Curr. Treat. Options in Oncol. (2016) 17: 49
DOI 10.1007/s11864-016-0422-4

Neuro-oncology (GJ Lesser, Section Editor)

Relapsed Glioblastoma: Treatment Strategies for Initial and Subsequent Recurrences

Alicia Tosoni, MD
Enrico Franceschi, MD
Rosalba Poggi, MD
Alba A. Brandes, MD[*]

Address
[*]Department of Medical Oncology, Bellaria Hospital, Azienda USL—IRCCS Institute of Neurological Sciences, Via Altura 4, Bologna, Italy
Email: alba.brandes@yahoo.it

Published online: 26 July 2016

This article is part of the Topical Collection on *Neuro-oncology*

Keywords Recurrent glioblastoma · Treatment · Chemotherapy · Radiotherapy · Surgery

Opinion Statement

At the time of glioblastoma (GBM) recurrence, a sharp analysis of prognostic factors, disease characteristics, response to adjuvant treatment, and clinical conditions should be performed. A prognostic assessment could allow a careful selection between patients that could be proposed to intensified approaches or palliative setting. Participation in clinical trials aims to improve outcome, and should be encouraged due to dismal prognosis of GBM patients after recurrence. Reoperation should be proposed if the tumor is amenable to a complete resection and if prognostic factors suggest that patient could benefit from a second surgery. Second-line chemotherapy should be chosen based on MGMT status, time to disease recurrence, and toxicity profile. If enrollment into a clinical trial is not possible, a nitrosourea-based regimen is the preferred choice, carefully evaluating any previous temozolomide (TMZ)-related toxicity. In MGMT-methylated patients relapsing after TMZ completion, a rechallenge could be proposed. After second progression, the clinical advantage of subsequent lines of chemotherapy still needs to be clarified. However, based on performance status, patients' preference, and disease behavior, a third-line treatment could be considered. Available treatments include nitrosoureas, bevacizumab, or carboplatin plus etoposide. However, more effective therapeutic options are needed.

Introduction

Glioblastoma is the most common malignant brain cancer in adults; despite surgery and chemoradiation, all patients experience relapse with a median survival of 12–15 months from initial diagnosis [1].

At recurrence, no standard approach has been established. Therapeutic options have to be carefully weighted taking into account tumor size and location, previous treatments, performance status (PS), and prognostic factors.

Two North American studies were conducted to identify prognostic factors in recurrent high-grade glioma patients enrolled in phase I–II clinical trials. The NABTT analysis, performed on 333 patients, found that age, KPS, and corticosteroids at baseline were important prognostic factors for survival in glioblastoma (GBM) patients [2•]. In particular, results of the recursive partitioning analysis divided GBM patients in four categories with median survival ranging from 10.4 months (patients younger than 50 with KPS 90–100) to 4.9 months (patients older than 50 with steroid use at baseline). Similarly, NCCTG-NABTC analysis on 596 high-grade patients, found grade, age, PS, baseline steroids, and time from initial diagnosis as most influential factors for survival [3•].

A pooled analysis of EORTC trials on 300 recurrent GBM patients confirmed these findings [4•]. The report identified poor PS and more than one target lesion as significant negative prognostic factors for both progression free survival (PFS) and survival. Patients with tumors larger than 42 mm and treated with steroids at baseline had shorter survival, whereas tumors with predominant frontal locations had better survival.

These models provide objective information to physicians, patients and their families, and needs to be discussed in order to identify the best therapeutic strategy at the time of recurrence.

Surgical resection in recurrent GBM

Many retrospective studies have demonstrated that in newly diagnosed GBM, the extent of surgical resection of the enhancing tumor is associated with a longer survival [5, 6]. However, even if at time of recurrence, surgical resection relieves symptoms related to mass effect, whether its role in prolonging survival remains controversial.

The Glioma Outcome Project prospectively analyzed the morbidity of second surgery. Perioperative complications occurred in 33 % of patients, 18 % displayed a worsened neurological status, 10 % had seizures, and intracranial bleeding and systemic infection both occurred in 4 % of patients. Depression occurred in 20 % of patients, and the perioperative mortality rate was 2.2 % [7]. Postoperative complications could delay or even prevent further lines of chemotherapy. Nevertheless, some patients with recurrent GBM can benefit from reoperation.

A prognostic preoperative scale based on patients who underwent reoperation for recurrent GBM was developed by NIH [8]. This scale, combining data on tumor involvement of eloquent/critical brain regions, KPS (> or ≤80), and tumor volume (< or ≥50 cm^3), identified patients likely to have poor (1 month), intermediate (4.5 months), and good (10.8 months) survival. However, the estimation of the eloquent/critical area and the measurement of tumor volume could be a subjective variable parameter. For this reason, another group few years later proposed a simplified preoperation scale based on KPS and ependymal involvement distinguishing patients with good (18 months), intermediate (10 months), and poor (4 months) survival [9].

Retrospective studies on large series of patients provide contradictory results with respect to the survival benefit of a surgical resection [10–13]. Patient characteristics, treatment profile, and measure of postsurgical residual tumor vary considerably between studies.

A literature review on this topic suggests a survival benefit in high-grade glioma patients receiving a reoperation at the time of recurrence, indicating time interval of at least 6 months between operations, favorable PS, and extent of resection as important predictors of benefit [14].

Brandes et al. recently published one of the largest studies of 270 consecutive patients who received second surgery for GBM. All patients have been treated with concomitant and adjuvant temozolomide (TMZ) and underwent postoperative CT scan within 48 h of surgery to determine the extent of tumor resection. Median survival from second surgery was 11.4 months and was influenced by the extension of surgery (gross total resection: 15.4 months; partial resection: 9.0 months), and O-6-methylguanine-DNA methyltransferase (MGMT) methylation at first surgery (MGMT methylated: 13.8 months, MGMT unmethylated: 10.0 months) [11•].

The Director trial evaluated the efficacy and tolerability of two different TMZ schedules at first progression. A post hoc analysis was made on the correlation between the extent of resection and outcome in GBM patients who underwent second surgery prior to randomization (68 % of enrolled patients). Extent of surgery was evaluated with MRI volumetrics within 72 h after surgery. Complete resection of enhancing tumor was achieved in 67.8 % of patients. The gross total resection was associated with a longer post-recurrence survival (12.9 months), compared to patients with partial surgery (6.5 months). However, patients who received partial surgery showed a trend to a worse survival compared to non-reoperated patients (6.5 vs 9.8 months, $p = 0.52$) [15•].

In conclusion, data suggest that reoperation can be an option if a gross total resection can be achieved, and accordingly, to prognostic preoperative scales.

Reirradiation

Although radiation is proven to be effective in GBM, the second course of radiotherapy has been applied reluctantly with conventional techniques as treatment outcome outweighs the risk of treatment-related side effects. In fact, the dose of 60 Gy typically applied in the first-line treatment generally hampers the use of a second full-dose radiotherapy course. Lack of prospective and randomized trials and high probability of selection bias in single-arm studies increase the concerns about safety and efficacy at recurrence after initial irradiation.

Systemic chemotherapy

Chemotherapy is probably the most used salvage treatment in recurrent setting. The interval between the end of adjuvant treatment and progression and toxicity profile are important variables to consider. Outcome after second-line treatments is poor with reported median PFS of 1.8 months and median overall survival (OS) of 6.2 months (Table 1) [4•].

Nitrosoureas

Nitrosoureas are standard treatment and are considered as control arm in randomized trials in recurrent GBM (Table 1). Their toxicity profile in

Table 1. Selected randomized studies in recurrent GBM

Author	Study type	Treatment	Nr of pts	PFS months	OS months
		TKI randomized studies			
Van den Bent	Phase II	BCNU/TMZ	54	2.4	7.3
		Erlotinib	54	1.8	7.7
Brandes	Phase II	CCNU + placebo	40	1.9	7.5
		Galunisertib	39	1.9	8
		Galunisertib + CCNU	79	1.8	6.7
Wick	Phase III	CCNU	84	1.6	7.1
		Ezastaurin	167	1.5	6.6
Batchelor	Phase III	Cediranib	128	3	8
		Cediranib + CCNU	123	4.1	9.4
		CCNU + placebo	64	2.7	9.8
		Bevacizumab randomized studies			
Friedman	Phase II	Bevacizumab	85	4.2	9.2
		Bevacizumab + CPT-11	82	5.6	8.7
Taal	Phase II	Bevacizumab	50	3	8
		CCNU	46	1	8
		CCNU + bevacizumab	52	4	12
Wick[a]	Phase III	CCNU	NR	1.5	8.6
		CCNU + bevacizumab	NR	4.2	9.1
Field	Phase II	Carboplatin + bevacizumab	60	3.5	6.9
		Bevacizumab	62	3.5	7.5
Brandes	Phase II	Fotemustine	32	3.4	8.7
		Bevacizumab	59	3.4	7.3
		TMZ rechallenge randomized studies			
Weller	Phase II	TMZ1 wk on/1 wk off	52	1.8	9.8
		TMZ3 wk on/1 wk off	53	2	10.6

The table summarizes selected randomized phase II and phase III studies on recurrent GBM discussed in the text
[a]Abstract

pretreated patients could be challenging, leading to grade 3–4 hematological toxicity, often causing treatment delays and discontinuation [16].

Lomustine (CCNU) demonstrated in phase II–III randomized studies a median PFS of 1–2.7 months and a median survival of 7.1–9.8 months [17–20]. An aspect that is worth mentioning is that, throughout the years, a progressive increase of survival in patients treated with CCNU at recurrence has been observed in the clinical trials [16]. This is probably due to an increasing efficacy of post-progression treatments, and in a better disease-related complications management, thus leading to improvement over years.

Fotemustine is an intravenous nitrosourea that has recently gained a role in the treatment of recurrent GBM, especially in Europe, where it is widely used in clinical practice [16].

A prospective multicenter phase II study by Brandes et al. [21] evaluated fotemustine (induction schedule 75 mg/mq on days 1–8–15 and maintenance with 100 mg/m^2 q 3 weeks) on 43 patients with recurrent GBM after standard radiotherapy and TMZ. PFS at 6 months (PFS-6) was 20.9 %, response rate (RR) was 7 %, and OS was 6 months. Disease control rate was higher in patients with methylated MGMT, while no difference in PFS-6 was seen between methylated and unmethylated tumors. The planned dose of induction at the beginning of the study was 100 mg/m^2 on days 1–8–15 (according to the licensing instructions for the drug). However, the protocol was amended to reduce fotemustine induction dose to 75 mg/m^2 because the first three patients experienced grade 4 thrombocytopenia during induction therapy. Fotemustine was the control arm in a randomized phase II study and showed a median PFS and OS of of 3.4 and 8.7 months, respectively [22]. Compared to other nitrosoureas, fotemustine is not associated with cumulative lung toxicity, which does not limit the number of administrations that can be delivered. The most important side effect is represented by long-lasting thrombocytopenia [16].

Temozolomide rechallenge

Alternative schedules of TMZ were developed to increase dose intensity aiming at overcoming TMZ resistance [23••]. The main alternative schedules were continuous slow dose (50 mg/m^2 daily), 1 week on/1 week off (150 mg/m^2 for 7 days every 14 days), and 3 weeks on/1 week off (75–100 mg/m^2 for 21 days every 28 days). In the Director trial [24••], 105 patients with GBM at first recurrence at least 3 months after the end of RT were randomized to two different TMZ schedules: 1 week on (120 mg/m^2 per day)/1 week off or 3 weeks on (80 mg/m^2 per day)/1 week off. There was a similar outcome in both arms for median time to treatment failure (1.8 vs 2.0 months) and OS (9.8 vs 10.6 months), showing no differences between the two dosing regimens, regarding either efficacy, safety, or tolerability. The most important result of this trial was the strong prognostic role of the MGMT promoter methylation status in patients rechallenged with TMZ, PFS-6 being 39.7 % in patients with methylated MGMT versus 6.9 % in patients without MGMT promoter methylation. An analysis was performed by interval of pre-exposure to TMZ (intervals below or above 2 months), demonstrating a significantly improved outcome in patients with a longer delay from previous TMZ, and largely confined to patients with MGMT methylated patients.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKI) therapy has been widely tested in all tumor types.

EGFR is amplified in 40 % of primary GBM patients whereas is absent in secondary GBM, being mutually exclusive with IDH 1/2 mutation. Half EGFR-amplified patients express EGFRvIII constitutively active ligand-independent mutant receptor [25].

Only one randomized phase II study has been conducted with EGFR TKIs in recurrent GBM patients. In this study, no significant activity of erlotinib was observed in unselected patients [26].

Other TKI inhibitors tested in randomized phase II–III studies, such as cediranib, an oral pan VEGFR TKI [19], or enzastaurin [17] directed against protein kinase C and the PI3K/AKT pathways, used alone or in combination with chemotherapy, demonstrated no difference in activity compared to CCNU alone.

Small molecule inhibitor of the TGF-ß signaling galunisertib, evaluated in randomized phase II–III studies, failed to demonstrate improved OS over standard chemotherapy in recurrent GBM [18].

Bevacizumab

Bevacizumab is a monoclonal antibody that binds to circulating VEGF-A and inhibits its biological activity by preventing the interaction with the VEGF receptor. This leads to a reduction in endothelial proliferation and vascular growth within the tumor. Uncontrolled trials showed promising results in recurrent GBM with impressive PFS-6 of 29–46 % [27–29].

These studies were followed by a randomized, phase II trial by Friedman et al. (the BRAIN trial) [30] in which 167 patients were randomized to receive bevacizumab alone or in association with irinotecan. In the bevacizumab-alone and the bevacizumab plus irinotecan groups, RR were 28.2 and 37.8 % and PFS-6 rates were 42.6 and 50.3 %, respectively, and median OS times were 9.2 and 8.7 months, respectively. However, this trial does not provide a direct comparison with standard chemotherapy (i.e., nitrosoureas).

The studies by Friedman and Kreisl led to the US FDA conditional approval of bevacizumab in USA. The EMA did not approve bevacizumab in this setting because the results from randomized phase II trials, without direct comparison with standard chemotherapy, were not considered sufficient, and due to weak criteria of eligibility and response evaluation.

The BELOB trial [20] was a phase II study that randomized 153 patients to receive bevacizumab alone or in combination with CCNU, or CCNU alone. Results showed median OS of 8 months in CCNU and bevacizumab arms while it reached 12 months in the combination arm. Overall, this study showed that the outcome of patients treated with bevacizumab alone or CCNU was similar, while an advantage in outcome was suggested in the combination of the two agents.

A recent multicenter randomized phase II randomized study AVAREG [22] evaluated bevacizumab or fotemustine on 91 patients with recurrent GBM. The results of the study showed a similar activity of bevacizumab and fotemustine. In particular, median OS was 7.3 months in the bevacizumab arm and 8.7 months in the fotemustine arm, while PFS-6 was 26.3 and 10.7 %, respectively.

The results of another randomized phase II trial have been recently reported [31]. In this trial, 122 patients with recurrent GBM were randomized to receive bevacizumab alone or in combination with carboplatin. Median PFS was 3.5 months for each arm. Median OS was 6.9 (combination) versus 7.5 months (monotherapy). Toxicities were higher in the combination arm. The study demonstrated that adding carboplatin resulted in more toxicity without additional

clinical benefit and furthermore showed outcome results that were far inferior from those obtained in other studies.

The hypothesis generated by the BELOB trial that the bevacizumab + CCNU arm may produce an overall survival benefit compared to either monotherapy was unfortunately not confirmed by the subsequent phase III trial (EORTC 26101, 32••]. This study randomized 437 patients to bevacizumab + CCNU versus CCNU, obtaining a significant difference in PFS (HR 0.49, CI 0.39–0.61) but no difference in OS (HR 0.95, 0.74–1.21). A Cochrane systemic review was published on the role of antiangiogenic therapy in high-grade glioma. Pooled HR for PFS for bevacizumab studies (three studies with 1712 participants) was significant at 0.66 (95 % CI 0.59 to 0.74; *P* value <0.00001), Nevertheless, this finding was not significant for OS (HR 0.92, 95 % CI 0.83 to 1.02; *P* value 0.12) [33].

Bevacizumab gives significant radiographic and, sometimes, clinical benefit in patients treated for recurrent GBM. However, the lack of survival benefit, as well as the significant cost and potential toxicities, has raised controversy about the future role of this drug in the management of GBM [34].

In order to explore the efficacy of bevacizumab beyond the second line of treatment, Piccioni et al. made a retrospective analysis on 468 GBM patients stratified according to the time of initiation of bevacizumab (upfront, first recurrence, second recurrence, or further). The authors found that PFS and OS were similar for all three recurrence groups (median: 4.1 and 9.8 months, respectively) [35]. The data from the studies seem to suggest that bevacizumab could have a role in the treatment of GBM independently of the line of treatment and that a delayed administration of the agent does not affect its efficacy. Bevacizumab is administered in GBM patients at the dose of 10 mg/kg every 2 weeks, but, at present, there is no evidence that supports the use of this schedule or another.

Levin et al. [36] reviewed data from 181 patients treated with different doses of bevacizumab for GBM in a single institution. The authors calculated the bevacizumab AUC (AUCBEV) and compared it to the outcome. In the study, the value of AUCBEV had an impact on OS (OS was 60 weeks for those treated at <3.6 mg per week/kg and 45 weeks for those treated with >3.6 mg per week/kg). Interestingly, no difference in toxicity was observed according to the dose received. The authors concluded that their data suggest that doses of bevacizumab lower than those recommended could determine an improvement in outcome. An explanation for the phenomenon observed could not be found. A meta-analysis of 18 publications of patients with malignant gliomas treated with bevacizumab showed no dose-response benefit comparing 10–15 mg/kg dose cohorts (462 patients) with 5 mg/kg dosing (86 patients). There were no significant differences in progression-free survival, overall survival, or in disease response [37]. Another retrospective study reviewed 162 recurrent GBM patients treated with two different bevacizumab schedules 5 and 10 mg/kg every 2 weeks. There was no significant difference in OS or PFS between the groups treated with bevacizumab 5 versus 10 mg/kg. There were more adverse events seen with bevacizumab 10 mg/kg. Therefore, what is the optimal dose and schedule of administration of bevacizumab in GBM remains an open question [38, 39].

The future challenge should be the identification of potential biomarkers able to predict the response to bevacizumab in GBM, even if at present neither markers of endothelial proliferation nor expression of microvascular density

signature genes has reliably predicted bevacizumab efficacy across indications [40].

Molecular profiling was performed in phase III randomized trials comparing chemoradiation with or without bevacizumab in patients with newly diagnosed GBM [40, 41]. Mesenchymal subtype was associated with worse outcome in GBM patients treated with bevacizumab in association with temozolomide and radiotherapy [41]. Sandman et al. [40] showed that adding bevacizumab to standard therapy conferred a significantly longer OS for patients with proneural IDH1 wild-type tumors (17.1 vs 12.2 months; HR: 0.42; $p = 0.002$).

Similarly, a gene expression profile from participants to the BELOB trial was retrospectively performed, demonstrating a significant benefit in PFS and a trend towards OS only in classical GBM subtype. An important limitation of this study is the use of primary tumor tissue [42].

The difference among these studies could be explained by the dismal prognosis of proneural IDH 1 wild-type tumor that often are not offered second-line treatment due to worse prognosis.

Immunotherapy

Immunotherapy with CTLA-4 inhibitor ipililumab and anti-PD-1 antibodies nivolumab and pembrolizumab has recently obtained encouraging results in metastatic melanoma. These results have prompted the development of a series of clinical studies in various types of solid tumors. For neuro-oncology, recent data demonstrated an interaction of the immune system between systemic and CNS compartments [43].

Safety of the checkpoint inhibitors nivolumab (NIVO) and ipilimumab (IPI) has been investigated in GBM patients at first recurrence [44]. The study randomized 20 patients to receive NIVO or NIVO + IPI followed by NIVO, demonstrating a considerable toxicity in the combination arm with 80 % of patients reporting grade 3 or 4 adverse events and 50 % of patients discontinuing therapy for toxicity (including colitis, cholecystitis, diabetic ketoacidosis, confusion, and increased lipase). An encouraging clinical outcome (OS at 6 months of 75 %) was reported. The subsequent phase III study comparing single agent NIVO with bevacizumab in patients with recurrent GBM has completed accrual, and we are waiting for the results.

Different vaccination approaches against GBM have been studied. Epidermal growth factor variant type III (EGFRvIII) is a deletion mutation that generates a novel extracellular tumor-specific epitope that is heterogeneously expressed in 30–35 % of primary GBM [45]. The efficacy of rindopepimut, a peptide vaccine targeting EGFRvIII, has been assessed in a randomized phase II study in which 72 GBM patients at first or second recurrence were randomized to receive bevacizumab plus double-blinded injection of rindopepimut or control (KLH) [46]. The combination arm obtained an increase in PFS-6 (27 vs 11 %) and OS (12.0 vs 8.8 months). However, a randomized phase III study, adding rindopepimut versus GMCSF (control) to adjuvant TMZ in newly diagnosed GBM, has been prematurely closed due to not reaching the prespecified end points.

Another immunization approach has leveraged heat shock proteins (HSP). In a phase I study, HSP-96 was purified from autologous tumor and pulsed

onto patient APCs and then administered as an autologous vaccine to patients with resectable recurrent GBM [47].

In the subsequent phase 2 single-arm study, 41 recurrent GBM patients were treated obtaining a 6 months OS of 90.2 % with decreased OS in patients with reduced lymphocyte count [48]. A randomized phase III trial within the Alliance Consortium is ongoing comparing the use of heat-shock protein peptide complex-96 (HSPCC-96) administered concomitantly to bevacizumab or at the time of progression when compared with bevacizumab alone in patients with resected recurrent GBM.

Dendritic cell-based therapy requires the isolation of patient-derived monocytes, followed by ex vivo amplification, maturation, and subsequent exposure to a source of tumor antigens. No randomized studies have been conducted in the recurrent setting.

Third-line treatments

After second progression, the clinical advantage of subsequent lines of chemotherapy still needs to be clarified. However, based on previous treatments, performance status, patients' preference, and disease behavior, a third-line treatment could be considered.

Available treatments include TMZ rechallenge, nitrosoureas, and bevacizumab. Bevacizumab could have a role in the treatment of GBM at recurrence independently of the line of treatment. Carboplatin plus etoposide could be an option, taking into account toxicities from previous treatments, due to an unfavorable risk-benefit profile in heavily pretreated glioma patients [49].

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
2•. Carson KA, Grossman SA, Fisher JD, Shaw EG. Prognostic factors for survival in adult patients with recurrent glioma enrolled onto the new approaches to brain tumor therapy CNS consortium phase I and II clinical trials. J Clin Oncol. 2007;25(18):2601–6.
3•. Wu W, Lamborn KR, Buckner JC, Novotny PJ, Chang SM, O'Fallon JR, et al. Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma.

Neuro-Oncology. 2010;12(2):164–72. doi:10.1093/neuonc/nop019.

4•. Gorlia T, Stupp R, Brandes AA, Rampling RR, Fumoleau P, Dittrich C, et al. New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: a pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials. Eur J Cancer. 2012;48(8):1176–84. doi:10.1016/j.ejca.2012.02.004 .

These three studies analized the role of prognostic factors in large series of GBM recurrent patients

5. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001;95(2):190–8.

6. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg. 2011;115(1):3–8. doi:10.3171/2011.2.JNS10998.

7. Chang SM, Parney IF, McDermott M, Barker 2nd FG, Schmidt MH, Huang W, et al. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg. 2003;98(6):1175–81. doi:10.3171/jns.2003.98.6.1175.

8. Park JK, Hodges T, Arko L, Shen M, Dello Iacono D, McNabb A, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol Off J Am Soc Clin Oncol. 2010;28(24):3838–43. doi:10.1200/JCO.2010.30.0582.

9. Park CK, Kim JH, Nam DH, Kim CY, Chung SB, Kim YH, et al. A practical scoring system to determine whether to proceed with surgical resection in recurrent glioblastoma. Neuro-Oncology. 2013;15(8):1096–101. doi:10.1093/neuonc/not069.

10. Nava F, Tramacere I, Fittipaldo A, Bruzzone MG, Dimeco F, Fariselli L, et al. Survival effect of first- and second-line treatments for patients with primary glioblastoma: a cohort study from a prospective registry, 1997-2010. Neuro-Oncology. 2014;16(5):719–27. doi:10.1093/neuonc/not316.

11•. Brandes AA, Bartolotti M, Tosoni A, Poggi R, Bartolini S, Paccapelo A, et al. Patient outcomes following second surgery for recurrent glioblastoma. Future Oncol. 2016;12(8):1039–44. doi:10.2217/fon.16.9 .

This study conducted in a large series of GBM patients reoperated at recurrence demonstrated that extent of resection and MGMT methylation status were correlated with survival

12. Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, et al. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro-Oncology. 2016;18(1):96–104. doi:10.1093/neuonc/nov145.

13. Clarke JL, Ennis MM, Yung WK, Chang SM, Wen PY, Cloughesy TF, et al. Is surgery at progression a prognostic marker for improved 6-month progression-free survival or overall survival for patients with recurrent glioblastoma? Neuro-Oncology. 2011;13(10):1118–24. doi:10.1093/neuonc/nor110.

14. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. Neurosurgery. 2014;75(5):491–9 . doi:10.1227/NEU.0000000000000486.discussion 8-9

15•. Suchorska B, Weller M, Tabatabai G, Senft C, Hau P, Sabel MC, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro-Oncology. 2016;18(4):549–56. doi:10.1093/neuonc/nov326 .

The study demonstrated that complete resection was associated with improved survival in GBM reoperated patients

16. Brandes AA, Bartolotti M, Tosoni A, Franceschi E. Nitrosoureas in the Management of Malignant Gliomas. Curr Neurol Neurosci Rep. 2016;16(2):13. doi:10.1007/s11910-015-0611-8.

17. Wick W, Puduvalli VK, Chamberlain MC, van den Bent MJ, Carpentier AF, Cher LM, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol. 2010;28(7):1168–74. doi:10.1200/JCO.2009.23.2595.

18. Brandes AA, Carpentier AF, Kesari S, Sepulveda-Sanchez JM, Wheeler HR, Chinot O, et al. A phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma. Neuro-Oncology. 2016. doi:10.1093/neuonc/now009.

19. Batchelor TT, Mulholland P, Neyns B, Nabors LB, Campone M, Wick A, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol. 2013;31(26):3212–8. doi:10.1200/JCO.2012.47.2464.

20. Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014;15(9):943–53. doi:10.1016/S1470-2045(14)70314-6.

21. Brandes AA, Tosoni A, Franceschi E, Blatt V, Santoro A, Faedi M, et al. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). Cancer Chemother Pharmacol. 2009;64(4):769–75. doi:10.1007/s00280-009-0926-8.

22. Brandes AA, Finocchiaro G, Zagonel V, Reni M, Caserta C, Fabi A, et al. AVAREG: a phase 2, randomized, noncomparative study of fotemustine or bevacizumab

for patients with recurrent glioblastoma. Neuro-Oncology. 2016. doi:10.1093/neuonc/now035.

23••. van den Bent MJ, Taal W. Are we done with dose-intense temozolomide in recurrent glioblastoma? Neuro-Oncology. 2014;16(9):1161–3. doi:10.1093/neuonc/nou157 .

This review evaluated the role of intensified temozolomide schedules in recurrent GBM

24••. Weller M, Tabatabai G, Kastner B, Felsberg J, Steinbach JP, Wick A, et al. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: the DIRECTOR trial. Clin Cancer Res. 2015;21(9):2057–64. doi:10.1158/1078-0432.CCR-14-2737 .

This study provides the evidence for temozolomide rechallange in MGMT methylated patients in recurrence after temozolomide interruption

25. Reardon DA, Wen PY, Mellinghoff IK. Targeted molecular therapies against epidermal growth factor receptor: past experiences and challenges. Neuro-Oncology. 2014;16(Suppl 8):viii7–13. doi:10.1093/neuonc/nou232.

26. van den Bent MJ, Brandes AA, Rampling R, Kouwenhoven MC, Kros JM, Carpentier AF, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. J Clin Oncol. 2009;27(8):1268–74. doi:10.1200/JCO.2008.17.5984.

27. Vredenburgh JJ, Desjardins A, Herndon 2nd JE, Dowell JM, Reardon DA, Quinn JA, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res. 2007;13(4):1253–9.

28. Vredenburgh JJ, Desjardins A, Herndon 2nd JE, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol. 2007;25(30):4722–9. doi:10.1200/JCO.2007.12.2440.

29. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27(5):740–5.

30. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733–40. doi:10.1200/JCO.2008.19.8721.

31. Field KM, Jordan JT, Wen PY, Rosenthal MA, Reardon DA. Bevacizumab and glioblastoma: scientific review, newly reported updates, and ongoing controversies. Cancer. 2015;121(7):997–1007. doi:10.1002/cncr.28935.

32••. Wick W, Brandes A, Gorlia T, Bendszus M, Sahm F, Taal W et al. Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of glioblastoma: the EORTC 26101 trial. Neuro Oncol. 2015;(17).

This phase III study randomized recurrent GBM patients to bevacizumab in combination with CCNU or CCNU alone demonstrating a significant increase in PFS not translating in a survival advantage.

33. Khasraw M, Ameratunga M, Grommes C. Bevacizumab for the treatment of high-grade glioma: an update after phase III trials. Expert Opin Biol Ther. 2014;14(5):729–40. doi:10.1517/14712598.2014.898060.

34. Lu-Emerson C, Duda DG, Emblem KE, Taylor JW, Gerstner ER, Loeffler JS, et al. Lessons from anti-vascular endothelial growth factor and anti-vascular endothelial growth factor receptor trials in patients with glioblastoma. J Clin Oncol. 2015;33(10):1197–213. doi:10.1200/JCO.2014.55.9575.

35. Piccioni DE, Lai A. Deferred use of bevacizumab for recurrent glioblastoma is not associated with diminished efficacy. Neuro-Oncology. 2014;16(10):1427–8. doi:10.1093/neuonc/nou214.

36. Levin VA, Mendelssohn ND, Chan J, Stovall MC, Peak SJ, Yee JL, et al. Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma. J Neuro-Oncol. 2015;122(1):145–50. doi:10.1007/s11060-014-1693-x.

37. Wong ET, Gautam S, Malchow C, Lun M, Pan E, Brem S. Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis. J Natl Compr Cancer Netw. 2011;9(4):403–7.

38. Franceschi E, Bartolotti M, Brandes AA. Bevacizumab in recurrent glioblastoma: open issues. Future Oncol. 2015;11.

39. Franceschi E, Brandes AA. The role of bevacizumab in recurrent glioblastoma: new insights from randomized trials. CNS Oncol. 2015;4(3):117–9. doi:10.2217/cns.15.7.

40. Sandmann T, Bourgon R, Garcia J, Li C, Cloughesy T, Chinot OL, et al. Patients with proneural glioblastoma may derive overall survival benefit from the addition of bevacizumab to first-line radiotherapy and temozolomide: retrospective analysis of the AVAglio trial. J Clin Oncol. 2015;33(25):2735–44. doi:10.1200/JCO.2015.61.5005.

41. Sulman EP, Won M, Blumenthal A, Vogelbaum M, Colman H, Jenkins RB et al. Molecular predictors of outcome and response to bevacizumab (BEV) based on analysis of RTOG 0825, a phase III randomized trial comparing chemoradiation with or without BEV in patients with newly diagnosed glioblastoma (GBM) J Clin Oncol. 2013;31:suppl;abstr.

42. Erdem-Eraslan L, van den Bent MJ, Hoogstrate Y, Naz-Khan H, Stubbs A, van der Spek P, et al. Identification of patients with recurrent glioblastoma who may benefit from combined bevacizumab and CCNU therapy: a report from the BELOB trial. Cancer Res.

2016;76(3):525–34. doi:10.1158/0008-5472.CAN-15-0776.
43. Fecci PE, Heimberger AB, Sampson JH. Immunotherapy for primary brain tumors: no longer a matter of privilege. Clin Cancer Res. 2014;20(22):5620–9. doi:10.1158/1078-0432.CCR-14-0832.
44. Sampson J, Vlahovic G, Sahebjam S, Omuro A, Baehring J, Hafler D, et al. Preliminary safety and activity of nivolumab and its combination with ipilimumab in recurrent glioblastoma (GBM): CHECKMATE-143. J Clin Oncol. 2015;33(No 15_suppl (May 20 Supplement)):3010.
45. Sampson JH, Mitchell DA. Vaccination strategies for neuro-oncology. Neuro-Oncology. 2015;17(Suppl 7):vii15–25. doi:10.1093/neuonc/nov159.
46. Reardon D, Desjardins A, Schuster J, Tran D, Fink KL, Nabors BL, et al. ReACT: long-term survival from a randomized phase ii study of rindopepimut (CDX-110) plus bevacizumab in relapsed glioblastoma. Neuro-Oncology. 2015;17:v107–12.
47. Crane CA, Han SJ, Ahn B, Oehlke J, Kivett V, Fedoroff A, et al. Individual patient-specific immunity against high-grade glioma after vaccination with autologous tumor derived peptides bound to the 96 KD chaperone protein. Clin Cancer Res. 2013;19(1):205–14. doi:10.1158/1078-0432.CCR-11-3358.
48. Bloch O, Parsa AT. Heat shock protein peptide complex-96 (HSPPC-96) vaccination for recurrent glioblastoma: a phase II, single arm trial. Neuro-Oncology. 2014;16(5):758–9. doi:10.1093/neuonc/nou054.
49. Tonder M, Weller M, Eisele G, Roth P. Carboplatin and etoposide in heavily pretreated patients with progressive high-grade glioma. Chemotherapy. 2014;60(5–6):375–8. doi:10.1159/000440678.