Neurooncol 2018; 139: 383-388.
[125] Brandes AA, Gil-Gil M, Saran F, Carpentier AF, Nowak AK, Mason W, Zagonel V, Dubois F, Finocchiaro G, Fountzilas G, Cernea DM, Chinot O, Anghel R, Ghiringhelli F, Beauchesne P, Lombardi G, Franceschi E, Makrutzki M, Mpofu C, Urban HJ and Pichler J. A randomized phase II trial (TAMIGA) evaluating the efficacy and safety of continuous bevacizumab through multiple lines of treatment for recurrent glioblastoma. Oncologist 2019; 24: 521-528.
[126] Schaub C, Schäfer N, Mack F, Stuplich M, Kebir S, Niessen M, Tzaridis T, Banat M, Vatter H, Waha A, Herrlinger U and Glas M. The earlier the better? Bevacizumab in the treatment of recurrent MGMT-non-methylated glioblastoma. J Cancer Res Clin Oncol 2016; 142: 1825-1829.
[127] Rahman R, Hempfling K, Norden AD, Reardon DA, Nayak L, Rinne ML, Beroukhim R, Doherty L, Ruland S, Rai A, Rifenburg J, LaFrankie D, Alexander BM, Huang RY, Wen PY and Lee EQ. Retrospective study of carmustine or lomus-

tine with bevacizumab in recurrent glioblastoma patients who have failed prior bevacizumab. Neuro Oncol 2014; 16: 1523-1529.
[128] Shi W, Blomain ES, Siglin J, Palmer JD, Dan T, Wang Y, Werner-Wasik M, Glass J, Kim L, Bar Ad V, Bhamidipati D, Evans JJ, Judy K, Farrell CJ and Andrews DW. Salvage fractionated stereotactic re-irradiation (FSRT) for patients with recurrent high grade gliomas progressed after bevacizumab treatment. J Neurooncol 2018; 137: 171-177.
[129] Dixit KS, Sachdev S, Amidei C, Kumthekar P, Kruser TJ, Gondi V, Grimm S, Lukas RV, Nicholas MK, Chmura SJ, Fought AJ, Mehta M and Raizer JJ. A multi-center prospective study of re-irradiation with bevacizumab and temozolomide in patients with bevacizumab refractory recurrent high-grade gliomas. J Neurooncol 2021; 155: 297-306.
[130] You WC, Lee HD, Pan HC and Chen HC. Re-irradiation combined with bevacizumab for recurrent glioblastoma beyond bevacizumab failure: Survival outcomes and prognostic factors. Sci Rep 2023; 13: 9442.
[131] Yonezawa H, Ohno M, Igaki H, Miyakita Y, Takahashi M, Tamura Y, Shima S, Matsushita Y, Ichimura K and Narita Y. Outcomes of salvage fractionated re-irradiation combined with bevacizumab for recurrent high-grade gliomas that progressed after bevacizumab treatment*. Jpn J Clin Oncol 2021; 51: 1028-1035.
[132] Bergman D, Modh A, Schultz L, Snyder J, Mikkelsen T, Shah M, Ryu S, Siddiqui MS and Walbert T. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. J Neurooncol 2020; 148: 353-361.
[133] Iwamoto FM, Tanguturi SK, Nayak L, Wang TJ, Desai A, Lustig RA, Bagley S, Wong ET, Hertan LM, McCluskey C, Hayden J, Muzikansky A, Nakhawa S, Japo J, Bossi CC, Meylan M, Tian Y, Barlow GL, Speliakos P, Ayoub G, Meredith DM, Ligon KL, Haas-Kogan D, Huang K, Wucherpfennig KW, Wen PY and Reardon DA. Re-irradiation plus pembrolizumab: a phase ii study for patients with recurrent glioblastoma. Clin Cancer Res 2025; 31: 316-327.
[134] Pasqualetti F, Pace A, Gonnelli A, Villani V, Cantarella M, Delishaj D, Vivaldi C, Molinari A, Montrone S, Pellerino A, Franchino F, Baldaccini D, Lombardi G, Lolli I, Catania F, Bazzoli E, Morganti R, Fabi A, Zagonel V, Bocci G, Fabrini MG, Rudà R, Soffietti R and Paiar F. Single-agent bevacizumab in recurrent glioblastoma after second-line chemotherapy with fotemustine: the experience of the italian association of neuro-oncology. Am J Clin Oncol 2018; 41: 1272-1275.
[135] Wenger KJ, Wagner M, You SJ, Franz K, Harter PN, Burger MC, Voss M, Ronellenfitsch MW, Fokas E, Steinbach JP and Bähr O. Bevacizumab as a last-line treatment for glioblastoma following failure of radiotherapy, temozolomide and lomustine. Oncol Lett 2017; 14: 1141-1146.
[136] Brenner AJ, Floyd J, Fichtel L, Michalek J, Kanakia KP, Huang S, Reardon D, Wen PY and Lee EQ. Phase 2 trial of hypoxia activated evofosfamide (TH302) for treatment of recurrent bevacizumab-refractory glioblastoma. Sci Rep 2021; 11: 2306.
[137] Ahluwalia MS, Rogers LR, Chaudhary R, Newton H, Ozair A, Khosla AA, Nixon AB, Adams BJ, Seon BK, Peereboom DM and Theuer CP. Endoglin inhibitor TRC105 with or without bevacizumab for bevacizumab-refractory glioblastoma (ENDOT): a multicenter phase II trial. Commun Med (Lond) 2023; 3: 120.
[138] Ahluwalia MS, Ozair A, Drappatz J, Ye X, Peng S, Lee M, Rath S, Dhruv H, Hao Y, Berens ME, Walbert T, Holdhoff M, Lesser GJ, Cloughesy TF, Sloan AE, Takebe N, Couce M, Peereboom DM, Nabors B, Wen PY, Grossman SA and Rogers LR. Evaluating the base excision repair inhibitor TRC102 and temozolomide for patients with recurrent glioblastoma in the phase 2 adult brain tumor consortium trial BERT. Clin Cancer Res 2024; 30: 3167-3178.
[139] Takei J, Fukasawa N, Tanaka T, Yamamoto Y, Tamura R, Sasaki H, Akasaki Y, Kamata Y, Murahashi M, Shimoda M and Murayama Y. Impact of neoadjuvant bevacizumab on neuroradiographic response and histological findings related to tumor stemness and the hypoxic tumor microenvironment in glioblastoma: paired comparison between newly diagnosed and recurrent glioblastomas. Front Oncol 2022; 12: 898614.
[140] Scheer KG, Ebert LM, Samuel MS, Bonder CS and Gomez GA. Bevacizumab-induced hypertension in glioblastoma patients and its potential as a modulator of treatment response. Hypertension 2023; 80: 1590-1597.
[141] Hiller-Vallina S, Mondejar-Ruescas L, Caamaño-Moreno M, Cómitre-Mariano B, Alcivar-López D, Sepulveda JM, Hernández-Laín A, Pérez-Núñez Á, Segura-Collar B and Gargini R. Sexual-biased necroinflammation is revealed as a predictor of bevacizumab benefit in glioblastoma. Neuro Oncol 2024; 26: 1213-1227.
[142] Joshkon A, Tabouret E, Traboulsi W, Bachelier R, Simoncini S, Roffino S, Jiguet-Jiglaire C, Badran B, Guillet B, Foucault-Bertaud A, Leroyer AS, Dignat-George F, Chinot O, Fayyad-Kazan H, Bardin N and Blot-Chabaud M. Soluble CD146, a biomarker and a target for preventing resistance to anti-angiogenic thera-

py in glioblastoma. Acta Neuropathol Commun 2022; 10: 151.
[143] Lallemand C, Ferrando-Miguel R, Auer M, Iglseder S, Czech T, Gaber-Wagener A, Di Pauli F, Deisenhammer F and Tovey MG. Quantification of bevacizumab activity following treatment of patients with ovarian cancer or glioblastoma. Front Immunol 2020; 11: 515556.
[144] Carvalho B, Lopes JM, Silva R, Peixoto J, Leitão D, Soares P, Fernandes AC, Linhares P, Vaz R and Lima J. The role of c-Met and VEGFR2 in glioblastoma resistance to bevacizumab. Sci Rep 2021; 11: 6067.
[145] Schell M, Pflüger I, Brugnara G, Isensee F, Neuberger U, Foltyn M, Kessler T, Sahm F, Wick A, Nowosielski M, Heiland S, Weller M, Platten M, Maier-Hein KH, Von Deimling A, Van Den Bent MJ, Gorlia T, Wick W, Bendszus M and Kickingereder P. Validation of diffusion MRI phenotypes for predicting response to bevacizumab in recurrent glioblastoma: post-hoc analysis of the EORTC-26101 trial. Neuro Oncol 2020; 22: 1667-1676.
[146] Gilbert MR, Pugh SL, Aldape K, Sorensen AG, Mikkelsen T, Penas-Prado M, Bokstein F, Kwok Y, Lee RJ and Mehta M. NRG oncology RTOG 0625: a randomized phase II trial of bevacizumab with either irinotecan or dose-dense temozolomide in recurrent glioblastoma. J Neurooncol 2017; 131: 193-199.
[147] Desjardins A, Herndon JE, McSherry F, Ravelo A, Lipp ES, Healy P, Peters KB, Sampson JH, Randazzo D, Sommer N, Friedman AH and Friedman HS. Single-institution retrospective review of patients with recurrent glioblastoma treated with bevacizumab in clinical practice. Health Sci Rep 2019; 2: e114.
[148] Cloughesy TF, Petrecca K, Walbert T, Butowski N, Salacz M, Perry J, Damek D, Bota D, Bettegowda C, Zhu JJ, Iwamoto F, Placantonakis D, Kim L, Elder B, Kaptain G, Cachia D, Moshel Y, Brem S, Piccioni D, Landolfi J, Chen CC, Gruber H, Rao AR, Hogan D, Accomando W, Ostertag D, Montellano TT, Kheoh T, Kabbinavar F and Vogelbaum MA. Effect of vocimagene amiretrorepvec in combination with flucytosine vs standard of care on survival following tumor resection in patients with recurrent high-grade glioma: a randomized clinical trial. JAMA Oncol 2020; 6: 1939-1946.
[149] Detti B, Scoccianti S, Teriaca MA, Maragna V, Lorenzetti V, Lucidi S, Bellini C, Greto D, Desideri I and Livi L. Bevacizumab in recurrent high-grade glioma: a single institution retrospective analysis on 92 patients. Radiol Med 2021; 126: 1249-1254.
[150] Smolenschi C, Rassy E, Pallud J, Dezamis E, Copaciu R, Parker F, Garcia G, Lezghed N, Colomba E, Khettab M, Ammari S, Fekhi M, Martanovschi L, Benadhou L, Knafo S, Guyon D, Cheaib B, Dhermain F and Dumont SN. Bevacizumab in real-life patients with recurrent glioblastoma: benefit or futility? J Neurol 2023; 270: 2702-2714.
[151] Witte HM, Riecke A, Steinestel K, Schulz C, Küchler J, Gebauer N, Tronnier V and Leppert J. The addition of chloroquine and bevacizumab to standard radiochemotherapy for recurrent glioblastoma multiforme. Br J Neurosurg 2024; 38: 404-410.
[152] Lee Y, Lee E, Roh TH and Kim SH. Bevacizumab alone versus bevacizumab plus irinotecan in patients with recurrent glioblastoma: a nationwide population-based study. J Korean Med Sci 2024; 39: e244.
[153] Puduvalli VK, Wu J, Yuan Y, Armstrong TS, Vera E, Wu J, Xu J, Giglio P, Colman H, Walbert T, Raizer J, Groves MD, Tran D, Iwamoto F, Avgeropoulos N, Paleologos N, Fink K, Peereboom D, Chamberlain M, Merrell R, Penas Prado M, Yung WKA and Gilbert MR. A Bayesian adaptive randomized phase II multicenter trial of bevacizumab with or without vorinostat in adults with recurrent glioblastoma. Neuro Oncol 2020; 22: 1505-1515.
[154] Lee EQ, Zhang P, Wen PY, Gerstner ER, Reardon DA, Aldape KD, deGroot JF, Pan E, Raizer JJ, Kim LJ, Chmura SJ, Robins HI, Connelly JM, Battiste JD, Villano JL, Wagle N, Merrell RT, Wendland MM and Mehta MP. NRG/RTOG 1122: a phase 2, double-blinded, placebo-controlled study of bevacizumab with and without trebananib in patients with recurrent glioblastoma or gliosarcoma. Cancer 2020; 126: 2821-2828.
[155] McCrea HJ, Ivanidze J, O'Connor A, Hersh EH, Boockvar JA, Gobin YP, Knopman J and Greenfield JP. Intraarterial delivery of bevacizumab and cetuximab utilizing blood-brain barrier disruption in children with high-grade glioma and diffuse intrinsic pontine glioma: results of a phase I trial. J Neurosurg Pediatr 2021; 28: 371-379.
[156] Galanis E, Anderson SK, Twohy E, Butowski NA, Hormigo A, Schiff D, Omuro A, Jaeckle KA, Kumar S, Kaufmann TJ, Geyer S, Kumthekar PU, Campian J, Giannini C, Buckner JC and Wen PY. Phase I/randomized phase II trial of TRC105 plus bevacizumab versus bevacizumab in recurrent glioblastoma: North Central Cancer Treatment Group N1174 (Alliance). Neurooncol Adv 2022; 4: vdac041.
[157] Cardona AF, Jaramillo-Velásquez D, Ruiz-Patiño A, Polo C, Jiménez E, Hakim F, Gómez D, Ramón JF, Cifuentes H, Mejía JA, Salguero F, Ordoñez C, Muñoz Á, Bermúdez S, Useche N, Pineda D, Ricaurte L, Zatarain-Barrón ZL, Rodríguez J, Avila J, Rojas L, Jaller E, Sotelo C,

Garcia-Robledo JE, Santoyo N, Rolfo C, Rosell R and Arrieta O. Efficacy of osimertinib plus bevacizumab in glioblastoma patients with simultaneous EGFR amplification and EGFRvIII mutation. J Neurooncol 2021; 154: 353-364.

[158] Bota DA, Taylor TH, Lomeli N, Kong XT, Fu BD, Schönthal AH, Singer S, Blumenthal DT, Senecal FM, Linardou H, Rokas E, Antoniou DG, Schijns VEJC, Chen TC, Elliot J and Stathopoulos A. A prospective, cohort study of SITOIGA-NAP to treat glioblastoma when given in combination with granulocyte-macrophage colony-stimulating factor/cyclophosphamide/bevacizumab/nivolumab or granulocyte-macrophage colony-stimulating factor/cyclophosphamide/bevacizumab/pembrolizumab in patients who failed prior treatment with surgical resection, radiation, and temozolomide. Front Oncol 2022; 12: 934638.

[159] Ahluwalia MS, Rauf Y, Li H, Wen PY, Peereboom DM and Reardon DA. Randomized phase 2 study of nivolumab (nivo) plus either standard or reduced dose bevacizumab (bev) in recurrent glioblastoma (rGBM). J Clin Oncol 2021; 39: 2015-2015.

[160] She L, Su L and Liu C. Bevacizumab combined with re-irradiation in recurrent glioblastoma. Front Oncol 2022; 12: 961014.

[161] Zhang JF, Okai B, Iovoli A, Goulenko V, Attwood K, Lim J, Hess RM, Abad AP, Prasad D and Fenstermaker RA. Bevacizumab and gamma knife radiosurgery for first-recurrence glioblastoma. J Neurooncol 2024; 166: 89-98.

[162] Mantica M, Drappatz J, Lieberman F, Hadjipanayis CG, Lunsford LD and Niranjan A. Phase II study of border zone stereotactic radiosurgery with bevacizumab in patients with recurrent or progressive glioblastoma multiforme. J Neurooncol 2023; 164: 179-190.

[163] Morris SL, Zhu P, Rao M, Martir M, Zhu JJ, Hsu S, Ballester LY, Day AL, Tandon N, Kim DH, Shepard S, Blanco A and Esquenazi Y. Gamma knife stereotactic radiosurgery in combination with bevacizumab for recurrent glioblastoma. World Neurosurg 2019; 127: e523-e533.

[164] Abbassy M, Missios S, Barnett GH, Brewer C, Peereboom DM, Ahluwalia M, Neyman G, Chao ST, Suh JH and Vogelbaum MA. Phase I trial of radiosurgery dose escalation plus bevacizumab in patients with recurrent/progressive glioblastoma. Neurosurgery 2018; 83: 385-392.

[165] Herrlinger U, Schäfer N, Steinbach JP, Weyerbrock A, Hau P, Goldbrunner R, Friedrich F, Rohde V, Ringel F, Schlegel U, Sabel M, Ronellenfitsch MW, Uhl M, Maciaczyk J, Grau S, Schnell O, Hänel M, Krex D, Vajkoczy P, Gerlach R, Kortmann RD, Mehdorn M, Tüttenberg J, Mayer-Steinacker R, Fietkau R, Brehmer S, Mack F, Stuplich M, Kebir S, Kohnen R, Dunkl E, Leutgeb B, Proescholdt M, Pietsch T, Urbach H, Belka C, Stummer W and Glas M. Bevacizumab plus irinotecan versus temozolomide in newly diagnosed O^6-methylguanine-DNA methyltransferase nonmethylated glioblastoma: the randomized GLARIUS trial. JCO 2016; 34: 1611-1619.

[166] Nagane M, Ichimura K, Onuki R, Narushima D, Honda-Kitahara M, Satomi K, Tomiyama A, Arai Y, Shibata T, Narita Y, Uzuka T, Nakamura H, Nakada M, Arakawa Y, Ohnishi T, Mukasa A, Tanaka S, Wakabayashi T, Aoki T, Aoki S, Shibui S, Matsutani M, Ishizawa K, Yokoo H, Suzuki H, Morita S, Kato M and Nishikawa R. Bevacizumab beyond progression for newly diagnosed glioblastoma (BIOMARK): phase II safety, efficacy and biomarker study. Cancers (Basel) 2022; 14: 5522.

[167] Matsuda KI, Sakurada K, Nemoto K, Kayama T and Sonoda Y. Treatment outcomes of hypofractionated radiotherapy combined with temozolomide followed by bevacizumab salvage therapy in glioblastoma patients aged > 75 years. Int J Clin Oncol 2018; 23: 820-825.

[168] Kanamori M, Shibahara I, Shimoda Y, Akiyama Y, Beppu T, Ohba S, Enomoto T, Ono T, Mitobe Y, Hanihara M, Mineharu Y, Ishida J, Asano K, Yoshida Y, Natsumeda M, Nomura S, Abe T, Yonezawa H, Katakura R, Shibui S, Kuroiwa T, Suzuki H, Takei H, Matsushita H, Saito R, Arakawa Y, Sonoda Y, Hirose Y, Kumabe T, Yamaguchi T, Endo H and Tominaga T. Efficacy and safety of carmustine wafers, followed by radiation, temozolomide, and bevacizumab therapy, for newly diagnosed glioblastoma with maximal resection. Int J Clin Oncol 2025; 30: 51-61.

[169] Tanaka T, Tamura R, Takei J, Morimoto Y, Teshigawara A, Yamamoto Y, Imai R, Kuranari Y, Tohmoto K, Hasegawa Y, Akasaki Y, Murayama Y, Miyake K and Sasaki H. An exploratory prospective phase II study of preoperative neoadjuvant bevacizumab and temozolomide for newly diagnosed glioblastoma. J Neurooncol 2024; 166: 557-567.

[170] Strauss JD, Gilbert MR, Mehta M, Li A, Zhou R, Bondy ML, Sulman EP, Yuan Y, Liu Y, Vera E, Wendland MM, Stieber VW, Puduvalli VK, Choi S, Martinez NL, Robins HI, Hunter GK, Lin CF, Guedes VA, Richard MA, Pugh SL, Armstrong TS and Scheurer ME. Clinical and genetic markers of vascular toxicity in glioblastoma patients: insights from NRG Oncology RTOG-0825. Neuro Oncol 2025; 27: 767-778.

[171] Kessler T, Schrimpf D, Doerner L, Hai L, Kaulen LD, Ito J, van den Bent M, Taphoorn M, Brandes AA, Idbaih A, Dômont J, Clement PM, Campone M, Bendszus M, von Deimling A, Sahm F, Platten M, Wick W and Wick A. Prognostic markers

of DNA methylation and next-generation sequencing in progressive glioblastoma from the EORTC-26101 trial. Clin Cancer Res 2023; 29: 3892-3900.

[172] Kim M, Park JE, Yoon SK, Kim N, Kim YH, Kim JH and Kim HS. Vessel size and perfusion-derived vascular habitat refines prediction of treatment failure to bevacizumab in recurrent glioblastomas: validation in a prospective cohort. Eur Radiol 2023; 33: 4475-4485.

[173] Breda-Yepes M, Rodríguez-Hernández LA, Gómez-Figueroa E, Mondragón-Soto MG, Arellano-Flores G, Hernández-Hernández A, Rodríguez-Rubio HA, Martínez P, Reyes-Moreno I, Álvaro-Heredia JA, Gutiérrez Aceves GA, Villanueva-Castro E, Sangrador-Deitos MV, Alonso-Vanegas M, Guerrero-Juárez V and González-Aguilar A. Relative cerebral blood volume as response predictor in the treatment of recurrent glioblastoma with anti-angiogenic therapy. Clin Neurol Neurosurg 2023; 233: 107904.

[174] Ellingson BM, Hagiwara A, Morris CJ, Cho NS, Oshima S, Sanvito F, Oughourlian TC, Telesca D, Raymond C, Abrey LE, Garcia J, Aftab DT, Hessel C, Rachmilewitz Minei T, Harats D, Nathanson DA, Wen PY and Cloughesy TF. Depth of radiographic response and time to tumor regrowth predicts overall survival following anti-VEGF therapy in recurrent glioblastoma. Clin Cancer Res 2023; 29: 4186-4195.

[175] Jiguet-Jiglaire C, Boissonneau S, Denicolai E, Hein V, Lasseur R, Garcia J, Romain S, Appay R, Graillon T, Mason W, Carpentier AF, Brandes AA, Ouafik L', Wick W, Baaziz A, Gigan JP, Argüello RJ, Figarella-Branger D, Chinot O and Tabouret E. Plasmatic MMP9 released from tumor-infiltrating neutrophils is predictive for bevacizumab efficacy in glioblastoma patients: an AVAglio ancillary study. Acta Neuropathol Commun 2022; 10: 1.