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TOPIC REVIEW

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

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Abstract

The following questions and recommendations are pertinent to the following:

Target population These recommendations apply to adults with progressive GBM who have undergone standard primary treatment with surgery and/or chemoradiation.

Question 1 In adults with progressive glioblastoma is the use of bevacizumab as monotherapy superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation **Level III:** Treatment with bevacizumab is suggested in the treatment of progressive GBM, as it provides improved disease control compared to historical controls as measured by best imaging response and progression free survival at 6 months, while not providing evidence for improvement in overall survival.

Question 2 In adults with progressive glioblastoma is the use of bevacizumab as combination therapy with cytotoxic agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation **Level III:** There is insufficient evidence to show benefit or harm of bevacizumab in combination with cytotoxic therapies in progressive glioblastoma due to a lack of evidence supporting a clearly defined benefit without significant toxicity.

Question 3 In adults with progressive glioblastoma is the use of bevacizumab as a combination therapy with targeted agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation There is insufficient evidence to support a recommendation regarding this question.

Question 4 In adults with progressive glioblastoma is the use of targeted agents as monotherapy superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation There is insufficient evidence to support a recommendation regarding this question.

Question 5 In adults with progressive glioblastoma is the use of targeted agents in combination with cytotoxic therapies superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation There is insufficient evidence to support a recommendation regarding this question.

Question 6 In adults with progressive glioblastoma is the use of immunotherapy monotherapy superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Recommendation There is insufficient evidence to support a recommendation regarding this question.

Question 7 In adults with progressive glioblastoma is the use of immunotherapy in combination with targeted agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Sponsors: Congress of Neurological Surgeons (CNS) and the Section on Tumors.

Endorsement: Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Extended author information available on the last page of the article

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Recommendation There is insufficient evidence to support a recommendation regarding this question.
Question 8 In adults with progressive glioblastoma is the use of immunotherapy in combination with bevacizumab superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?
Recommendation There is insufficient evidence to support a recommendation regarding this question.

Keywords Progressive glioblastoma · Guidelines update · Targeted therapy · Immunotherapy

Abbreviations

BEV	Bevacizumab
GBM	Glioblastoma
PFS	Progression free survival
PFS6	6 month progression free survival
mOS	Median overall survival
OS	Overall survival
PRISMA	Preferred reporting items for systematic reviews and meta-analyses

Introduction

In 2014, guidelines for the management of progressive glioblastoma and the role of targeted therapies were published by the AANS and CNS [1]. We now present the updated set of data and studies regarding targeted therapies as well as immunotherapy with and without targeted therapies. Despite maximal therapy, the median overall survival for a patient with newly diagnosed glioblastoma remains 14.6 months [2]. Recurrence typically occurs by one year and the median overall survival at recurrence ranges from 24 to 44 weeks [3–5]. Despite significant effort, the prognosis after recurrence in glioblastoma remains dismal. While cytotoxic therapies have long been used to treat malignancy, more recent attempts utilizing therapies targeting tumor progression and growth pathways, anti-angiogenic agents designed to target neovascular proliferation pathways, and immunotherapies aimed at utilizing a patient's immune system to attack tumor cells have been studied. We present a systematic review and evidence-based practice guideline to help practicing physicians to determine the role of these treatments in progressive glioblastoma.

Rationale

Tumor stabilization and radiographic response are the current goals in designing treatment of progressive glioblastoma. There are several strategies for treatment with targeted therapies, especially with the large amount of information being uncovered regarding the molecular characteristics of glioblastoma and the differing aberrations that occur in subgroups of the tumor. Exploration of immunotherapy has been a growing subject of study as well, with a goal of utilizing the patient's own immune response to attack the tumor.

Objectives

The objectives of this guideline are to assess the therapeutic value of targeted therapies and immunotherapies in patients with progressive glioblastoma based on radiographic response and in terms of survival outcomes.

Methods

Writing group and question establishment

The evidence-based clinical practice guideline taskforce members and the Joint Tumor Section of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) have prioritized updating the guidelines for the management of progressive glioblastoma with targeted therapies and immunotherapy. A series of authors for the development of guidelines related to the role of targeted therapy and immunotherapy in progressive glioblastoma were identified and screened for conflicts of interest. This group in turn agreed on a set of questions addressing the topic at hand and conducted a systematic review of the literature relevant to management of progressive glioblastoma with the aforementioned therapeutic strategies, both alone and in combination. Additional details of the systematic review are provided below and within the introduction and methodology chapter of the guideline.

Literature search

The task force collaborated with a medical librarian and searched for articles published on targeted therapies for progressive glioblastoma between July 1, 2012 and March 31, 2019, and on immunotherapy for progressive glioblastoma between January 1, 1990 to March 31, 2019 (to complete the same search dates as had previously been performed in the original guideline document) in three electronic databases: Pubmed, EMBASE and Cochrane. Strategies for searching electronic databases were constructed by the evidence-based clinical practice guideline taskforce members and the medical librarian using standard strategies to identify relevant

studies [6–13]. As can be seen below, progression, recurrence and relapse were all used in the search strategy. As progression clearly implies glioblastoma persists and is not completely controlled with any intervention, this term is chosen as the primary term describing the clinical circumstance addressed throughout this guideline.

Search strategy

- Targeted: July 1, 2012 through March 31, 2019
  - o (progress* OR recurren* OR relaps*) AND (glioma OR glioblastoma) AND (targeted therap* OR immunotherapy OR molecular agent* OR surgical technique* OR surgery OR radiotherap* OR alternative particles OR radiosensitizer* OR convection enhanced) AND (quality of life OR survival OR mortality)
- Immunotherapy: January 1, 1990 to March 31, 2019
  - o (progress* OR recurren* OR relaps*) AND (glioma OR glioblastoma) AND (vaccin* OR peptide vaccin* OR heat shock protein vaccin* OR immune checkpoint inhibitor* OR dendritic cell vaccin* OR adoptive T Cell*) AND (quality of life OR surival OR mortality)

The authors supplemented the searches of electronic databases with manual screening of the bibliographies of all retrieved publications. The authors also searched the bibliographies of recent systematic reviews and other review articles for potentially relevant citations. All articles identified were subject to the study selection criteria listed below. As noted above, the guideline committee also examined lists of included and excluded studies for errors and omissions. The authors went to great lengths to obtain a complete set of relevant articles. Having a complete set ensured that this guideline was not based on a biased subset of articles.

Study selection and eligibility criteria

A total of 4417 articles were identified including 3513 for targeted therapies and 904 for immunotherapy (Figs. 1 and 2). Based on a Pubmed search, a total of 2727 articles in targeted therapy and 627 articles in immunotherapy related to progressive glioblastoma were reviewed by the team with specific inclusion and exclusion criteria outlined below. A search of Embase yielded 748 additional articles relating to targeted therapy and 253 in immunotherapy. Cochrane yielded an additional 38 articles for targeted therapy and 24 for immunotherapy. The same methodology of review was conducted for the Embase and Cochrane data. Independent reviewers evaluated and abstracted full-text data for each article and the two sets of data were compared for agreement by a third party. Inconsistencies were re-reviewed and disagreements were resolved by consensus. Citations were included that prospectively or retrospectively reviewed the

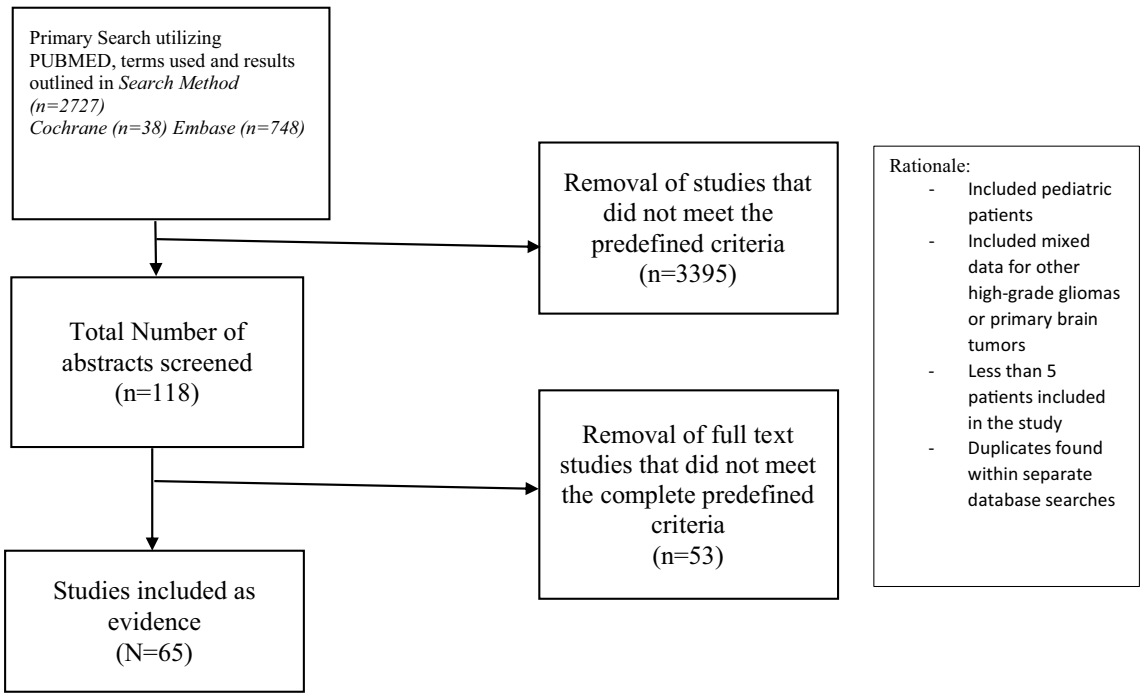

Fig. 1 PRISMA diagram—depicting the process of searching for, including, and excluding (as well as rationale) studies on targeted therapies for treating progressive glioblastoma

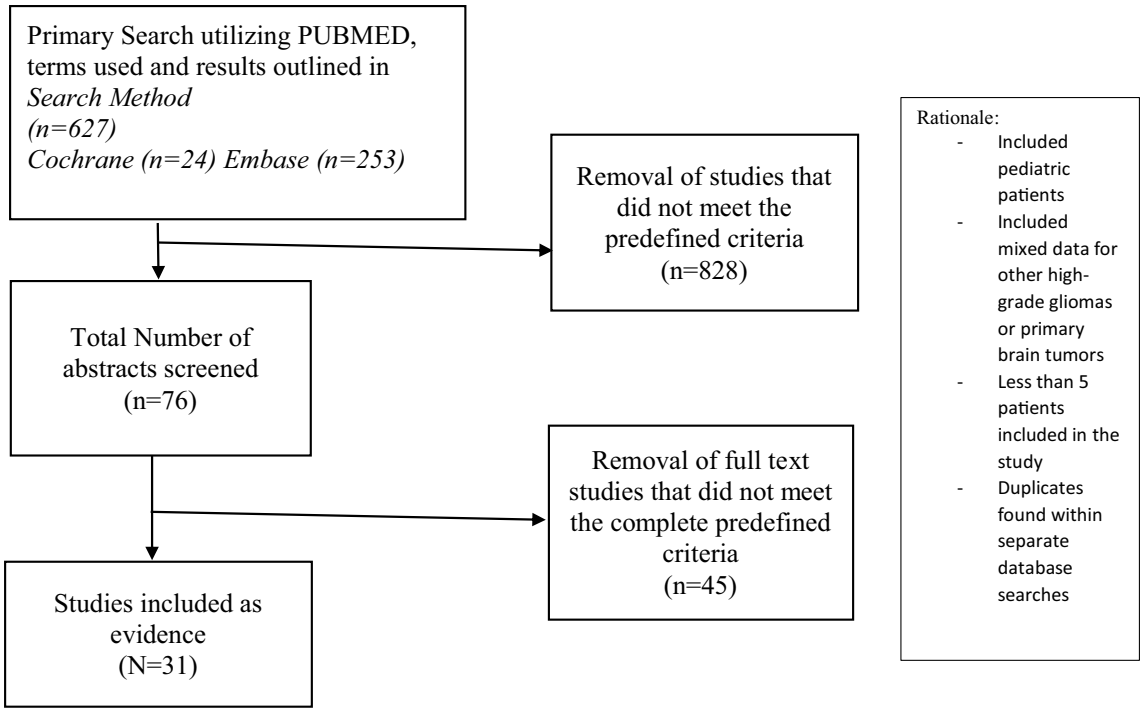

Fig. 2 PRISMA diagram—depicting the process of searching for, including, and excluding (as well as rationale) studies on immunotherapy for treating progressive glioblastoma

treatment effect and outcomes of targeted therapies and immunotherapies, as monotherapy or combination therapies, on progressive glioblastoma patients. To be included in the guideline, a publication had to meet the following inclusion criteria:

- Investigated patients had progressive/recurrent glioblastoma
- Patients ≥ 18 years of age
- Humans, only
- Published between:
    - Targeted: July 1, 2012 through March 31, 2019
    - Immunotherapy: January 1, 1990 to March 31, 2019
- Quantitatively presented results
- Was not an in vitro study
- Was published in English
- Studies may include mixed pathology; however, the data pertaining to progressive glioblastoma was extractable from the paper
- Had ≥ 5 patients or patient samples

The authors did not include systematic reviews, guidelines, or meta-analyses conducted by others. These documents are developed using different inclusion criteria than those specified in this guideline. Therefore, they may include studies that do not meet the inclusion criteria specified above. These documents were recalled if their abstract suggested that they might address one of the recommendations, and their bibliographies were searched for additional studies.

Data collection process

The abstracts that met the selection criteria mentioned above were retrieved in full-text form. Each article's adherence to the selection criteria was confirmed. To determine how the data could be classified, the information in the full-text articles were then evaluated to determine whether they were providing results of therapy or were more centered on diagnostic or prognostic information. Agreement on these assessments and on the salient points regarding the type of study design and objectives, and the conclusions and data classification was then reached by exchanging drafts and comments by e-mail. The information was then used for construction of the evidence tables. A summary of the search process and results are provided in the PRISMA diagrams (Figs. 1 and 2).

Assessment for risk of bias

Our search generated 4417 abstracts. These were screened, and the articles that addressed our pre-defined questions

underwent full independent review by the authors. Reviewers were critical in their assessment to account for selection bias, survivorship bias, etc., by evaluating studies specifically in regard to trial design including factors such as: adequacy of control group, randomization of treatment, blinding, prospective character, size of study population, etc. Other factors that could account for survivorship bias or selection bias, as well as appropriate or inappropriate use of statistics of the reported data was also critically assessed.

Classification of evidence and guideline recommendation and formulation

The concept of linking evidence to recommendations has been further formalized by the American Medical Association (AMA) and many specialty societies, including the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), and the American Academy of Neurology (AAN). This formalization involves the designation of specific relationships between the strength of evidence and the strength of recommendations to avoid ambiguity. In the paradigm for therapeutic maneuvers, evidence is classified into that which is derived from the strongest clinical studies (e.g., well-designed, randomized controlled trials), or class I evidence. Class I evidence is used to support recommendations of the strongest type, defined as level 1 recommendations, indicating a high degree of clinical certainty. Nonrandomized cohort studies, randomized controlled trials with design flaws, and case–control studies (comparative studies with less strength) are designated as class II evidence. These are used to support recommendations defined as level 2 reflecting a moderate degree of clinical certainty. Other sources of information, including observational studies such as case series and expert opinion, as well as randomized controlled trials with flaws so serious that the conclusions of the study are truly in doubt are considered class III evidence and support level 3 recommendations, reflecting unclear clinical certainty. A summary of these categories of evidence can be viewed at https://www.cns.org/guidelines/guideline-development-methodology.

Results

Role of targeted therapies in progressive glioblastoma

All questions and recommendations in this section apply to the following target population: Adults with progressive GBM who have undergone standard primary treatment with surgery and/or chemoradiation. For each of the provided evidence tables, data extraction included study design, total number of patients, study parameters including treatment regimen, results including metrics of survival and progression free survival, complications including toxicity data, and author conclusions.

Question 1 In adults with progressive glioblastoma is the use of bevacizumab as monotherapy superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Summary of prior recommendations

In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, it was recommended that bevacizumab be utilized to provide improved disease control in comparison to historical controls as measured by best imaging response and progression free survival at 6 months [1]. This was a Level III recommendation based on the available data. The previous data included both prospective trials and retrospective reviews, all of which were Class III evidence [1].

Recommendation: Level III

Treatment with bevacizumab is suggested in the treatment of progressive GBM, as it provides improved disease control compared to historical controls as measured by best imaging response and progression free survival at 6 months, while not providing evidence for improvement in overall survival.

Study selection and characteristics for the updated search

The initial search strategy included 3513 candidate articles. A total of 65 articles remained for full text review. From these, 7 articles were included in the final review for Question 1 and are included in Table 1 [14–20].

Only two of the studies were prospective trials. One was performed in Japan, by Nagane et al. [17] They evaluated 29 progressive glioblastoma patients given a regimen of standard dose BEV and found mOS was 10.5 months. They had a significant number of radiographic responses with 21 patients experiencing reduction in tumor size during treatment and a PFS 6 of 33.9%. They concluded that, similar to other studies performed outside Japan, their native patient population with progressive glioblastoma experienced a significant survival benefit [21–23]. Cai et al. reviewed 20 patients in a double arm comparative study comparing BEV to a placebo treatment [14]. Of the patients with glioblastoma (n = 20), mOS was 8.9 months with BEV and 5.6 months with placebo, and a 6 month survival of 83% versus 47% respectively. The authors concluded that bevacizumab conferred a survival benefit.

Table 1 Bevacizumab monotherapy in progressive GBM

Author (year)	Description of study	Data class	Conclusions
Balana et al. (2017)	Study description: Retrospective review of Prolonged Survival in glioblastoma patients rechallenged with Bevacizumab after a previous response to Bevacizumab Patient population: 12 newly diagnosed (BEV-F), 16 patients with progressive glioblastoma (BEV-S) retreated with Bevacizumab at varying recurrences Treatment regimen: Treatment doses reportedly conformed to standard treatment regimens in patients with a prior response before progression of disease	III	Results: Median OS: BEV-F – 26.7 m BEV-S—52.1 m Median PFS: BEV-F: BEV-1—7.9 m, BEV-2 – 9.1 m, BEV-3 – 5.6 m BEV-S: BEV-1 – 23.3 m months. BEV-2 – 7.3 m Median Post progression survival: BEV-F – 26.7 m (designated as survival after first occurrence of progression) BEV-S – 39.6 m RR: of rechallenges – 3.4% CR, 55.2% PR, 31.0% SD, 10.4% PD Clinical response 89.6% Toxicity: Author's Conclusions: Patients who have a first objective response to bevacizumab and stop bevacizumab before progression can attain a second response or clinical benefit from a re-introduction of bevacizumab at subsequent recurrences Comments and Conclusions: A small retrospective review warrants Class III designation
Wenger et al. (2017)	Study description: Retrospective review of Bev as last line treatment for rGBM after RT, TMZ lomustine Patient population: 62 adult patients with progressive GBM Treatment regimen: As a retrospective design, various treatments with Bev as monotherapy or a part of multidrug therapy were utilized at unreported dosing regimens	III	Results: Response Rate: PD 35.5%, 9.7% SD, 51.6% PR, 3.2% CR median PFS 3.5 m, OS 7.5 m, PFS6 21.5%, OS-12 11.5% Authors' conclusions: Objective response rate and the PFS and OS times and rates indicate that bevacizumab has activity in patients with glioblastoma following the failure of radiotherapy, temozolomide, and lomustine Comments and Conclusions: A mixed retrospective cohort warrants Class III designation
Flieger et al. (2014)	Study description: Retrospective review of Avastin and reirradiation in progressive GBM patients Patient population: 71 adult patients with progressive high-grade glioma, 43 with Grade IV received BEV + reirradiation, 9 reirradiation only Treatment regimen: Patients received a total dose of 36 Gy in 18 fractions (2 Gy single doses) employing 3D conformal radiotherapy or IMRT if adjacent critical structures were present. Patients treated with bevacizumab received 10 mg/kg at days 1 and 15 during radiotherapy. If applied in patients who had no previous progression after TMZ pre-treatment a dosage of 75 mg/m2 daily was chosen	III	Results: median PFS: 5.1 m, vs 3.4 m without Bev Median PFS: 9.3 m vs 6.1 m without Bev Toxicity: one death (grade 5) with known diverticulosis, suffered GI perforation. 2 grade 4—thrombocytopenia and wound healing, 1 grade 3—DVT Authors' conclusions: In conclusion, the results of the randomized controlled trials on the use of bevacizumab concomitantly to irradiation are expected—treatment will probably become more diverse; especially in those patients who were treated with a temozolomide-based radiochemotherapy Comments and Conclusions: A retrospective study warrants Class III designation

Table 1 (continued)

Author (year)	Description of study	Data class	Conclusions
Piccioni et al. (2014)	Study description: retrospective study of participants treated with BEV at several institutions to determine factors impacting survival with progressive GBM Patient population: 388 adult participants who received BEV at recurrence, 121 received BEV monotherapy, and 267 were treated with BEV plus concurrent chemotherapy (BV +)	III	Results: median PFS with BEV—1st recurrence 4.1 m, 2nd 4.2 m, 3rd 3.4 m median OS with BEV: 1st 8.4 m, 2nd 9.3 m, 3rd 6.4 m PFS for BEV alone 3.6 m, BV + other treatment 4.3 m Toxicities: NR Authors' conclusions: BEV efficacy is not diminished at later recurrences and suggests that delayed use of BEV may be preferable Comments and Conclusions: A retrospective study warrants Class III designation
Cai et al. (2013)	Study description: Bevacizumab rescue therapy in patients with progressive malignant glioma: a retrospective analysis Patient population: 20 adult patients enrolled with progressive GBM, 12 received Bev rescue, 8 received placebo Treatment regimen: Twenty-two patients with second recurrence or poor response to dense-dose chemotherapy received salvage bevacizumab therapy at a dose of 10 mg/kg. The remaining 29 patients received best care support, with or without other chemotherapeutic regimens including temozolomide plus cisplatin, nimustine and teniposide, or nimustine, cisplatin and VP-16, and nimustine monotherapy. Bevacizumab was terminated upon disease progression or treatment-related toxicity (grade 4 or above)	III	Results: OS: with BEV—8.9 m, placebo 5.6 m 6 m Survival: 83% with BEV, 47% placebo PFS: 3 m for BEV, 1 m for Placebo Toxicity: No grade 3–4 adverse events reported Authors' conclusions: Salvage therapy with BEV is effective and safe for patients with grade IV glioma, conferring a survival benefit without incurring additional side effects Comments and Conclusions: A study with few patients and retrospective in nature warrants Class III designation
Kaloshi et al. (2013)	Study description: Retrospective study of bevacizumab 5 mg/kg every 3 weeks for adult patients with progressive GBM Patient population: 14 patients with progressive GBM were included (most with surgical debulking n = 11) Treatment regimen: Bevacizumab 5 mg/kg alone every 3 weeks until progression, administered IV over 90 min first cycle and over 60 min for following cycle with no dose escalation permitted. Treatment continued until disease progression, toxicity or withdrawal of consent	III	Results: Median OS: 6.4 mos Response to treatment: The median number of cycles was 4. Five patients had PR, 7 SD, 2 PD. When present, clinical improvement followed second week of the cycle. Dexamethasone dose was decreased in patients with radiological or clinical improvement Toxicity: Fatigue was the most common adverse event (4 patients, grade 1 and 2). There was no grade 3 or 4 hematological or clinical toxicities, no symptomatic intracerebral bleeding and no treatment-related death Authors' conclusions: In view of tolerance, patient comfort and economic issues, the finding that BEV at 5 mg/kg every 3 weeks has significant activity in progressive GBM warrants further investigation Comments and Conclusions: A retrospective study design warrants Class III designation

Table 1 (continued)

Author (year)	Description of study	Data class	Conclusions
Nagane et al. (2012)	Study description: A single-arm open-label Phase II study using single-agent bevacizumab in progressive malignant glioma in Japanese patients Patient population: Adult Japanese patients with progressive GBM (n = 29) or AA (n = 2) Treatment regimen: bevacizumab IV 10 mg/kg every 2 weeks	III	Results: Median OS: 10.5 mos Response to treatment: Among the GBM subset, 21 patients experienced tumor shrinkage during the treatment period. 8 PR. PFS6 33.9% Toxicity: All 31 patients had AE, serious AE in 11 patients (two convulsion, 1 Grade 1 cerebral hemorrhage, 3 patients with Grade 3 HTN, 1 patient died of cerebral edema, 1 CHF, 1 VTE Authors' conclusions: The results of this study show that single agent BEV could provide significant clinical benefit for Japanese patients with progressive GBM Comments and Conclusions: A single arm study without control warrants Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism

Six of the studies were retrospective reviews. [14–16, 18–20] Kaloshi et al. evaluated the survival effect on 11 patients receiving low-dose BEV, finding mOS of 6.4 months and only five patients with a partial response, at best. The coupling of low toxicity and some efficacy lead them to conclude BEV was effective in these patients [16]. Wenger et al. reviewed 62 patients with multiple treatment regimens, however all had undergone and failed initial standard therapy with RT, TMZ, and lomustine [19]. Ultimately, their RR showed 51.6% PR and 3.2% with CR, a median PFS of 3.5 months and mOS 7.5 months. They felt this data showed BEV remained effective after failed standard treatment and lomustine. Meanwhile, Piccioni et al. reviewed data from multiple institutions including 388 patients receiving BEV at recurrence, however in varying methodologies including combination therapy [18]. Progression free survival for BEV alone was 3.6 months and 4.6 months in combination therapy. Their data showed that BEV retained its efficacy throughout multiple recurrences, with data including the varying recurrences at which BEV was started, however the data was mixed with multiple therapy modalities. Balana et al. also studied patients rechallenged with BEV after prior treatment response to the drug, and noted a survival benefit, possibly in the subset of patients that displayed sensitivity and response to initial treatment with BEV, if BEV was halted for reasons other than progression [20]. Flieger et al. reviewed their data on patients receiving repeat RT therapy along with BEV [15]. PFS was 5.1 months with and 3.4 months without bevacizumab. Median OS was 9.3 months in combination therapy, 6.1 months with RT alone and the authors concluded that BEV concomitantly given with reirradiation was feasible and effective based on comparison to historical data.

Synthesis

Historically, PFS-6 ranged from 29 to 50.3% based on three studies evaluating BEV monotherapy compared with combination therapy with irinotecan, with Friedman et al. showing in a prospective, randomized Phase II trial a mOS of 9.2 months with BEV alone [22–24]. Two prospective trials with BEV above showed a PFS-6 of 33.9% and 83%, compatible with the historical data [17]. In one, the data was a single arm study without a control group, and the other a small case series where the controls fared better than controls in other studies. For this reason, these prospective studies remained Class III evidence. The remainder of the data was retrospective, all of which were downgraded to Class III evidence, as well [14–19]. While these studies met the inclusion criteria, they did not provide enough high level evidence to change or upgrade the recommendation from the previous guideline.

Question 2 In adults with progressive glioblastoma is the use of bevacizumab as combination therapy with cytotoxic agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendation: In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, bevacizumab combined with cytotoxic agents was reviewed and no specific recommendations were made based on a lack of strong evidence supporting a clearly defined benefit without significant toxicity [1].

Recommendation Level: III

There is insufficient evidence to show benefit or harm of bevacizumab in combination with cytotoxic therapies in progressive glioblastoma due to a lack of evidence supporting a clearly defined benefit without significant toxicity.

Study selection and characteristics of the updated search

The initial search strategy included 3513 candidate articles. A total of 65 articles remained for full text review. From these, 21 articles were included in the final review for Question 2 and are included in Table 2 [25–44].

Bevacizumab with cytotoxic therapy

There were six studies regarding BEV combined with cytotoxic therapy included in our search that met criteria for inclusion. In a small series, Arakawa et al. evaluated combination therapy with ifosfamide, carboplatin, and etoposide at second recurrence, finding an mOS of 6 months [25]. In a similar study, Brenner et al. added evofosfamide to BEV in BEV resistant patients compared to placebo, finding a mOS of 4.4 months with SD in 60.9% and a response in 17.4% [29]. They found preliminary evidence of synergistic activity. Two further studies combined TMZ with BEV. Badruddoja et al. combined BEV with TMZ and found a mOS of 11.0 months and PFS6 of 52% [26]. Sepulveda et al. similarly studied BEV with TMZ and found a PFS6 of 21.9%, finding the regimen was safe and possibly effective [39]. Another study by Peters et al. combined Vorinostat, BEV, and TMZ at recurrence, but found their results limited by their cohort's heavy pretreatment prior to enrollment [37]. Mrugala et al. retrospectively studied BEV with carboplatin at varying recurrences, finding a mOS of 9.3 months, determining some activity and tolerability of the combined therapy [44]. Ultimately, the data here regarding cytotoxic therapy with BEV at recurrence warranted Class III data designation as the studies were small and/or lacked randomization.

However, there was one study that yielded class II evidence. Field et al. randomized 122 patients with BEV and carboplatin versus BEV monotherapy [30]. PFS6 was 15% in combination therapy, 18% in monotherapy, thus they found no additional benefit with combination therapy.

Nitrosoureas with bevacizumab

The only Class I designation was afforded to Wick et al. for evaluating combination therapy with BEV and lomustine as a prospective, randomized phase III trial in 437 adult progressive glioblastoma patients [43]. Monotherapy OS was 8.6 months and PFS 1.5 months. Combination therapy OS was 9.1 months and PFS 4.2 months. The trial concluded there was not a survival advantage using combination therapy beyond that obtained with monotherapy.

Brandes et al. performed a phase II randomized trial of 91 patients receiving fotemustine or BEV for progressive glioblastoma [27]. The authors concluded there may be a role for single agent BEV in progressive glioblastoma as median OS was 7.3 months with BEV and 8.7 months with fotemustine. RANO response rates were 29% with BEV and 9% with fotemustine. They had also completed a phase II randomized and double blinded study on 123 patients given BEV and Lomustine or Lomustine with placebo in first recurrence of glioblastoma [28]. At second recurrence or progression of disease, patients continued BEV or placebo. Results showed CCNU + BEV median overall survival (mOS) to be 6.4 months, PFS2 2.3 months, PFS3 2.0 months (PFS2 and PFS3 refer to the progression free survival at the second and third recurrence, respectively). There was no survival benefit and no detriment determined by the authors in continuing BEV through multiple lines of treatment. These were both designated Class II data as they were prospective, randomized trials with small cohorts.

In another randomized, controlled, Phase II study, Taal et al. evaluated BEV with lomustine vs BEV monotherapy or lomustine monotherapy in 153 patients [40]. Combination therapy showed an improved OS and treatment response with 9 months OS in 63%, surpassing the monotherapy groups. Authors concluded the combination treatment met their predetermined criteria for further evaluation. Another study by Weathers et al. was a randomized phase II trial of BEV standard dose vs low dose BEV with lomustine, which found nonsuperiority of combination therapy [42]. These studies warranted Class II designation.

The remainder of the data was Class III as the cohorts were small, the data was retrospective, or the study lacked a control group. Heiland et al. retrospectively reviewed BEV with lomustine against BEV monotherapy in 35 patients [33]. Median OS was 6.6 months with improved median

Table 2 The role of bevacizumab combined with cytotoxic therapy in progressive GBM

Author (year)	Description of study	Data class	Conclusions
Brandes et al. (2019)	Study description: TAMIGA (NCT01860638) was a phase II, randomized, double-blind, placebo-controlled, multicenter trial in adult patients with glioblastoma Patient population: 123 patients were randomized at the time of progressive disease (PD1) with 61 in the CCNU + BEV group, 62 in the Placebo + CCNU group. 25 patients in each group received 3rd line treatment at PD2 Treatment regimen: Randomization occurred at PD1 (second line), and patients received lomustine (CCNU) plus BEV (CCNU + BEV) or CCNU plus placebo (CCNU + placebo) until further disease progression (PD2). At PD2 (third line), patients continued BEV or placebo with chemotherapy (investigator's choice)	II	Results: CCNU + BEV OS: 6.4 m, PFS2—2.3 m, PFS3—2.0 CCNU + BEV OS: 6.4 m, PFS2—2.3 m, PFS3—2.0 Toxicity: In the CCNU + BEV and the CCNU + placebo groups, respectively, 86% and 83% experienced at least one AE, 19% and 15% experienced at least one treatment related AE greater than grade 3, 21% and 15% experienced an AE leading to study discontinuation Authors' conclusions: There was no survival benefit and no detriment observed with continuing BEV through multiple lines in patients with progressive glioblastoma Comments and Conclusions: A double-blind, placebo-controlled multicenter trial in a moderate, but relatively small cohort, warrants Class II designation
Brenner et al. (2018)	Study description: Phase I Surgical Study giving evofosfamide and Bevacizumab to bevacizumab resistant progressive GBM patients vs. Bev + Placebo Patient population: 28 patients randomized to cohorts of Presurgical Evofosfamide + Bev vs Bev + Placebo, vs no surgery and only dose escalation evaluation of combination therapy. 2 patients withdrew consent post op, 3 patients did not recover sufficiently, 9 total patients continued to combination therapy after surgery Treatment regimen: Twenty-eight patients with Bev-refractory GBM were enrolled in a dose escalation study receiving from 240 mg/m2 (cohort 1) to 670 mg/m2 (cohort 4) of Evo every 2 weeks in combination with Bev. Patients deemed surgical candidates underwent a single dose of Evo or placebo with pimonidazole immediately prior to surgery for biomarker evaluation, followed by dose escalation upon recovery	III	Results: OS: 4.41 m Time to progression: 2.2 m Tumor response: Complete and partial response—17.4%. Disease Control (complete, partial, and stable disease) in 60.9% Toxicity: No grade 4 adverse events. 3 grade 3 adverse events, including oral mucositis, skin ulceration, thrombocytopenia. 11 patients developed rash Authors' conclusions: Evo plus Bev was well tolerated in patients with Bev-refractory GBM, with preliminary evidence of activity that merits further investigation Comments and Conclusions: A small randomized cohort warrants Class III designation
Johansen et al. (2018)	Study description: BEV therapy in patients with progressive GBM treated with angiotensin system inhibitors (retrospective) Patient population: Adult patients in a national prescription registry were combined with a clinical database with progressive GBM patients (n = 243, 26 in both databases) Treatment regimen: BEV 10 mg/kg and irinotecan 125 mg/m^2 both every 2 weeks	III	Results: Median OS: NR Response to treatment: In univariate analysis, use of angiotensin system inhibitors was associated with a trend towards improved PFS (HR 0.75) and OS (HR: 0.80). Calcium antagonists significantly improved OS (HR = 0.57) Toxicity: NR Authors' conclusions: Overall the study supports a potential beneficial effect of antihypertensive treatment on prognosis of BEV treated GBM patients Comments and Conclusions: A retrospective study warrants Class III designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Pasqualetti et al. (2018)	Study description: BEV in progressive GBM after second-line chemotherapy with fotemustine (retrospective) Patient population: 51 patients with progressive GBM Treatment regimen: Fotemustine previously given at varied dosing paradigms. BEV 10 mg/kg every 2 weeks in 43 patients, 15 mg/kg every 3 weeks in 5 patients, and 7.5 mg/kg every 2 weeks in 3 patients	III	Results: Median OS: 6 mos Response to treatment: PFS6 18%, PFS12 13% Toxicity: Grade 3 toxicity in 3 patients (5.8%) including 1 GI fistula. 2 Grade 4 toxicities with thromboembolic event and massive PE Authors' conclusions: The failure of second-line chemotherapy with cytotoxic agents might not exclude the administration of BEV as third-line chemotherapy Comments and Conclusions: A retrospective study warrants Class III designation
Badruddoja et al. (2017)	Study description: Phase 2 study of bi-weekly TMZ plus BEV with progressive GBM Patient population: 30 adult patients with progressive GBM Treatment regimen: Bevacizumab (10 mg/kg i.v.) was given on days 1 and 15 of a 28-day cycle combined with temozolomide (100 mg/m^2) on days 1–5 and 15–19 on a 28-day cycle	III	Results: Median OS: 51 weeks Response to treatment: PFS6 was 52% with median PFS 22.7 weeks Toxicity: Most common side effects were fatigue, urinary tract infection, nausea, insomnia, leukopenia and HTN. Most serious were status epilepticus, PE, nocardia pneumonia (one patient) Authors' conclusions: BEV plus bi-weekly TMZ was well tolerated and may be a salvage regimen to be considered in a subset of patients with progressive GBM Comments and Conclusions: A study without randomization or control warrants Class III designation
Gilbert et al. (2017)	Study description: A randomized phase 2 trial of BEV + either irinotecan or dose-dense TMZ in progressive GBM Patient population: 60 adult patients were enrolled on the TMZ arm and 57 patients on the irinotecan arm Treatment regimen: BEV 10 mg/kg IV every 2 weeks, irinotecan 125 mg/m^2 every two weeks or TMZ 75–100 mg/m^2 days 1–21 of 28-day cycle	II	Results: Response to treatment: TMZ had 2 CR (3%), 9 PR (16%); irinotecan had 2 CR (4%) and 13 PR (24%) Toxicity: TMZ had 33 (55%) grade 3, 11 (18%) grade 4 and 1 (2%) grade 5 (fatal) toxicities. Irinotecan had 22 (39%) grade 3, 7 (12%) grade 4 and 3 (5%) grade 5 toxicities Authors' conclusions: The 6-month-PFS surpassed the predetermined efficacy threshold for both arms, even after prior TMZ exposure. Toxicities were within anticipated frequencies with a moderately high rate of venous thrombosis, moderate HTN and one ICH Comments and Conclusions: A randomized trial warrants Class II designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Jakobsen et al. (2017)	Study description: Toxicity and efficacy of lomustine and BEV vs irinotecan plus BEV in progressive GBM retrospective analysis Patient population: 70 patients were treated with lomustine and BEV, 219 patients with irinotecan and BEV Treatment regimen: lomustine 90 mg/m^2 every 6 weeks, BEV 10 mg/kg every 2 weeks, irinotecan 125 mg/m^2 every 2 weeks	III	Results: Median OS: 37 weeks for lom-bev and 32 weeks for iri-bev Response to treatment: lom-bev 37.1% response rate, iri-bev 30.1% response rate Toxicity: Lom-bev caused more thrombocytopenia (11.4% vs 3.5%) while iri-bev caused more GI toxicity with nausea, vomiting, diarrhea, constipation, stomatitis Authors' conclusions: No significant differences between lom-bev and iri-bev were observed with regard to PFS or OS Comments and Conclusions: A retrospective study warrants Class III designation
Peters et al. (2017)	Study description: Phase 1/2 vorinostat, BEV and daily TMZ for progressive malignant gliomas Patient population: Phase 1 was a mixed high-grade glioma population of 9 patients, phase 2 included 39 patients with progressive GBM Treatment regimen: vorinostat 400 mg (one patient 200 mg in error), BEV 10 mg/kg every other week starting on day 1 with TMZ 50 mg/m^2/day and vorinostat 400 mg days 1–7 and days 15–21 of each 28-day cycle (after dose escalation phase 1 determined dose)	III	Results: Median OS 12.5 mos Response to treatment: PFS6 was 53.8% Toxicity: Most common grade 3 or higher complications included neutropenia (4), elevated ALT (2), fatigue (2), diarrhea (2), hyponatremia (2), hyperglycemia (2) Authors' conclusions: While PFS6 was not statistically improved beyond historical controls, it is important to note that this was a heavily pretreated GBM population and further consideration is warranted in a less pretreated group Comments and Conclusions: An uncontrolled trial without randomization warrants Class III designation
Wick et al. (2017)	Study description: Bev + Lomustine in rGBM—Phase 3 Patient population: 437 adult GBM patients randomized for treatment in two arms of the study Treatment regimen: Patients in the monotherapy group received lomustine at a dose of 110 mg per square meter of body surface area every 6 weeks (maximum dose, 200 mg). Patients in the combination group received lomustine at a dose of 90 mg per square meter every 6 weeks (maximum dose, 160 mg) plus bevacizumab at a dose of 10 mg per kilogram of body weight every 2 weeks	I	Results: Monotherapy: OS 8.6 m, PFS 1.5 m Combo: OS 9.1 m, PFS 4.2 m Toxicity: Grade 3 to 5 adverse events occurred in 38.1% of the patients in the monotherapy group and in 63.6% of the patients in the combination group. Adverse events of grade 3 to 5 of special interest were pulmonary embolism, arterial hypertension, and hematologic toxic effects Authors' conclusions: Despite somewhat prolonged progressionfree survival, treatment with lomustine plus bevacizumab did not confer a survival advantage over treatment with lomustine alone in patients with progressive glioblastoma Comments and Conclusions: A large, prospective randomized trial warrants Class I designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Brandes et al. (2016)	Study description: Phase II randomized, noncomparative trial of fotemustine or bevacizumab in progressive GBM Patient population: 91 adult patients with progressive GBM (59 BEV 32 fotemustine) Treatment regimen: BEV: 10 mg/kg every 2 weeks; fotemustine: 75 mg/m^2 on days 1, 8 and 15 then 100 mg/m^2 every 3 weeks after a 35-day interval	II	Results: Median OS: 7.3 mos BEV, 8.7 mos fotemustine Response to treatment: Response rates by RANO were 29% for BEV and 9% for fotemustine Toxicity: Toxicity profiles were in line with known BEV and fotemustine toxicities with serious AE in 11 BEV (18.6%) patients and 3 (9.4%) fotemustine patients Authors' conclusions: single-agent BEV may have a role in patients with progressive GBM Comments and Conclusions: A randomized controlled trial with a moderate number of patients warrants Class II designation
Odia et al. (2016)	Study description: Phase II trial of tandutinib plus BEV in progressive GBM Patient population: 41 BEV-naïve progressive adult GBM patients Treatment regimen: tandutinib 500 mg twice daily and BEV 10 mg/kg every 2 weeks starting day 15	III	Results: Median OS: 11 mos Response to treatment: 9 had PR Toxicity: All patients had treatment-related toxicities; common grade 3 or higher included HTN (17.1%), muscle weakness (17.1%), lymphopenia (14.6%), hypophosphatemia (9.8%) Authors' conclusions: Tandutinib with bevacizumab was as effective but more toxic than BEV monotherapy Comments and Conclusions: A study without control arm or randomization warrants Class III designation
Weathers et al. (2016)	Study description: Randomized phase 2 trial of standard dose BEV vs low dose Bev plus lomustine Patient population: 69 adult patients with progressive GBM Treatment regimen: BEV 10 mg/kg IV every two weeks (standard dosing) or BEV 5 mg/kg IV every three weeks in combination with lomustine 90 mg/m^2 every 6 weeks, reduced to 75 mg/m^2 following 17 grade 3 and 7 grade 4 hematologic adverse events in 12 patients and 27 cycles of treatment	II	Results: Median OS: BEV alone 8.8 mos, BEV plus lomustine 9.6 mos Response to treatment: Median PFS and OS was not significantly longer in either arm, with trial closed early for futility Toxicity: All toxicities are in accordance with known toxicities of both drugs (lomustine dose reduced as under treatment regimen due to hematologic toxicity) Authors' conclusions: The combination of low dose BEV plus lomustine was not superior to standard dose BEV Comments and Conclusions: A randomized phase 2 trial with control warrants Class II designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Field et al. (2015)	Study description: multicenter, sequential, stratified, nonblinded, randomized phase 2 study in 2 parts, recruiting from 18 Australian studying carboplatin and bevacizumab in progressive glioblastoma, Patient population: 122 adult patients with progressive GBM after receiving standard therapy. 106 patients were initially diagnosed with GBM, the rest with Grade I-III Gliomas that were confirmed Grade IV on recurrence Treatment regimen: Eligible patients were randomized 1:1 to receive bevacizumab 10 mg/kg IV every 2 weeks plus carboplatin AUC 5 every 4 weeks (4 weeks was deemed to be the length of one cycle), or bevacizumab monotherapy at the same dose (Part 1). Study therapy continued until progressive disease, unacceptable toxicity, participant withdrawal, noncompliance with protocol guidelines, or death	II	Results: PFS6 15% for combination therapy, 18% monotherapy median PFS 3.5 m for both median OS 6.9 m combination, 7.5 m mono Toxicity: most common—fatigue, anemia, neurological symptoms/signs, hypertension, nausea, thrombocytopenia, constipation. 2 deaths, one to ICH, another to bowel perforation, both on combo therapy Authors' conclusions: In summary, we did not find that the combination of bevacizumab and chemotherapy resulted in additional PFS or OS benefit compared with bevacizumab monotherapy in progressive GBM. Hematologic toxicities were more common in the combination arm but were generally manageable, and preliminary analysis of QOL data suggests no differences between arms while patients are on treatment Comments and Conclusions: A randomized control trial warrants Class II designation
Heiland et al. (2015)	Study description: Retrospective evaluation of BEV vs BEV with lomustine in progressive GBM Patient population: 17 patients received BEV monotherapy and 18 patients received combination BEV + CCNU. Retrospectively evaluated Treatment regimen: BEV 10 mg/kg BW IV every 2 weeks, BEV/CCNS had BEV 5 mg/kg BW IV every 2 weeks, CCNU 90 mg/m^2 BSA every 6 weeks	III	Results: Median OS: 6.59 mos Response to treatment: BEV/CCNU showed improved median PFS and OS than BEV monotherapy Toxicity: In general, BEV monotherapy or BEV/CCNS were equally tolerated with rare cses of grade 3/4 and only 1 grade 5 toxicity Authors' conclusions: Last line therapy with BEV/CCNU results in a longer PFS and OS compared to BEV monotherapy and is well-tolerated Comments and Conclusions: A retrospective analysis warrants Class III designation
Odia et al. (2015)	Study description: Phase II trial of enzastaurin (LY317615) plus BEV in adults with progressive malignant glioma Patient population: 40 adult patients with progressive GBM were evaluable Treatment regimen: Patients received enzastaurin as a loading dose of 1125 mg followed by 500 or 875 mg daily for patients on non-enzyme-inducing or enzyme-inducing antiepileptics, respectively. BEV 10 mg/kg IV every two weeks	III	Results: Median OS: 7.5 mos Response to treatment: Three GBM patients were not evaluable, 8 had partial or complete response and 20 had stable disease for 2 + mos Toxicity: Most common grade 3/4 toxicities were lymphopenia (15%) hypophosphatemia (8.8%) and thrombotic events (7.5%). Two GBM patients died suddenly Authors' conclusions: Enzastaurin in combination with BEV is well-tolerated, with response and PFS similar to BEV monotherapy Comments and Conclusions: With no control arm or randomization, this study warrants Class III designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Sepulveda et al. (2015)	Study description: A phase II study of BEV with TMZ in progressive GBM Patient population: 32 adult patients with first recurrence GBM Treatment regimen: BEV 10 mg/kg IV every 2 weeks, TMZ 150 mg/m^2 days 1–7 and days 15–21 every 28 days	III	Results: Median OS: 7.3 mos Response to treatment: PFS6 rate of 21.9%, 13 patients with objective response (OR), 12 patients with SD Toxicity: Most common grade 3/4 toxicities were lymphopenia and fatigue. 2 patients had grade 3/4 thrombosis. No patient died from treatment toxicity Authors' conclusions: This regimen showed to be feasible and well tolerated. Further investigation is warranted Comments and Conclusions: A small, nonrandomized study without control warrants Class III designation
Rahman et al. (2014)	Study description: Retrospective study of carmustine or lomustine with bevacizumab in progressive GBM who failed prior bevacizumab Patient population: 42 adult patients with progressive GBM who failed prior bevacizumab (33 lomustine, 9 carmustine) Treatment regimen: lomustine doses ranged from 80–120 mg/m^2, carmustine doses ranged from 150–200 mg/m^2; one patient on BEV and lomustine also on erlotinib	III	Results: Median OS: 18.7 weeks Response to treatment: RR was 44% udring the initial BEV regimen, but 0% during the nitrosourea-containing regimen. PFS6 rate was 2.7% Toxicity: Grade 3 or 4 toxicities were 19% during initial BEV regimen, but 45.2% during the combination with nitrosourea-BEV regimen Authors' conclusions: The addition of lomustine or carmustine to bevacizumab after a patient has progressed on a bevacizumab-containing regimen does not appear to provide benefit for most patients and is associated with additional toxicity with the doses used in this cohort Comments and Conclusions: A retrospective study warrants Class III designation
Taal et al. (2014)	Study description: bevacizumab or lomustine vs combination of bevacizumab plus lomustine in patients with progressive GBM (BELOB): randomized controlled phase 2 trial Patient population: 153 adult patients from the Netherlands with progressive GBM Treatment regimen: lomustine 110 mg/m^2 orally once every six weeks, IV bevacizumab 10 mg/kg once every 2 weeks, or combination at same doses. Due to toxicity with combination treatment, lomustine reduced to 90 mg/m^2 after first 8 patients	II	Results: Median OS: 8 mos for BEV alone, 8 mos for lomustine alone, and 12 mos for combination Response to treatment: 9 mo OS was 43% with lomustine, 38% in bevacizumab 63% for bevacizumab and lomustine Authors' conclusions: The combination of bevacizumab and lomustine met prespecified criteria for assessment of this treatment in further phase 3 studies. However, the results in the bevacizumab alone group do not justify further studies of this treatment Comments and Conclusions: A randomized trial with control warrants Class II designation

Table 2 (continued)

Author (year)	Description of study	Data class	Conclusions
Arakawa et al. (2013)	Study description: Bevacizumab in Combination with Ifosfamide, Carboplatin, and Etoposide in Patients with Second Recurrence of Glioblastoma Patient population: 8 adult patients with a second relapse of glioblastoma Treatment regimen: All patients were diagnosed with second recurrence of glioblastoma refractory to ice and received 3 cycles of 10 mg/kg bevacizumab, every two weeks, in combination with the same regimen of ice as before	III	Results: Median OS: 6 m Toxicity: 3 patients with grade 3 lymphopenia, no other high-grade events Authors' conclusions: We consider that the combination of bevacizumab and ice is well tolerated and may derive some clinical benefits in progressive glioblastoma patients, in spite of the limitations of our analysis. Bevacizumab seems to be more active with in patients with first recurrence of glioblastoma compared those with second recurrence Comments and Conclusions: A small case series without control warrants Class III designation
Gil et al. (2012)	Study description: Retrospective analysis of bevacizumab plus irinotecan in progressive malignant glioma Patient population: Retrospective pooled series of adult patients with progressive malignant glioma (n = 87 with GBM) Treatment regimen: bevacizumab 10 mg/kg IV + irinotecan 125 mg/m^2 IV every two weeks or 340 mg/m^2 if receiving enzyme-inducing antiepileptic drugs. Treatment continued until progression, unacceptable toxicity, or 12 mos of treatment	III	Results: Median OS: 8.8 mos (GBM) Response to treatment: 56% of GBM patients responded to treatment. Median PFS for GBM was 5.1 mos Toxicity: Most frequent grade 3–4 toxicities were astenia (7%), diarrhea (6%), thromboembolic events (5%). There were 5 toxic deaths (4%) Authors' conclusions: Bevacizumab plus irinotecan in progressive malignant glioma improves responses, PFS and OS compared with historical data Comments and Conclusions: A retrospective series warrants Class III designation
Mrugala et al. (2012)	Study description: Retrospective review of patients with progressive glioblastoma treated with carboplatin and Bevacizumab Patient population: 14 patients with progressive glioblastoma treated at either first or second recurrence Treatment regimen: Bevacizumab 10 mg/kg every 14 days and carboplatin at AUC of 4-6 mg/ml/min, each cycle 6 weeks long including 3 doses of Bevacizumab and 2 doses of carboplatin (every 28 days)	Class III	Results: PFS-6: 40% Mean Time to progression: 4.4 m Median OS; 9.3 m RR and Toxicity profiles for all patients included, not only glioblastoma recurrence Author Conclusions: the combination of carboplatin and Bevacizumab is well tolerated and active, in progressive HGG patients Comments and Conclusions: Small cohort in a retrospective review warrants a Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *CCNU* lomustine, *PD* disease progression, *IRI* irinotecan

PFS and OS in the BEV + CCNU arm, yielding a conclusion that combination therapy as a last line therapy resulted in an improved PFS and OS compared to monotherapy. Two studies found results that showed no overall benefit. Jakobsen et al. evaluated Bev + Lomustine against BEV + irinotecan [34]. They found there was no significant difference in regards to survival between the two groups. Rahman et al. evaluated carmustine or lomustine with BEV after prior BEV failure and found there was no benefit in adding a nitrosourea agent to BEV treatment [38].

There were two studies designated Class III regarding combination therapy with fotemustine. Pasqualetti et al. studied BEV with fotemustine retrospectively with varying doses of both drugs which concluded there was no rationale to exclude BEV in combination therapy after failure of second line therapies [36]. In another study that came to a similar conclusion, Vaccaro et al. prospectively studied BEV with fotemustine in 13 patients [41]. Median OS was not reported in a fashion separable for only progressive glioblastoma patients, but RR showed no CR, 2 PR, 5 SD, with PFS of 3 months.

ACE inhibitors and bevacizumab

Gilbert et al. performed the only prospective study on ACE Inhibitors combined with BEV in this group since the previous guidelines. This was a randomized phase 2 trial of BEV and irinotecan vs BEV with TMZ in 117 patients [32]. Response rate for the TMZ arm was 3% CR and 16% PR and for the irinotecan arm was 4% CR and 24% PR. The PFS6 for the TMZ group was 39% and for the Irinotecan group was 38.6%. The PFS6 surpassed the efficacy threshold in both arms regardless of prior TMZ sensitization. As this was a prospective, randomized trial, this warrants Class II designation.

Two retrospective studies involving irinotecan were performed. Johansen et al. retrospectively reviewed 26 patients treated with BEV and Irinotecan and found a trend toward improved PFS and OS, although toxicity and mOS were not reported [35]. They did notice a beneficial effect giving irinotecan and BEV together. Gil et al. completed another retrospective analysis of BEV with irinotecan in 87 patients pooling several series together [31]. Median OS was 8.8 months with Radiographic Response (RR) of 56% and a median PFS of 5.1 months. The authors concluded the combination therapy improved PFS and OS compared to historical data. These both warranted Class III designations as they were retrospective analyses.

Synthesis

The data from the prior guidelines found a PFS6 between 18.8 and 50.3% in the included studies. Based on the update of data, the PFS6 ranged from 2.7 to 53.8%, with survival data somewhat skewed in some cases using mixed populations of patients at first or second recurrence and beyond. This ultimately didn't show any significant improvement in either mOS or PFS6. The highest level data came from a Class I designated Phase III study combining nitrosoureas with BEV and ultimately finding no significant survival advantage over monotherapy with BEV [43]. Further Class II data on the topic revealed similar findings and one was actually closed early for futility [27, 28, 42]. The data in general supported the utility of anti-angiogenic therapy throughout multiple courses of treatment for recurrence, however there was no reliable and discernible benefit in providing combination therapies with cytotoxic agents.

Question 3 In adults with progressive glioblastoma is the use of bevacizumab as a combination therapy with targeted agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior recommendations

In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, bevacizumab combined with targeted therapies was reviewed and no specific recommendations were made based on a lack of strong evidence supporting a clearly defined benefit.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Study selection and characteristics of the updated search

The initial search strategy included 3513 candidate articles. A total of 65 articles remained for full text review. From these, 3 articles were included in the final review for Question 3 and are included in Table 3 [45–47].

There was only one study showing a survival benefit with combination targeted therapy and bevacizumab. D'alessandris et al. performed a prospective trial evaluating erlotinib and BEV in combination vs BEV alone based on molecular profile of 10 patients with EGFRvIII expression or VEGF over expression [47]. Combination therapy showed a mOS 17 months and PFS6 of 100% while BEV monotherapy showed a PFS6 50% and OS 6.75 months, at which point the authors concluded there was a significant survival benefit for combination therapy. As a small study lacking a control group, these were designated Class III data.

Table 3 The role of bevacizumab with other targeted therapies

Author (year)	Description of study	Data class	Conclusions
Lassen et al. (2015)	Study description: Phase 1 dose escalation study of RO5323441 (novel antiplacental growth factor monoclonal antibody) in combination with bevacizumab in progressive GBM Patient population: 153 adult patients from the Netherlands with progressive GBM Treatment regimen: Treatment of RO5323441 (625 mg, 1250 mg, or 2500 mg) plus bevacizumab (10 mg/kg) both every two weeks. A standard 3 + 3 dose-escalation trial design was used	III	Results: Median OS: 8.5 mos Response to treatment: 9 mo OS was 43% with lomustine, 38% in bevacizumab 63% for bevacizumab and lomustine Toxicity: Common adverse events included HTN, HA, dysphonia and fatigue. Maximum tolerated dose was not reached. Dose-limiting toxicities occurred with two patients: grade 3 miningitis with a spinal fluid leak at 1250 mg and grade 3 cerebral infarction at 2500 mg Authors' conclusions: The toxicity profile was acceptable and manageable. The observed clinical activity of the combination does not appear to improve on that obtained with single-agent bevacizumab in patients with progressive GBM Comments and Conclusions: An uncontrolled dose escalation trial warrants Class III designation
Gallego et al. (2014)	Study description: Erlotinib in progressive GBM patients Patient population: 7 patients within study (adult) with progressive GBM Treatment regimen: Patients treated with bevacizumab received 10 mg/kg at days 1 and 15 during radiotherapy. If applied in patients who had no previous progression after TMZ pre-treatment a dosage of 75 mg/m2 daily was chosen	III	Results: 1 PR. 3 SD PFS6—20% median PFS 3.9 m Toxicity: No Grade 3 or higher toxicity, no dose reductions, most common toxicity was dermatitis Authors' conclusions: In conclusion, we found that erlotinib provided minimal beneficial activity on relapse GBM patients and therefore, we consider that this drug is not cost-effective in the treatment relapsed GMB patients who express EGFRVIII and PTEN as identified by IHC Comments and Conclusions: A small nonrandomized study warrants Class III designation
Dalessandris et al. (2013)	Study description: Prospective study at a single center of targeted therapy based on molecular profile of patients with progressive GBM Patient population: 10 adult patients included and analyzed for VEGF overexpression and EGFRvIII expression Treatment regimen: Bevacizumab was administered only to patients harboring a VEGF overexpressing GBM, and erlotinib was added only in EGFRvIII positive GBM. Bevacizumab was administered at a dose of 10 mg/kg iv every 2 weeks in 6-weekcycles. Erlotinib was administered at a dose of 150 mg/day orally (or 300 mg/day in patients receiving CYP3A4 enzyme-inducing anti-epileptic drugs, EIAEDs)	Class III	Results: Erlotinib + BEV: 3 CR, 1PR. PFS6 100%, OS 17 m Bev only: 1PR, 2CR (50% RR), PFS6 50%, OS 6.75 m Toxicity: no Grade 3/4 events Authors' conclusions: Our results with the combination of bevacizumab/erlotinib are significantly better than those reported by Sathornsumetee et al. using bevacizumab and erlotinib in molecularly unselected progressive GBM Comments and Conclusions: A small single-arm study without controls warrants Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *PE* pulmonary embolism

Lassen et al. evaluated a novel antiplacental growth factor monoclonal antibody (RO5323441) with BEV in 22 adult patients with progressive glioblastoma in a Phase I trial [46]. Median OS was 8.5 months with PFS 3.5 months in combination therapy, with the overall finding being that no significant improvement over BEV monotherapy was found in comparison to historical controls. Odia et al. studied enzastaurin in combination with BEV in 40 adult patients [45]. Median OS was 7.5 months. The same group then evaluated tandutinib with BEV in 41 patients, finding nonsuperiority and slightly more toxicity than BEV alone [48]. All three of these studies found nonsuperiority and due to a lack of control arms in the latter two studies and the first being a dose-escalation trial, they were all deemed Class III data.

Synthesis

In the prior guidelines published, only two trials were included that combined BEV with erlotinib or dasatinib, neither of which saw any PFS benefit, and both of which were not designated high enough class data to make a recommendation. The data reviewed since then include only Class III designations. Only one revealed significant survival benefit with erlotinib, albeit in a very small, highly specific study based on molecular profiling, while the rest showed only nonsuperiority. With the available studies and their limitations, there was insufficient high level data with consistent findings to make a treatment suggestion. This conclusion is not meant to suggest such combination studies are not worthy of further investigation and it is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies of this issue.

Question 4 In adults with progressive glioblastoma is the use of targeted agents as monotherapy superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendations: In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, targeted therapies other than BEV were reviewed and no specific recommendations were made based on a lack of strong evidence supporting a clearly defined benefit or detriment.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Study selection and characteristics of the updated search

The initial search strategy included 3513 candidate articles. A total of 65 articles remained for full text review. From these, 23 articles were included in the final review for Question 4 and are included in Table 4 [49–71].

A total of 23 articles described the use of targeted therapies alone, not including BEV. [49–66, 68, 69, 72] Two studies used a targeted therapy in conjunction with repeat radiation therapy [49, 50]. One study discussed the use of a cytotoxic agent (temsirolimus) in conjunction with Sorafenib [72]. Another study involved intracavity delivery of a targeted agent [59]. Retinoic acid naphthalene was given in another study, which was the only update discovered on the use of retinoids in progressive glioblastoma [61]. Combination of targeted agents (cediranib and cilengitide) were given in one study while cediranib and gefitinib were administered in combination in another study, providing the only two studies using combinations of targeted therapies [63, 67]. The remainder of studies were single agent targeted therapies [51–58, 60, 62, 64–69].

Single agent targeted therapies

Targeted therapies have been gaining attention recently, especially with the identification and characterization of several molecular variations among glioblastoma and the possibility of temozolomide resistance. Furthermore, there is a renewed vigor to find an effective, individualized molecular treatment for glioblastoma, especially in the progressive setting, beyond BEV.

Several small molecule targeted therapies were evaluated. Pitz et al. evaluated the use of PX-866 in 33 adult patients with progressive glioblastoma [52]. The study found a PFS6 of 17%. The authors concluded that although the drug was well tolerated, it did not meet the predetermined efficacy end points. Aiken et al. provided a phase I clinical trial with dose escalation of a small molecule inhibitor of IGF1b in a small group of 7 patients [69]. They concluded there was a sustained clinical response. As it was a dose-escalation trial and had no control group, it was given a designation of Class III evidence. PLX3397, a Colony Stimulating Factor 1 Receptor inhibitor was given to 13 patients, finding a mOS of 9.5 months with no radiographic responses [66]. This was also designated Class III as it was a small cohort without randomization. Gilbert et al. studied cilengitide along with resection after recurrence in 26 patients and established the efficacy was only modest, yielding a Class III designation as a small Phase I trial in a small number of patients [71].

Depatux-m was studied by Gan et al. as a multicenter, Phase I dose escalation study, which combined newly diagnosed and progressive glioblastoma [64]. In the

Table 4 The role of targeted therapies other than bevacizumab in progressive GBM

Author (year)	Description of study	Data class	Conclusions
Lassman et al. (2019)	Study description: Adult patients with progressive GBM were entered in a multicenter, phase 1, open-label study of depatux-m alone or in combination with other agents in GBM Patient population: 60 adult patients with EGFR-amplified, measurable recurreng GBM (bevacizumab and nitrosourea naïve) Treatment regimen: Depatux-m (0.5–1.5 mg/kg) on days 1 and 15, and TMZ (150–200 mg/m^2) on days 1–5 on a 28-day cycle	III	Results: Median OS: 7.4 mos Response to treatment: 58/60 patients had measurable disease at baseline evaluable for radiographic response. 26 patients had SD, 24 PD with median duration of response 5.6 mos, median PFS 2.1 mos Toxicity: There were no new safety events observed from combined depatux-m and TMZ compared to depatux-m monotherapy or concurrent RT, TMZ and depatux-m, and represent common side effects associated with TMZ including rare thrombocytopenia. Common AE include ocular side effects, but no patient permanently discontiunued treatment while on study (nine patients up to nine months) Authors' conclusions: Depatux-m + TMZ displayed an AE profile similar to what was described previously. Antitumor activity in this TMZ-refractory population was encouraging Comments and Conclusions: A multicenter, nonrandomized trial without control warrants Class III designation
Lombardi et al. (2019)	Study description: Phase II open label, randomized, multicenter clinical Trial comparing Regorafenib with lomustine in progressive glioblastoma Patient population: 119 total patients with progressive glioblastoma treated with regorafenib (n = 59) or lomustine (n = 60) Treatment regimen: Regorafenib 160 mg once daily for 21 days of each 4 week cycle or lomustine 110 mg/m^2 once every 6 weeks until end point reached	Class II	Results: Median OS: 7.4 months in regorafenib, 5.6 m in lomustine group Toxicity: Regorafenib: Grade III-IV skin reaction, lipase elevation, bilirubin elevation in 10% of group for each Lomustine: Grade III-IV thrombocytopenia (13%), lymphopenia (13%), neutropenia (12%) No mortality from toxicity Authoers' Conclusions: Regorafenib showed an encouraging survival benefit in progressive glioblastoma warranting an adequately powered Phase 3 study Comments and Conclusions: A Phase II multicenter, randomized trial with a moderate sized patient cohort warrants Class II Designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Wen et al. (2019)	Study description: Buparlisib in Patients with Progressive Glioblastoma Harboring Phosphatidylinositol 3-Kinase Pathway Activation: An Open-Label, Multicenter, Multi-Arm, Phase II Trial Patient population: 65 total patients, adult with progressive GBM at first or second relapse Treatment regimen: Cohort 1—15 patients receiving pre-op buparlisib for 7-13d, received surgery, then resumed treatment. Cohort 2—100 mg daily of buparlisib for every 28-day cycle until progression of disease	III	Results: Response Rate: Cohort 1—40% SD, 60% PD. Cohort 2—42% SD, 54% PD, 4% not evaluable PFS6—Cohort 1 67%, Cohort 2 8% PFS 1.8 m v 1.7 m. OS 17.9 m v 9.8 m Toxicity: 40% with Grade 3–4 AE. 1.5% (n = 1) with grade 4 event possibly related to treatment.3.1% discontinued (n = 2) Authors' conclusions: This study shows that the brain-penetrant PI3K inhibitor buparlisib has minimal single-agent efficacy in patients with progressive glioblastoma.5,20,21 Buparlisib did not meet the primary pharmacodynamic and efficacy end points of this study. These findings are consistent with previous results wherein PI3K/mTOR inhibitors alone or in combination with cytotoxic or targeted therapies in patients with glioblastoma unselected for PI3K pathway activation showed no clinical benefit Comments and Conclusions: A multicenter trial without randomization or control warrants Class III designation
Gan et al. (2018)	Study description: Multicenter, phase I dose escalation study in patients with newly diagnosed and progressive GBM Patient population: 38 adults with newly diagnosed or progressive supratentorial GBM (24 progressive) Treatment regimen: A dose escalation model (3 + 3) was used with depatux-m administered beginning at 0.5 mg/kg with dose level increased by no more than 100% until the first grade > / = 2 drug-related AE was observed. Patients in one arm of recurrence received TMZ (150 mg/m^2) concomitantly. Once arm C (progressive GBM without TMZ) had started, RP2D of depatux-m had been established at 1.25 mg/kg with TMZ, so dosing began without TMZ at this dose. Depatux-m was given on days 1 and 15 of every 28-day cycle. Dexamethasone (0.1%) eye drops were administered prophylactically to all patients with 1.0 mg/kg or higher depatux-m	III	Results: Median OS: 10.7 mos for progressive GBM Response to treatment: For progressive patients, 1 had CR, 2 had PR, 10 had SD and 11 and PD Toxicity: The most important toxicities were ocular, occuring in 92% of patients, reducing with dose reduction or interruption, leading to only 5% study discontinuation rate due to toxicity (5%). Additional common AE (over 25% of patients) included fatigue, nausea, thrombocytopenia, headache, and seizure Authors' conclusions: We observed an encouraging 30.8% PFS6 in progressive GBM patients treated with depatux-m. Thus, further evaluation of depatux-m versus depatux-m + TMZ is warranted in progressive GBM Comments and Conclusions: A phase 1 study in a small cohort with no control warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Krolicki, et al. (2018)	Study description: Adult patients with progressive GBM in a single-arm prospective trial of 213Bi-DOTA-substance P Patient population: Twenty adult patients with histologically confirmed progressive GBM, tumor volume less than 90 mL without hydrocephalus and KPS > 40 were included Treatment regimen: One or two catheters connected to a subcutaneous port were placed into the postsurgical cavity stereotactically or intratumorally 2–4 weeks before treatment. 1 to 3 injections (up to 2.1 GBq) were performed depending on the activity of 213Bi available from the 225Ac/213Bi generator. Patients received between 1–7 cycles, receiving 213Bi-DOTA-SP every 2 mos	III	Results: Median OS: 10.9 mos Response to treatment: 55%, 40% and 30% of patients remained alive during the 6 mo, 12 mo and 18 mo follow-up from start of radioisotope treatment Toxicity: Two patients had facial flushing, one had ventricular enhancement on MRI without symptoms (patient received high dose steroids), 10 patients had seizures within 2–5 days of injection, one patient had transient worsening of paresis Authors' conclusions: Median OS after recurrence of 10.9 mos compares favorably to standard treatments Comments and Conclusions: A small series without randomization or control warrants Class III designation
Schiff et al. (2018)	Study description: Phase I/II Trial of Temsirolimus and Sorafenib in Treatment of Patients with Progressive Glioblastoma: North Central Cancer Treatment Group Study/Alliance N0572 Patient population: Phase 1 arm A—12 patients with progressive GBM. Phase 2 arm B (VEGF Naïve), 50 adult patients with progressive GBM, 46 patients treated at Phase 2 dose, 3 patients at phase 2 dose. Arm C—9 patients treated at phase II MTD, presurgical exposure. Arm D 50 patients with prior VEGF treatment Treatment regimen: The phase I component (Arm A) utilized a standard "3 + 3" dose escalation design. The starting dose was sorafenib 200 mg orally twice daily and temsirolimus 25 mg intravenously (IV) weekly. Six escalating dose levels were planned beyond the starting dose (range: sorfenib 200 mg – 400 mg, temsirolimus 25 mg – 250 mg)	III	Results: Arm B PFS6 17.1%, PFS 2.7 m, OS 6.6 m 64% SD, 27% PD, 9% PR (3 regressed) Arm C: PFS6 22.2%, PFS 4.3 m, OS 6.7 m Arm D: PFS6 9.1%, PFS 1.9 m, OS 3.9 m, 2% regression, 46% SD, 51% PD Toxicity: Grade 3 + events Arm A 75.5%, B 73.9%, C 77.8%, A 66.7% Authors' conclusions: Limited activity of sorafenib and temsirolimus in this dose and schedule was observed with considerable grade 3 + toxicity. Significant dose reductions required in this treatment combination compared to tolerated single-agent doses may have contributed to the lack of efficacy Comments and Conclusions: A phase I/II study without randomization or control warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Aiken et al. (2017)	Study description: Phase I Clinical Trial of AXL1717 (small molecule inhibitor of IGF-1b), open label, single-center, with 3 + 3 dose escalation schedule Patient population: 9 adult patients with progressive malignant glioma, one with gliosarcoma, one with transition from AA to GBM, 7 with GBM all treated with AXL1717 Treatment regimen: Patients dosed twice daily as an oral suspension for cycles of 28 consecutive days followed by a 7-day holiday	III	Results: Median OS: 10.1 m Toxicity: 5 SAE. 1 patient with 400 mg BID dosing had neutropenia, died of gram negative sepsis. Grade 3–4 events included 5 with neutropenia, 1 with anemia, 2 with thrombocytopenia Authors' conclusions: In conclusion, this phase I clinical trial reveals that AXL1717 is a promising drug having the capability as a single agent to produce sustained clinical responses in patients with relapsed malignant astrocytomas Comments and Conclusions: A small, phase 1 study without control warrants Class III designation
Kalpathy-Cramer et al. (2017)	Study description: Phase 2 study of tivozanib in progressive GBM Patient population: 10 adult patients with progressive GBM Treatment regimen: Tivozanib 1.5 mg daily, 3 weeks on/1 week off in 28-day cycle	III	Results: Median OS: 8.1 mos Response to treatment: 1 CR, 1 PR, 4 SD and 4 PD Toxicity: Two patients were taken off study for toxicity Authors' conclusions: Despite functional changes in tumor vasculature, tivozanib had limited anti-tumor activity Comments and Conclusions: A small cohort without randomization or control warrants Class III designation
Phuphanich et al. (2017)	Study description: phase II, multicenter, single-arm, open-label study using MEDI-575 in progressive GBM Patient population: 56 adult patients with progressive malignant gliomas, 51 with GBM at first diagnosis Treatment regimen: Patients received intravenous MEDI-575 25 mg/kg over 60 min every 21 days until disease progression, unacceptable toxicity, or other reason for discontinuation	III	Results: PFS6: 15.4%, median PFS: 1.4 m, median OS 9.7 m No complete/partial responses, 41% stable disease Toxicity: most common—diarrhea (16%), nausea (13%), fatigue (13%). 12 patients with grade 3 or higher, 3 hydrocephalus, 2 dysphagia, 2 seizure. Serious AE in 17 patients (30%), 7 (13%) discontinued due to pneumonia, resp failure, sepsis in one patient, gait/aphasia/hemiparesis in 1 patient, hydrocephalus and AMS in 1 patient, seizure (1), cerebral edema (1), confusion (1), cardiac failure (1) Authors' conclusions: MEDI-575 has an acceptable tolerability profile but limited activity in patients with a frst recurrence of glioblastoma. Whether PDGF is an appropriate target is uncertain given other negative studies using imatinib in progressive glioblastoma Comments and Conclusions: A single-arm nonrandomized study without control warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Van Den Bent et al. (2017)	Study description: Efficacy of depatuxizumab mafodotin (ABT-414) monotherapy in patients with EGFR-amplified, progressive glioblastoma: results from a multi-center, international study (Phase 1) Patient population: 66 adult patients with EGFR amplified rGBM Treatment regimen: RPTD of depatux-m monotherapy was determined previously as 1.25 mg/kg via intravenous (IV) infusion every 2 weeks [25]. All patients received 1.25 mg/kg of depatuxm via intravenous infusion over 30–40 min on Days 1 and 15 of a 28-day cycle	III	Results: Response Rate: 41% SD, 52% PD, PFS6 28.8%, PFS 1.7 m, OS 9.3 m EGFRvIII mutation: PFS6 17.2%, PFS 1.6 m Toxicity: 91% experienced ocular AE, 42% experienced Grade 3/4 AE Authors' conclusions: We observed in this multicenter, dose expansion study that depatux-m monotherapy administered at the RPTD in patients with EGFR-amplified, rGBM demonstrated promising efficacy and manageable toxicity, indicating that further study of this novel targeted therapy in GBM is justified Comments and Conclusions: A nonrandomized study without control warrants Class III designation
Batchelor et al. (2016)	Study description: Phase 1 and 2 studies of tandutinib in progressive GBM Patient population: 19 adult patients with progressive GBM were treated in phase 1 and 30 in phase 2 Treatment regimen: Tandutinib in phase 1 was given at 500, 600 and 700 mg twice daily dosing, and 600 mg twice daily on phase 2 (maximum tolerated dose)	III	Results: Median OS: 8.8 mos Response to treatment: There was one complete response (3%) and 5 patients reached PFS6 (16%) Toxicity: Dose limiting toxicity occurred in 1/6 patients at 500 mg, 1/6 at 600 mg, and 2/3 at 700 mg. Toxicities included grade 3 phosphorus, fatigue, somnolence or weakness Authors' conclusions: The phase 2 study was closed at interim analysis due to lack of efficacy, despite relevant intratumoral drug concentrations Comments and Conclusions: A small study without a control arm warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Brown et al. (2016)	Study description: multi-center randomized, two-armed, double-blinded phase II study comparing cediranib plus gefitinib versus cediranib plus placebo in subjects with first relapse/first progression of glioblastoma following surgery and chemoradiotherapy Patient population: 38 adult patients with progressive GBM (after standard first line therapy) were randomized to cediranib + gefitinib or cediranib + placebo, 19 in each group. Cediranib development was discontinued midstudy resulting in premature termination of recruitment Treatment regimen: Patients were randomized to receive cediranib plus gefitinib or cediranib plus placebo. All patients received 30 mg cediranib (AZD2171) orally every day along with a daily oral dose of either 500 mg gefitinib or a matched placebo. Dose selection was based on reported toxicity and the maximum tolerated dose in the phase 1 study of cediranib in combination with gefitinib	II	Results: median OS: 7.2 m for C + G, 5.5 m for C + Placebo PFS: 3.6 m for C + G, 2.8 m for C + placebo. PFS6 for both was 15.8% No complete responses, PR in 42% of C + G, 26% in C + Placebo Toxicity: 16 patients on C + G reported Grade 3 event, 14 in C + placebo Authors' conclusions: Cediranib and gefitinib in combination is tolerated in patients with glioblastoma. Incomplete recruitment led to the study being underpowered. However, a trend towards improved survival and response rates with the addition of gefitinib to cediranib was observed. Further studies of the combination incorporating EGFR and VEGF inhibition are warranted Comments and Conclusions: This was a multicenter, double-blind, randomized control trial that reached only Class II designation due to small sample size
Butowski et al. (2016)	Study description: Orally administered colony stimulating factor 1 receptor inhibitor PLX3397 in progressive glioblastoma Patient population: 37 patients were enrolled, with 13 treated for 7 days prior to and after a planned surgical resection (Cohort 1) and 24 treated without surgery (Cohort 2) Treatment regimen: PLX3397 was given orally 1000 mg daily beginning 7 days prior to surgery (Cohort 1) or without surgery (Cohort 2)	III	Results: Median OS: 9.4 m PFS6: 8.8% No partial or complete response on imaging Toxicity: 12 patients with Grade 3–4 AE likely related to study drug, most commonly alkaline phosphatase elevation. Only reported death was attributed to tumor progression Authors' conclusions: PLX3397 is a potent inhibitor of tumor-associated macrophages and microglia, readily entered GB tumor tissue, and demonstrated PD effects in some patients. However, there was no significant improvement in efficacy in the present study compared with historical controls Comments and Conclusions: This phase II study had a small cohort without randomization or control. This warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Gerstner et al. (2015)	Study description: Phase I study of cediranib in combination with cilengitide in patients with progressive GBM Patient population: 45 adult patients with progressive GBM Treatment regimen: 40 patients enrolled in a dose expansion cohort with 20 being exposed to anti-VEGF therapy and 20 patients naïve. Cediranib was 30 mg by mouth daily and cilengitide was 2000 mg IV twice weekly to determine MTD. No dose-limiting toxicities were observed in the first five patients, so dose reductions were not required	III	Results: Median OS: 6.5 mos Response to treatment: 2 CR, 2 PR, 13 SD 21 PD. Total response rate of 8.9% Toxicity: No dose limiting toxicities were observed, with grade 3/4 toxicities including elevated ALT/AST, cognitive disturbance, diarrhea, duodenal hemorrhage, HA, HTN, decreased lymphocytes, hypophosphatemia, thrombocytopenia, seizures, abdominal cramping and fatigue Authors' conclusions: The combination of cediranib with cilengitide was well tolerated and associated with pharmacodynamic blood and imaging biomarkers. However, the survival and response rates do not warrant further development of this combination Comments and Conclusions: A phase 1 study without randomization or control warrants Class III designation
Jia et al. (2015)	Study description: Prospective nonrandomized trial of adult patients with progressive malignant supratentorial glioma Patient population: Progressive high-grade glioma patients (19 with progressive GBM) Treatment regimen: Retinoic acid naphthalene triazole was given orally at a dosage of 50 or 80 mg/m^2 once daily for 3 weeks followed by no treatment for one week, three patients received 3 days of 100 mg/m^2 but dose reduced to 80 due to toxicity. Treatment continued until disease progression, toxicity or withdrawal of consent	III	Results: Median OS: 69 weeks Response to treatment: 0 PR 5 minor response (less than 25% decrease in lesion on imaging), 6 SD and 8 PD. Median PFS 28 weeks Toxicity (all patients): Skin erythema, cheilitis and conjunctivitis in most patients, requiring dose reduction in patients over 80 mg/m^2 Authors' conclusions: Retinoic acid naphthalene triazole seems to have a role in the treatment of progressive malignant glioma by increasing median survival and keeping 45% of patients progression-free for six months Comments and Conclusions: A nonrandomized trial without control in a small cohort warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Lassman et al. (2015)	Study description: Adult patients with progressive GBM in a single arm dose escalation Phase 2 trial Patient population: 50 patients with bevacizumab-naïve progressive GBM harboring overexpression of SRC, PDGFR, EPHA2 and/or c-KIT were treated in a single arm Phase 2 trial of dasatinib as monotherapy Treatment regimen: Dasatinib was initiated at 100 mg twice daily until disease progression or intolerable toxicity, cycle defined as 28 days although treatment was continuous for Stage 1 patients (21) until disease progression or intolerable toxicity. Stage 1B patients had dose escalation escalation by 50 mg per day per cycle up to a maximum of 400 mg total per day, absent intolerable toxicity	III	Results: Median OS: 7.9 mos Response to treatment: Of 50 patients, best response was 12 SD while 36 had PD. There were no responses Toxicity: Grade 3 or higher toxicities included: 9 patients with hematologic toxicities, 1 cardiac toxicity, 6 fatigue, 6 insomnia, one pyrexia, 3 GI toxicities, 2 hemorrhages, 7 metabolic toxicities, 2 musculoskeletal toxicities, 2 neurological toxicities, and one pain Authors' conclusions: Intraparticipant dose escalation was feasible, but dasatinib was ineffective in progressive GBM Comments and Conclusions: A trial without randomization or control arm warrants Class III designation
Pitz et al. (2015)	Study description: multicenter, open-label, single arm, phase II study using PX-866 in progressive GBM Patient population: 33 adult patients with progressive GBM Treatment regimen: Eligible patients were given 8 mg of PX-866 by mouth daily, starting within 2 days of registration. Each cycle was 8 weeks long	III	Results: Response: 73% progressive disease, 3% partial response, 24% stable (maintained 6.3 m) PFS6 17%, Toxicity: 6 discontinued therapy for disease toxicity (ALT elevation, 1 allergic rxn), 27 for disease progression. Grade 3—6 with lymphopenia, 4 with ALT elevation, 6 with AST elevation, 1 with hyponatremia, 5 with diarrhea, 1 with nausea, 1 with vomiting, 2 with fatigue, 1 weakness, 1 thromboembolic event. Grade 4: 1 lymphopenia, 4 ALT, 1 AST Authors' conclusions: This agent was reasonably well tolerated but did not meet the predefined efficacy endpoints. Despite this, a notable portion of the participants had prolonged stable disease while on PX-866 Comments and Conclusions: A single-arm nonrandomized study without control warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Hassler et al. (2014)	Study description: Open label single center trial of patients with progressive GBM treated with imatinib if patient tumor IHC positive for PDGF-R, c-abl, c-kit, arg, or c-fms Patient population: 24 Adult patients with progressive GBM within at least three months of initial treatment end with tissue available for IHC, IHC had to be positive for one or more imatinib targets, but any number of recurrences or prior treatments were allowed Treatment regimen: Imatinib was given 400 mg fixed dose per day continuous oral dosing until tumor progression, unacceptable toxicity or consent withdrawal	III	Results: Median OS: 6 mos Response to treatment: Two patients achieved PR, 10 reached stable disease, 12 showed progression on first scan Toxicity: Transient peripheral edema of legs or eyelids in six patients, abdominal pain in 3 patients (until all started on PPI), nausea and vertigo each in one patient, all grade 2 or lower. No patients stopped imatinib due to doxicity and none withdrew consent Authors' conclusions: Marginal benefit of imatinib was shown in progressive GBM Comments and Conclusions: A single center trial without controls in a small patient population warrants Class III designation
Wick et al. (2014)	Study description: A Phase II, Randomized, Study of Weekly APG101 Reirradiation versus Reirradiation in Progressive Glioblastoma Patient population: 91 adult patients with 1st or 2nd recurrence GBM Treatment regimen: Patients were centrally randomized 1:2 to receive rRT (36 Gy) or rRT (36 Gy) + APG101 400 mg weekly until progression	II	Results: rRT PFS6 3.8% < PFS 2.5 m, OS rRT + APG101: PFS6 20.7%, PFS 4.5 m OS 11.5 m for both Toxicity: 22 patients with severe AE, none discontinued treatment Authors' conclusions: CD95 pathway inhibition in combination with rRT is an innovative concept with clinical efficacy. It warrants further clinical development. CD95L promoter methylation in the tumor may be developed as a biomarker Comments and Conclusions: A Phase II trial with randomization in a moderate patient population warrants Class II designation
Wuthrick et al. (2014)	Study description: Pilot Study of Hypofractionated Stereotactic Radiation Therapy and Sunitinib in Previously Irradiated Patients With Progressive High-Grade Glioma Patient population: 11 adult patients with HGG, 7 patients with progressive GBM Treatment regimen: During the treatment period, 37.5 mg sunitinib was given starting on RT day 1 and then daily including weekends	III	Results: OS GBM Only 12.7 m, PFS 6.4 m, PFS6 50%, RR—PR/CR 10%, SD 60%, PD 30% Toxicity: generalized data, not specific to GBM: 5 patients had grade 1 toxicity including thrombocytopenia (n = 4), leukopenia (n = 3) and hyponatremia (n = 3). Five patients had grade 2 toxicity including hematologic disorders, fatigue, hypertension, esophagitis and elevated liver enzymes. One patient had a grade 4 oral ulcer Authors' conclusions: Sunitinib at a daily dose of 37.5 mg given concurrently with hypofractionated stereotactic reirradiation for rHGG yields acceptable toxicities and an encouraging 6-month progression-free survival Comments and Conclusions: A phase 1 study in 11 patients without control or randomization warrants Class III designation

Table 4 (continued)

Author (year)	Description of study	Data class	Conclusions
Muhic et al. (2013)	Study description: An open-label, uncontrolled phase II study of nintedanib in patients with progressive GBM Patient population: Adult patients with progressive GBM who failed either radiotherapy plus TMZ (n = 13) or had failed radiotherapy and TMZ as well as second-line BEV (n = 12) Treatment regimen: Nintedanib orally 200 mg twice daily	III	Results: Median OS: 6 mos Response to treatment: Best response was stable disease in three patients. All others progressed within the first four 28-day cycles Toxicity: Grade 1–2 fatigue, loss of appetite, diarrhea and nausea Authors' conclusions: Single-agent nintedanib demonstrated limited, but clinically non-relevant antitumor activity in patients with progressive GBM who had failed 1–2 prior lines of therapy Comments and Conclusions: A nonrandomized study without control in a small cohort warrants Class III designation
Gilbert et al. (2012)	Study description: Prospective phase I trial of post-re-resection treatment with cilengitide Patient population: 30 pts, 26 pts available for evaluation, with progressive GBM Treatment regimen: Cilengitide 2000 mg i.v. twice weekly (maximum of 2 years of treatment)	III	Results: The 6-month progression free survival rate was 12% Toxicity: There were 9 grade 3–4 toxicities, mainly lymphopenia, likely related to prior cytotoxic chemotherapy. There were no dose reductions for toxicity and no treatment related deaths Authors' conclusions: This study provides evidence that with established dosing, cilengitide is adequately delivered to the tumor, although as a signle agent, efficacy in progressive GBM is modest Comments and Conclusions: A prospective phase 1 trial in a small patient cohort without a control warrants class III designation
Pan (2012)	Study description: A prospective phase II single-institution trial of sunitinib for progressive malignant glioma Patient population: 16 adult patients with progressive GBM Treatment regimen: Trial patients received sunitinib 50 mg daily for 4 weeks without regard to meals, followed by a 2-week rest period. This 6-week regimen constituted 1 cycle. Patients were treated for up to 9 cycles (~ 1 year) or until disease progression or death or if persistent toxicities occurred	III	Results: PFS6: 12.5%, PFS 1.4 m, OS 12.6 m Response Rate: Stable Disease or better: 31.3% Toxicity: 4 patients had Grade 3, 1 grade 4 neutropenia/thrombocytopenia, 56.3% had fatigue, 43.8% diarrhea, 31.3% neutropenia, 25% thrombocytopenia Authors' conclusions: Although sunitinib was deemed to be a potentially effective treatment for progressive MAG, the current study is concordant with prior studies confirming lack of significant anti-glioma activity. This may be due to the possibility that the tolerated dose of sunitinib may be insufficient to significantly affect tumor growth or induce tumor responses Comments and Conclusions: A small nonrandomized trial without control warrants Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *PE* pulmonary embolism, *ALT* alanine aminotransferase, *AST* aspartate aminotransferace, *GBq* Gigabecquerel, *IHC* immunohistochemistry, *PDGF-R* platelet derived growth factor receptor, *arg* arginine

data separable for progressive patients, median OS was 10.7 months with 30.8% of patients reaching PFS6. Results were considered encouraging, the study was small without a control. Lassman et al. also studied administration of depatux-m in 60 patients with EGFR amplification in progressive glioblastoma without prior BEV or nitrosourea administration [57]. Median OS was 7.4 months and median PFS 2.1 months, with authors concluding the TMZ refractory population showed encouraging results. Van Den Bent et al. studied the efficacy of depatux-m in 66 patients [70]. All patients had EGFR amplified glioblastoma, and results showed a PFS6 of 28.7%, PFS 1.7 months, mOS 9.3 months. The authors concluded that monotherapy in these patients showed some efficacy and tolerable toxicity requiring further study. These three trials lacked control groups and were non-randomized, designating each as Class III evidence.

Tyrosine kinase inhibitors

Several studies also focused on tyrosine kinase inhibitors. Gallego et al. evaluated erlotinib in 13 progressive glioblastoma patients harboring PTEN, EGFR, and EGFRvIII overexpression [65]. PFS6 was 20%. Authors felt this was of no benefit and that it was not cost-effective in this patient population. Tivozanib was evaluated in a phase II study of 10 patients by Kalpathy-Cramer et al. and showed a mOS of 8.1 months but discovered limited anti-tumor activity [60]. Lassman et al. evaluated 50 patients with BEV naïve recurrence, overexpression of SRC, PDGFR, EPHA2, and/or c-kit and administration of dasatinib monotherapy, also without any benefit [58].

Several of the included studies revolved around Tyrosine Kinase inhibitors with a focus on PDGFR interaction. Muhic et al. evaluated the use of nintedanib in 25 progressive glioblastoma patients with similar findings of a lack of anti-tumor activity [55]. Phuphanich reviewed the utility of targeting PDGFRalpha with MEDI-575 in a Phase II, multicenter, open-label study in 51 progressive glioblastoma patients [53]. PFS6 was 15.4% and mOS 9.7 months, but also showed limited activity in comparison to historical controls at first recurrence. Batchelor et al. completed Phase I and II trials of the PDGFRa inhibitor tandutinib in 19 patients and 30 patients, respectively [68]. Median OS was 8.8 months and PFS6 was 16% and the study was closed early due to a lack of efficacy. Hassler et al. studied the utilization of imatinib in 24 patients with PDGF-R, c-abl, c-kit, arg, or c-fms detected [62]. In a group that combined patients at varying numbers of recurrences, mOS was 6 months and only marginal benefit was seen.

Pan et al. attempted sunitinib administration in a phase II single institution trial of 16 patients [54]. 12.5% of patients reached PFS6, PFS was 1.4 months, and mOS was 12.6 months. 31.3% of patients had stable disease or better. The authors concluded sunitinib could be a potentially effective treatment for progressive glioblastoma, although this and prior studies showed a lack of significant anti-glioma activity. This was designated Class III for a small, nonrandomized trial design without a control group.

Regorafenib, an oral receptor tyrosine kinase inhibitor targeting VEGFR-2, was compared with lomustine in a moderately sized, multi-center, randomized trial which showed an encouraging survival benefit with the use of regorafenib [56]. In about 119 patients trialed with progressive glioblastoma, the group given regorafenib saw mOS of 7.4 months compared to 5.6 months in the lomustine group. This study design warranted Class II designation.

Retinoids

Prior studies showed minimal to no activity of retinoids alone at recurrence, with a single example of a retinoid combined with TMZ showing a survival benefit compared to TMZ alone, but with only minimal radiographic response rates [73]. In our update, a study by Jia et al. was a prospective nonrandomized trial with administration of retinoic acid naphthalene in 19 patients [61]. Median OS was 69 weeks (16.1 months), Median PFS was 28 weeks and the authors concluded retinoic acid naphthalene triazole may have a role in the treatment of progressive glioblastoma with 45% of patients reaching PFS6.

Stereotactic intratumoral delivery

Krolicki et al. evaluated the efficacy of placement of a subcutaneous port with catheters stereotactically driven into the tumor cavity for future administration of 213Bi-DOTA-substance P in a single arm prospective study [59]. Median OS was 10.9 months, 55% of patients remained alive at 6 months, 40% at 12 months, and 30% were alive at 18 months of follow up from the start of treatment. The authors concluded the mOS of 10.9 months compared favorably to standard treatments. This was also designated Class III as the study was a small sample size without a control group.

Buparlisib (PI3K inhibition)

Wen et al. used buparlisib to target phosphatidylinositol-3-kinase in 65 patients with progressive glioblastoma at their first or second relapse [51]. Results showed PFS6 of 67% in cohort 1, 8% in cohort 2. PFS was 1.8 months in Cohort 1 and 1.7 months in cohort 2 with OS of 17.9 versus 9.8 months, respectively. The authors concluded the PI3K inhibitor, known to penetrate the blood brain barrier, had efficacy as a single agent but did not meet pharmacodynamic

and efficacy end points and the findings were consistent with prior studies showing no clinical benefit in patients unselected for PI3K pathway activation. This was designated Class III as the trial lacked randomization and there was no control group.

Dual agent targeted therapy

We encountered two studies using a combination of targeted therapies [63, 67] One, a study by Gerstner et al., gave cilengitide, an anti-angiogenic small molecule targeting integrins, and cediranib, an oral VEGF inhibitor, in a phase I trial, warranting class III designation [63]. Forty patients were treated and results showed a mOS of 6.5 months and response rates at 8.9%, with a conclusion that although the regimen was well tolerated, there was no overall benefit discerned to warrant further study. Brown et al. compared cediranib and gefitinib to cediranib and placebo with 19 patients in each group [67]. Response rates were 42% PR in the combination group and 26% in the placebo arm and mOS of 7.2 months in the combination group and 5.5 months in the placebo arm. PFS was 3.6 months in the combination therapy group and 2.8 months in the placebo group. The study suffered from incomplete recruitment due to discontinuation of cediranib production mid-study, but concluded there was a trend toward improved survival and response rate. This was designated Class II data as it was a multicenter, double-blind, randomized, control trial with a small sample size.

Radiation and targeted therapies

We found two studies regarding targeted therapies specifically and intentionally used in combination with repeat radiation therapy [49, 50]. Wuthrick et al. completed a pilot study of hypofractionated stereotactic radiation therapy in conjunction with sunitinib [49]. Eleven patients were studied, 7 of which were progressive glioblastoma previously treated with radiotherapy. Results specifically for progressive glioblastoma patients included an OS of 12.7 months, PFS of 6.4 months, PFS6 of 50%, and response rates including 10% PR/CR, 60% with SD and 30% with PD. The authors concluded the results were encouraging in terms of PFS6 and safety and warrant further study. This was designated Class III for a small, nonrandomized cohort without a control group.

Wick et al. studied the effect of APG101 (CD95/CD95L inhibitor) with reirradiation (rRT) versus only reirradiation [50]. 91 patients at the first or second recurrence were randomized and the irradiation only group had a PFS6 of 3.8% and PFS 2.5 months, while the combination treatment group had a PFS6 of 20.7% and PFS 4.5 months. They concluded CD95 pathway inhibition with rRT had clinical efficacy and needed further study and potentially more identification of patients with CD95L promoter methylation as a biomarker. This was designated Class II evidence with a moderate size population and randomization.

Synthesis

The prior guidelines on targeted therapy included studies on a wide array of targeted therapies. The only new studies providing encouraging results but without significant discernible benefit were the studies regarding Depatux-m, showing mOS of 7.4 to 10.7 months in early phase trials, and radiation with targeted therapies with one Class II study showing a significant benefit compared to RT alone at recurrence. Another promising Class II study showed only a trend toward a survival benefit when combining Gefitinib and cediranib, improving slightly upon the data in the prior guidelines showing a gefitinib with at most a potential efficacy in monotherapy. Regorafenib, another set of class II data, saw a survival benefit compared to cytotoxic treatment. The rest of the evidence was Class III evidence with significant limitations in trial and study designs, with no new data showing improved clinical benefit with tyrosine kinase inhibitors, buparlisib, or retinoids. Thus, there was no significant evidence to provide a clear recommendation at this time. This conclusion is not meant to suggest that studies of targeted agents alone or in combination are not worthy of further investigation and it is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies that address these modalities.

Question 5 In adults with progressive glioblastoma is the use of targeted agents in combination with cytotoxic therapies superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendations: In the previously published guidelines on the role of targeted therapies in management of progressive glioblastoma in adults, targeted therapies other than bevacizumab in combination with cytotoxic therapies were reviewed and no specific recommendations were made based on a lack of strong evidence supporting a clearly defined benefit or detriment.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Table 5 The role of targeted therapies combined with cytotoxic therapies in progressive GBM

Author (year)	Description of study	Data class	Conclusions
Grisanti et al. (2019)	Study description: single-center, prospective, open-label, non-ran- domized phase 2 trial evaluating activity of sunitinib plus CPT-11 in progressive GBM Patient population: 6 Adult patients with first relapse of GBM or progression after surgical resection and radiotherapy plus concomitant and adjuvant TMZ Treatment regimen: CPT-11 was administered at 125 mg/sqm over 90 min IV infusion repeated every 14 days on 28 day cycle. Sunitinib was given at a dose of 37.5 mg orally once a day for 14 days followed by 14 day sunitinib rescue on each 28 day cycle. Cycle was repeated until disease progression or unacceptable toxicity	III	Results: Median OS: not reported since trial aborted early due to lack of efficacy Response to treatment: Among the first six patients enrolled in the Stage I of the trial, only one had stable disease with a response rate of 17%. Trial was aborted early and 6-PFS was not reached Toxicity: All toxicities were grade 1–2. All patients required steroid therapy and 5/6 required acetazolamide for symptomatic cerebral edema and prophylactic levetiracetam as anti-epileptic prophylaxis. Skin atrophy and decoloration was most common, with fatigue, nausea and leukopenia also common Authors' conclusions: The combination of carboplatin and bevacizumab is active and well-tolerated in progressive HGG Comments and Conclusions: A small, nonrandomized series warrants Class III designation
Di Cristofori et al. (2017)	Study description: TMZ + Tamoxifen in progressive glioblastoma Patient population: 32 adult patients with progressive GBM after standard first line therapy Treatment regimen: The treatment at tumor relapse consisted of TMZ dose-dense at 75–150 mg/m2 one week on/one week off plus daily tamoxifen at 80 mg/m^2	III	Results: RR: No response in 18 patients (56.2%), PR or Stable in 13 (40.6%), CR in 1 (3.1%) median OS: 17.5 m, methylated MGMT—20.5 m, unmethylated 15 m median TTP 9.5 m, MGMT methylated 11 m, unmethylated 7.5 m TTP2 (after tamoxifen + TMZ) 7 m Toxicity: No toxicity was observed in the 32 patients Authors' conclusions: Our experience in second-line treatment of progressive GBM with dose-dense TMZ plus tamoxifen confirmed that oral high-dose administration of tamoxifen was well-tolerated and easily used. Moreover, this study confirms the hypothesis that oral high-dose tamoxifen associated with dose-dense TMZ can increase OS and TTP in patients with progressive GBM. Patients with unmethylated MGMT might benefit more from this combined regimen Comments and Conclusions: A small study without a control group warrants Class III designation

Table 5 (continued)

Author (year)	Description of study	Data class	Conclusions
Duerinck et al. (2017)	Study description: Randomized phase 2 trial of axitinib monotherapy vs axitinib and lomustine in progressive GBM Patient population: 79 patients were randomized to axitinib monotherapy (n = 50) or axitinib + lomustine (n = 29) with crossover to the combination arm allowed at disease progression (n = 19) Treatment regimen: Axitinib 5 mg twice daily increased as tolerated to 7 or 10 mg BID, or dose reduced to 3 or 2 mg BID for toxicity. Axitinib same dosing in combination with lomustine. Lomustine 90 mg/m^2 every 6 weeks	III	Results: Median OS: 29 weeks in axitinib monotherapy and 27.4 weeks in combination with lomustine Response to treatment: Best overall response rate was 28% for axinitib monotherapy and 38% for combination, with disease control rates of 52 and 45%, respectively Toxicity: Axitinib monotherapy had 36% develop grade 3 or higher toxicity, 39% with combination and included thrombocytopenia, HTN, neutropenia (only lomustine arm), lymphopenia, and anorexia Authors' conclusions: The authors conclude that axitinib improves response rate and PFS in patients with progressive GBM in comparison to historical controls. There is no indication that combination of axitinib with lomustine improves results Comments and Conclusions: A randomized control trial with a modest number of patients, but with significant crossover, warrants Class III designation
Wang et al. (2017)	Study description: Pilot study of apatinib plus irinotecan in high-grade glioma Patient population: 10 adult patients with progressive high-grade glioma (6 with GBM) Treatment regimen: Irinotecan 125 mg/m^2 or 340 mg/m^2 depending on use of enzyme-inducing antiepileptic druges every 21-day cycle concurrently with oral apatinib 500 mg daily for first 6 cycles (dose dropped to 250 mg if grade 3 or 4 toxicity)	III	Results: Median OS: 12.8 mos Response to treatment: PR in 2 patients, SD in 2, PD in 1 and 1 not assessed Toxicity: Grade 3 or higher myelosuppression (1), GI (2), HTN (1) hand-foot syndrome (2) for all 10 patients Authors' conclusions: Apatinib combined with irinotecan seems to be a promising therapeutic option for progressive malignant glioma patients Comments and Conclusions: A small patient cohort without randomization or control warrants Class III designation

Table 5 (continued)

Author (year)	Description of study	Data class	Conclusions
Brandes et al. (2016)	Study description: A phase 2 randomized study of galunisertib monotherapy vs galunisertib plus lomustine vs lomustine monotherapy in progressive GBM Patient population: 158 patients with progressive GBM randomized to galunisertib (n = 39), lomustine + placebo (n = 40) or lomustine plus galunisertib (n = 79) Treatment regimen: galunisertib (300 mg/day) orally 14 days on/14 days off, lomustine at standard dosing (100 mg/m^2 after 7 days of galunisertib followed by 100–130 mg/m^2 orally once every 6 weeks)	II	Results: Median OS: galunisertib + lomustine was 6.7 mos, 8.0 mos for galunisertib alone and 7.5 mos for lomustine + placebo Response to treatment: One patient had CR in galunisertib + lomustine (1.3%), and 2 patients had PR in the galunisertib monotherapy arm (5.1%). Clinical responses occurred in 21.5% of combination, 30.8% in galunisertib monotherapy and 30.0% of lomustine + placebo Toxicity: 91.1% of patients had an adverse event. Drug-related Grade 3/4 events occurred in 10% of galunisertib alone arm, 26% of galunisertib + lomustine and 26% for lomustine + placebo Authors' conclusions: Galunisertib + lomustine failed to demonstrate improved OS relative to placebo + lomustine Comments and Conclusions: A randomized controlled trial with a modest number of patients warrants Class II designation
Blumenthal et al. (2015)	Study description: phase III study of radiation therapy (RT) and O6-benzylguanine, (O6-BG) plus BCNU versus RT and BCNU alone and methylation status in newly-diagnosed glioblastoma (GBM) and gliosarcoma Patient population: 88 patients enrolled in the O6BG + BCNU + RT group, 88 in the BCNU + RT alone group, all adult Treatment regimen: Patients were randomized to Arm 1: O6-BG + BCNU plus radiation therapy or Arm 2: BCNU plus radiation therapy. Chemotherapy began concurrently with radiation therapy. The Arm 1 treatment group received 40 mg/m2 BCNU six hours after the administration of 120 mg/m2 O6-BG intravenously over one hour every six weeks. The Arm 2 group received BCNU 200 mg/m2 intravenously over 1 h every six weeks. A maximum of seven cycles were allowed	II	Results: PFS-6 with O6BG: 4 m, without: 4 m OS with O6: 11 m, without: 10 m Methylated patients: 13 m OS, PFS-6 4 m. Unmethylated OS 11 m, PFS6 3 m Toxicity: 45 grade 4 events, mostly hematologic. 3 treatment related deaths (renal failure, sepsis, febrile neutropenia, ARDS). 10 patients removed due to SAE. Non O6BG patients—4 treatment related deaths (infection, ARDS, sudden death), 18 with Grade 4 toxicities, 9 removed due to toxicity Authors' conclusions: Based on the doses and treatments given to this cohort of patients, the results of SWOG S0001 do not support the hypothesis that extrinsic depletion of MGMT renders GBM more sensitive to alkylating therapy with BCNU Comments and Conclusions: A randomized, control trial, but in a smaller patient cohort, warrants Class II designation

Table 5 (continued)

Author (year)	Description of study	Data class	Conclusions
Odia et al. (2015)	Study description: Phase II trial of tamoxifen and bortezomib in progressive malignant glioma Patient population: 30 adult patients with progressive GBM Treatment regimen: Tamoxifen 120 mg PO twice daily, bortezomib 1.3 mg/m^2 IV on days 3, 6, 10, 13, 24, 27, 31, and 34 per six-week cycle	III	Results: Median OS: 14.7 weeks Response to treatment: No patients had response at 12 weeks, and no patients had stable disease. Three patients were treated beyond six weeks Toxicity: Grouped toxicity for all malignant glioma included lymphopenia (9.5%), hypophosphatemia (7.1%), thrombocytopenia (4.8%), and 2.4% each of hyponatremia, HA, dyspnea, infection, somnolence, and DVT. Two GBM patients were removed for toxicities, the rest for disease progression Authors' conclusions: The study was closed due to poor accrual and therapeutic futility. Poor penetration across BBB of bortezomib likely limited efficacy Comments and Conclusions: A nonrandomized trial in a moderate cohort without control warrants Class III designation
Batchelor et al. (2013)	Study description: Phase III randomized trial of cediranib monotherapy vs combination with lomustine vs lomustine alone in progressive GBM Patient population: 325 adulta patients with progressive GBM Treatment regimen: Randomly assigned (2:2:1) to (1) cediranib 30 mg monotherapy, (2) cediranib 20 mg plus lomustine 110 mg/m^2 or (3) lomustine 110 mg/m^2 plus placebo	I	Results: Median OS: cediranib monotherapy 8 mos, cediranib plus lomustine 9.4 mos, lomustine alone 9.8 mos Response to treatment: Primary end point of progression-free survival was not significantly different in any group Toxicity: Grade 3 or 4 thrombocytopenia and neutropenia in 38% and 20% of cases, respectively, in combination arm, 2% and 1% in cediranib alone arm, and 22% and 3% in lomustine alone arm Authors' conclusions: This study did not meet its primary end point of PFS prolongation with cediranib either as monotherapy or in combination with lomustine vs lomustine in patients with progressive GBM Comments and Conclusions: A large, prospectively randomized study warrants Class I designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *PE* pulmonary embolism, *ALT* alanine aminotransferase, *AST* aspartate aminotransferace

Study selection and characteristics of the updated search

The initial search strategy included 3513 candidate articles. A total of 65 articles remained for full text review. From these, 8 articles were included in the final review for Question 5 and are included in Table 5 [74–81].

A total of 8 papers were reviewed describing combination therapy with targeted therapy and cytotoxic therapy [74–81]. Two studies included the use of tamoxifen [75, 81]. Four of the studies included the use of nitrosoureas like lomustine and BCNU [77–80]. The remainder of studies evaluated the use of single agent targeted therapies with other cytotoxic chemotherapies [72, 74, 76].

Tamoxifen

Tamoxifen is a selective estrogen-receptor modulator that has been shown to have some effect in glioblastoma patients [82–84]. Di Cristofori et al. studied 32 adult patients receiving TMZ and tamoxifen [81]. Median OS was 17.5 months, with methylated MGMT patients showing a 20.5 month mOS and 15 months in unmethylated patients. Methylated patients had a time to progression interval of 11 months and 7.5 months in unmethylated patients, with a **median** time to progression of 9.5 months. The second time to progression (after TMZ + tamoxifen) was another 7 months. Authors concluded there was a benefit to the dual treatment regimen in both patient groups. This was designated Class III evidence as the study was small and without a control group. Next, Odia et al. combined tamoxifen with bortezomib (inhibits the mammalian 26S proteasome involved in the ubiquitin–proteasome pathway) in 30 patients [75]. They closed their study early and deemed bortezomib to be of limited efficacy due to poor crossing of the blood brain barrier, with minimal comment on tamoxifen. This was designated Class III as well with lack of a control group and a nonrandomized design.

Nitrosoureas

Batchelor et al. performed a phase III randomized trial using cediranib monotherapy, cediranib and lomustine, lomustine or lomustine alone in 325 patients [80]. The authors concluded the study did not produce a prolongation of mOS PFS either in combination therapies or as monotherapy of either lomustine or cediranib. As it was a large, prospective, randomized study, this warranted Class I designation. Blumenthal et al. performed a phase III study of RT with O6-benzylguanine with BCNU versus radiotherapy and BCNU alone with comparison to methylation status [79]. Results in 88 patients showed no significant difference between the treatment arms and methylation status. They concluded that extrinsic depletion of MGMT does not necessarily make glioblastoma more susceptible to BCNU alkylation therapy. The moderate size and randomized, control trial design portended a Class II designation.

Brandes et al. performed a phase II randomized study evaluating galunisertib (TGF-b inhibitor) monotherapy vs combination therapy with lomustine versus lomustine monotherapy in 158 patients [78]. mOS was 6.7 months in the combination group, 8 months with galunisertib monotherapy, and 7.5 months in lomustine with placebo. The authors concluded that combination therapy failed to show any overall improvement of OS relative to the placebo plus lomustine group. This warranted Class II designation for the randomized, control trial design with a moderate sized patient cohort. Duerinck et al. evaluated axitinib (a small molecule tyrosine kinase inhibitor) monotherapy in comparison to combination with lomustine in 79 patients [77]. The authors concluded that axitinib improved response rate but there was no overall benefit as combination therapy, with the small case series design designating the data Class III.

Kinase inhibitors

Grisanti et al. evaluated irinotecan in conjunction with sunitinib [76]. They evaluated a small number of patients (n = 6) and never reached their PFS6 endpoint before terminating the trial early, generating Class III data. Schiff et al. evaluated temsirolimus with sorafenib (protein kinase inhibitor with activity against VEGFR, PDGFR, RAF kinases) [72]. The study found toxicity prominent among all arms of the trial requiring dose reductions, resulting in a lack of efficacy compared to single agent administration. The combined Phase I and II trial was without randomization and there was no control group, generating a Class III designation.

Wang et al. evaluated irinotecan with apatinib (tyrosine kinase inhibitor selective for VEGFR2) in 10 patients, 6 of which had glioblastoma [74]. The conclusion was that the combination may be promising, but results were limited due to a small patient cohort without randomization or control group, giving it Class III designation.

Synthesis

In the prior guidelines, there were mixed reviews regarding combined targeted and cytotoxic therapy regimens, without any studies showing reproducible proof of positive PFS or OS benefit. In this update, tamoxifen studies yielded Class III data and no overall benefit. In the data for nitrosoureas, all the Class I and Class II evidence available revealed there was no benefit beyond monotherapy with a targeted agent and at times with the nitrosourea alone, thus not identifying any synergistic effect. The same held true for the kinase inhibitors combined with cytotoxic agents where all data was

Class III showing no overall efficacy beyond monotherapies. This did not provide sufficient evidence to make a recommendation regarding targeted therapies in combination with cytotoxic agents. This conclusion is not meant to suggest such combination studies are not worthy of further investigation and it is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies of targeted agents combined with cytotoxic agents.

Question 6 In adults with progressive glioblastoma is the use of immunotherapy alone superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendations: In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, immunotherapeutic agents were not reviewed.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Study selection and characteristics of the updated search

The initial search strategy included 904 candidate articles. A total of 31 articles qualified for full text review. From these, 26 articles met eligibility criteria and were included in the final review for Question 6 and are included in Table 6 [71, 85–111].

T-Cell therapies

Ahmed et al. performed a phase I open label dose escalation trial using HER2-specific CAR-T cells in 17 total patients, 10 of which were adult patients. Results showed PFS of 3.5 months and mOS 11.1 months after infusion, 24.5 months after initial diagnosis. They concluded the HER2-CAR virus specific T cells (VSTs) are safe and may portend a clinical benefit [85]. In another specific T-Cell study, Schuessler et al. reported on autologous CMV specific T cell administration in a study including 10 patients with complete data. Median OS of those with at least one infusion was 13.4 months and concluded the therapy was safe with a potential long-term clinical benefit [105]. Tsuboi et al. studied autologous tumor specific T-lymphocytes (ATTLs) and suggested efficacy however with a potentially only temporary antitumor effect [110]. As phase I trials with small patient populations, these were all designated Class III.

Vaccines

Two studies included revolved around the use of dendritic cell (DC) vaccination. Chang et al. prospectively investigated post-operative administration of a dendritic cell autologous tumor vaccine in 6 adult progressive glioblastoma patients. Median OS was 36 months. The results here suggest a potential benefit with this vaccine for adjuvant therapy after repeat resection, but as it was only in a small series of patients this was designated Class III evidence [89]. Sakai et al.'s Wilms' Tumor DC vaccine in 6 cases resulted in a mOS of 8.3 months and was deemed safe, but no conclusion was made on efficacy in this Class III designated phase I trial [102]. Yamanaka et al. evaluated a DC vaccine using peripheral blood dendritic cells generated with GMCSF and interleukin-4 (IL4) and pulsed with autologous tumor lysate in 24 patients. They were then vaccinated intratumorally, or both intratumorally and intradermally. Median OS was 15.5 months and the authors determined the vaccination trial proved safety in this Class III designated phase I trial [111].

Another group of vaccination trials utilized autologous tissue and tumors to generate specific, individualized vaccinations. Fakhrai et al. studied a whole-cell vaccine with autologous tumor cells modified with TGFb2 in 6 patients. Median OS was 15.9 months, and of those with an immune response having a median OS of 18.2 months. The comparison cited a historic mOS value of 11 months for conventional treatment, concluding that the humoral and cellular immunity inductions support further evaluation [94]. This was designated Class III as a small, nonrandomized series. Plautz et al. studied systemic adoptive therapy in 10 patients vaccinated with irradiated tumor cells. Median OS was 11.3 months and there was limited data which didn't provide evidence for a clinical benefit [100]. These data were designated Class III. Schijns et al. used Gliovac in 9 patients, found a 40 week OS of 77%, and received approval for development of a phase II clinical trial [104].

Shibao et al. prospectively studied a vaccine targeting angiogenesis factors in 9 progressive glioblastoma patients. There were limited outcome data included, with two patients achieving SD and six PD. The authors reported a preliminary sense of efficacy and safety. As a small series phase I trial, this is class III [106].

Tanaka et al. studied 17 adult patients receiving human umbilical vein endothelial cells. PFS was 5.5 months and authors concluded that although the vaccine had a low radiologic response rate, there was a favorable mOS compared to historical series for patients receiving salvage therapy after a varying number of previous lines of treatment through multiple recurrences [107]. This study warranted Class III designation.

Several peptide vaccination studies were also included. Bloch et al. achieved a PFS of 4.5 months, PFS6 29.3%,

Table 6 The role of immunotherapy in progressive GBM

Author (year)	Description of study	Data class	Conclusions
Cloughesy et al. (2019)	Study description Multi-institution, randomized, open-label pilot study of pembrolizumab in patients with progressive, surgically resectable glioblastoma Patient population 35 adult patients with progressive GBM, 16 in neoadjuvant and 19 in adjuvant only Treatment regimen Patients randomized to the neoadjuvant + adjuvant treatment group received pembrolizumab 200 mg intravenous infusions 14 ± 5 days prior to scheduled surgical resection. Tumor resection was performed according to institutional standards. After recovery from surgery, patients received pembrolizumab 200 mg intravenous infusions every 3 weeks until tumor progression or an adverse event requiring study drug discontinuation. The adjuvant only group received the same regimen only after surgery	III	Results Neoadjuvant OS: 13.7 m, Adjuvant OS: 7.5 m median PFS-6: 3.3 m neoadjuvant, 2.4 m adjuvant Toxicity 10 patients with grade 3/4 toxicity in neoadjuvant, 7 in adjuvant. No neoadjuvant patients had surgery delayed due to toxicity. Two patients in neoadjuvant group required discontinuation of pembrolizumab, one for ALT elevation, another for pneumonitis Authors' conclusions In this study, PD-1 monoclonal antibody blockade was associated with statistically significant improvements in overall survival and progression-free survival when administered in the neoadjuvant setting to patients with progressive glioblastoma, in comparison to the adjuvant only group Comments and conclusions Classified as Class II due to its multi-institutional randomized design with a larger patient population
Narita et al. (2019)	Study description Prospective randomized, double-blind Phase III trial for personalized peptide vaccine Patient population Adult HLA-A24 positive patients with supratentorial progressive GBM with positive IgG responses to at least 2 of 12 warehouse peptides in pre-vaccination plasma and good functional status randomized to vaccination (n = 58) or placebo (n = 30) Treatment regimen Four of the 12 warehouse peptides selected based on the patient's pre-existing peptide-specific IgG levels or corresponding placebos were injected subcutaneously once weekly for 12 weeks, followed by biweekly vaccinations until disease progression	I	Results Median OS: 8.4 months Response to treatment: immune related response (IR) of 3 vs 0 IR partial response, 21 vs 9 IR stable disease and 33 vs 19 IR progressive disease for 57 PPV and 27 placebo patients, respectively Toxicity: In the 58 PPV and 30 placebo patients there were 340 or 120 events in 54 or 26 patients (93.11% or 86.7%). There was one grade 3 PPV-related pulmonary embolism in the trial Authors' conclusions This phase III trial met neither the primary nor secondary endpoints or OS from day of randomization (primary), 1-year survival rate, antitumor responses, PFS, PFS at 6 months, peptide-specific IgG responses and cytotoxic T lymphocyte (CTL) activity (all secondary) Comments and conclusions A prospective, randomized phase III, double blinded trial meets criteria for Class I designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Schalper et al. (2019)	Study description: Prospective, single-arm phase II trial of nivolumab in resectable glioblastoma Patient population: Adult patients undergoing surgery for primary (3 patients) or progressive (27 patients) glioblastoma Treatment regimen: 3 mg kg^-1 dose of nivolumab given 2 weeks (±3 days) before surgery and then postsurgical doses of nivolumab every two weeks until radiologic progression or unacceptable toxicity	III	Results: Median OS: 7.3 mos (mixed patient cohort, progressive GBM patients not extractable) Response to treatment: Samples from patients treated with nivolumab showed upregulation of numerous immune-related transcripts, indicating prominent immunomodulatory effects that were elicited by adjuvant treatment Toxicity: For the whole cohort, only one patient experienced a grade > 2 immune-related adverse event (elevated serum alanine aminotransferase and aspartate aminotransferase) and one patient with grade 2 hyperthyroidism.Two patients had bleeding episodes after nivolomab while waiting for surgery. An additional patient had a bleeding episode after surgery, two months later in the context of documented disease progression Authors' conclusions: There was no obvious clinical benefit substantiated following salvage surgery at recurrence Comments and conclusions: A single-arm study in a small group of patients without control warrants Class III designation
Tsuboi et al. (2019)	Study description: Phase I trial of Wilms' tumor 1 (WT1) HLA I and II peptides for progressive malignant glioma Patient population: 12 adult patients with progressive glioblastoma were treated with WT1 HLA I and II peptides Treatment regimen: WT1 HLA class II peptide was dose escalated from 0.75 to 1.5 and then to 3.0 mg/body while doses of WT1 HLA class I peptide remained at 3.0 mg. 3 + 3 cohort design was used. Patients received intradermal administration of a coctail vaccine comprising 3 mg of WT1 HLA class I peptide and one of WT1 HLA class II peptides as the vaccine, followed by a vaccine containing only the WT1 HLA class I peptide the second week. These two regimens were alternated every week. If safety was determined at 6 weeks, then vaccination continued at 2–4-week intervals until dose-limiting toxicity	III	Results: Median OS of the 9 patients with progressive GBM: 24.7 weeks (6.175 mos) Response to treatment: Three patients had SD and 6 had PD at 12 weeks Toxicity: All patients developed Grade 1 skin reactions at the injection site. No grade 3 or 4 toxicity or dose-limiting toxicity was observed Authors' conclusions: The safety of WT1 HLA class I and II peptide for malignant gliomas was verified Comments and conclusions: A phase 1 trial with few patients and no controls warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Desjardins et al. (2018)	Study description: Phase I dose escalation trial of intratumoral CED of recombinant non-pathogenic polio-rhinovirus chimera (PVSRIPO) Patient population: 61 progressive GBM pts Treatment regimen: Dose escalation followed by dose expansion evaluating seven doses ranging between 10^7 and 10^10 50% tissue-culture infectious doses (TCID50) with intratumoral CED of the recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO)	III	Results: OS reached a plateau of 21% at 24 months that was sustained at 36 months Toxicity: 9% of the patients had a PVSRIPO-related adverse event of grade 3 or higher. Dose level -1 (5.0 × 107 TCID50) was identified as the phase II dose Authors' conclusions: Intratumoral infusion of PVSRIPO in patients with progressive WHO Grade IV malignant glioma confirmed the absence of neurovirulent potential. The survival rate among patients with PVSRIPO immunotherapy was higher at 24 and 36 months than the rate among historical controls Comments and conclusions: While this study included a moderate number of patients, it was designed as a dose-escalation and dose-expansion phase I trial without a control
Lukas et al. (2018)	Study description: Open-label phase 1 dose-escalation study in pts treated with Atezolizumab Patient population: 16 patients with progressive GBM Treatment regimen: Atezolizumab was administered 1200 mg IV every 3 weeks until progression/toxicity	III	Results: One patient experienced a PR, 3 had SD Median OS: 4.2 mos Toxicity: All 16 patients had at least 1 AE. 3 patients had grade 3 asthenia, increased aspartate aminotransferase and brain edema. All patients discontinued due to PD Authors' conclusions: Atezolizumab was safe and well tolerated Comments and conclusions: A phase 1 dose escalation trial in a limited number of patients warrants class III designation
Mantica et al. (2018)	Study description: Retrospective, single institution trial of nivolumab Patient population: Adult patients with progressive high-grade glioma with any prior therapy receiving greater than one cycle of nivolumab with at least one post-treatment radiographic follow-up. (n = 37 with progressive GBM) Treatment regimen: Patients received nivolumab IV 3 mg/kg over 60 min once every 2 weeks	III	Results: Median PFS: 4.6 months Median OS: 6.5 months Response to treatment: CR: 0 PR: 0 SD: not specific for Grade IV but 72% of full cohort at 2-month assessment (36/50) Toxicity: Includes data on Grade III and IV combined, including 39 treatment-related AE, and included fatigue (n = 8), constipation (n = 5), Grade 3–4 AE (n = 4), 3 autoimmune toxicities and several varied neurological complications Authors' conclusions: Treatment with nivolumab has a manageable safety profile consistent with that of other PD-1 agents, with disease stabilization in a small subset of patients including in the bevacizumab refractory setting Comments and Conclusions: A single-center nonrandomized trial warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Shibao et al. (2018)	Study description: Prospective, Phase I trial of vaccine targeting angiogenesis factors in progressive GBM Patient population: Nine adult (16–80 years) patients with progressive high-grade glioma including GBM with HLA-A*2402 genotyping, good performance status, and at least four weeks since last treatment Treatment regimen: 2 mg/kg body weight (previously determined preferred dose) of VEGFR1 and VEGFR2 were emulsified in incomplete Freund's adjuvant and admi9nistered subcutaneously close to axillary or inguinal lymph node 8 times weekly	III	Results: Median OS: not reported Response to treatment: Patient received a mean of 11.5 (± 3.46) peptide vaccination. Two patient achieved SD and six had PD at the end of eight vaccinations Toxicity: No major toxicity was fouhd. All eight patents developed a skin reaction at the injection site, and one patient developed an ulcer at the injection site Authors' conclusions: Our findings demonstrated the safety and immunogenicity, as well as preliminary efficacy, of this approach Comments and Conclusions: A small, nonrandomized cohort without control warrants Class III designation
Ahmed et al. (2017)	Study description: Phase 1 open-label dose-escalation study testing HER2-specific chimeric antigen receptor-modified virus-specific T Cells for safety and anti-GBM activity Patient population: Progressive HER2-positive GBM (n = 17, but only 10 patients > 18y) Treatment regimen: received one or more infusions of HER2-CAR VSTs (1 × 10^6/m^2 to 1 × 10^8/m^2) without prior lymphodepletion	III	Results: Median time to progression: 3.5 months Median OS: 11.1 months after infusion, 24.5 months after diagnosis Toxicity: No dose-limiting toxicity. 2 patients had seizures and headaches Authors' conclusions: Infusion of autologous HER2-CAR VSTs is safe and can be associated with clinical benefit for patients with progressive glioblastoma Comments and Conclusions: This study was classified as Class III due to a small sample size and it was a Phase I, dose-escalation, nonrandomized sample
Chamberlain et al. (2017)	Study description: Nivolumab for patients with progressive glioblastoma progressing on bevacizumab: a retrospective case series Patient population: 16 adult patients with progressive GBM were treated Treatment regimen: Nivolumab was administered intravenously to all patients at a dose of 3 mg/kg over 60 min once every 2 weeks. Low dose (< 2 mg/day) concurrent dexamethasone was permitted for control of neurologic signs and symptoms. A cycle of therapy was operationally defined as 28 days, during which nivolumab was administered on day 1 and 14. Treatment was repeated every 14 days	III	Results: OS: median OS from nivolumab initiation 3.5 m PFS: 2 m Toxicity: 2 grade 3 events in 2 patients (fatigue and infection). No grade 4 or 5 events Authors' conclusions: This small retrospective study suggests minimal benefit with nivolumab following disease progression on bevacizumab in patients with progressive GBM, a finding not previously documented in the literature, and begs the question of whether any current therapy warrants employment in this setting Comments and Conclusions: A small study without control arm warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Fenstermaker et al. (2016)	Study description: Prospective phase I trial of subcutaneous injections of SurVaxM (500 mug) in Montanide ISA 51 with sargramostim (100 mug) at 2-week intervals Patient population: 9 pts with progressive GBM and survivin-positive, who had either HLA-A*02 or HLA-A*03 MHC class I allele-positivity Treatment regimen: Patients received SurVaxM (500 ug) in emulsion with Montanide ISA 51 with sargromostim (100 ug) every 2 weeks for a total of four doses per patient (prime-boost phase). Patients who survived 6 months without tumor progression or adverse events were eligible to receive additional vaccine every 3 months (booster phase)	III	Results: Median progression-free survival was 17.6 weeks, and median overall survival was 86.6 weeks from study entry with seven of nine patients surviving more than 12 months Toxicity: No serious adverse events during the prime-boost phase. Six of 9 patients had at least one injection site reaction (grade 1), others with grade 1 or 2 fatigue, myalgias, lymphopenia and leukopenia. No vaccine-related grade 3 or 4 toxicity Authors' conclusions: This first-in-human study demonstrated the safety, tolerability and immunogenicity of SurVaxM in patients with progressive malignant glioma following failure of standard therapy Comments and Conclusions: A prospective phase 1 trial in nine patients without a control warrants class III designation
Sakai et al. (2015)	Study description: Prospective phase I study of Wilms' tumor 1 dendritic cell vaccine in progressive malignant glioma Patient population: Adult patients with progressive malignant glioma (6 with glioblastoma) Treatment regimen: 1 × 10^7 to 2 × 10^7 WT1-pulsed and/or autologous tumor lysate-pulsed DC were injected into the axillary region with OK-432 every two weeks for at least 5–7 sessions	III	Results: Median OS: 8.3 mos Response to treatment: Among the six patients with progressive glioblastoma (one converted from AA to GBM) one patient had stable disease after first course and the remainder had progressive disease. Overall response after final session was progressive disease in all patients Toxicity: For the whole cohort, there were no grade 3 or higher toxicities. Common toxicities incldued erythema at the injection site, postvaccination fever and fatigue Authors' conclusions: DC-based immunotherapy targeting WT1 was safe and feasible for the management of advanced malignant gliomas Comments and Conclusions: A phase I study in a small number of patients without controls warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Schijns et al. (2015)	Study description: Prospective Phase I trial of Gliovac vaccine in progressive GBM Patient population: 9 adult patients with second recurrence of GBM after failure of surgery, TMZ chemoradiation and/or bevacizumab who qualify for surgical intervention to obtain an operable tumor mass Treatment regimen: Six cycles of five intradermally administered treatment doses of Gliovac. Each dose includes a cellular component and a lysate component prepared from freshly, surgically removed, GBM tumor tissue. Cell vial has 250 uL of a suspension of 1×10^5–1×10^6 irradiated DNFB-modified tumor cells and lysate vial has equivalent lysate of a similar number of cells. Allogeneic A, B and C product doses are prepared from three different GBM donors, while autologous Gliovac D dose is from the patient's own tumor. Gliovac treatment is administered with GM-CSF following 3 days of low dose cyclophosphamide. Six treatment cycles were repeated every 28 days	III	Results: Median OS: not achieved over follow-up period, but 40 week OS was 77% Response to treatment: Survival was improved in comparison to historical controls, with 40 week OS 77% and little toxicity Toxicity: Two patients had grade 2 headaches, 4 had grade 2 local erythema at the injection site, other mild systemic reactions including self-limiting fever and chills Authors' conclusions: The observed safety and promising clinical results of Gliovac led to approval for the development of a Phase II clinical trial Comments and Conclusions: A phase 1 trial in a small cohort of patients without control warrants Class III designation
Bloch et al. (2014)	Study description: Single Arm Phase II trial, multi institution study on the safety and efficacy of HSPPC-96 vaccine in patients with progressive glioblastoma Patient population: 41 adult patients with progressive glioblastoma, Karnofsky of at least 70, resection of at least 90% of progressive tumor, and without disease progression at 4 weeks post operatively underwent vaccination with HSPPC-96 Treatment regimen: 38 patients treated with at least 6 vaccinations of HSPPC-96, 3 received less than the protocol minimum of 4 and were excluded from efficacy population	III	Results: median PFS: 19.1w, 6 m PFS 29.3% median OS: 42.6w, 6 m OS: 90.2%, 12 m OS: 29.3% Toxicity: 1 patient with Grade III fatigue, no grade IV events or deaths associated with vaccine, 17 serious adverse events associated with surgical resection and consistent with known risks of surgery Authors' conclusions: The findings of the current study are also comparable to the best outcomes reported with Bevacizumab. A proper comparison of the efficacy of HSPPC-96 vaccination with bevacizumab would require equivalent surgical resection in both groups. We believe the findings in the current study support the value of a comparison between the HSPPC-96 vaccine and bevacizumab in surgically accessible progressive tumors Comments and Conclusions: Classified as Class III because, while it is a multicenter prospective study, it is without a control group. This study and its conclusions have significant limitations, although promising, and this methodology warrants further research

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Schuessler et al. (2014)	Study description: Prospective Phase I trial of autologous CMV-specific T-cell therapy for progressive GBM Patient population: Nineteen adult patients with progressive GBM whow had positive CMV serology (four patients were withdrawn before venesection due to progressive disease, while insufficient CMV-specific T cells were expanded from two patients due to low precursor frequency or poor cell viability, with a total of 10 patients completing a minimum of three infusions as required Treatment regimen: A minimum of three T-cell infusions consisting of 25 to 40×10^6 autologous CMV-specific T cells in sterile saline were administered in 4 (±2) weeks intervals, coordinated with periods of chemotherapy to avoid unwanted side effects	III	Results: Median OS: of those who received at least one infusion was 403 days Response to treatment: CMV-specific immunotherapy was coincident with disease stabilization and prolonged PFS in some patients. Four of the 10 patients who completed T-cell therapy remained progression free. This includes one patient disease free four years after infusion Toxicity: The majority of adverse events were minor, with a single serious adverse event (seizure within 12 hourse of first T-cell infusion, without subsequent seizures with other infusions) Authors' conclusions: Adoptive immunotherapy of patients with progressive GBM with CMV-specific T cells is safe and may provide long-term clinical benefit Comments and Conclusions: A nonrandomized, phase 1 trial without control in a small cohort warrants Class III designation
Tanaka et al. (2013)	Study description: Prospective, nonrandomized trial of HUVEC vaccine therapy in progressive GBM Patient population: 17 adult patients with progressive GBM (no limit on previous regimens or salvage treatments) Treatment regimen: Human umbilical vein endothelial cells (HUVEC) were isolated from healthy donors at delivery, and cultured on 0.1% gelatin (w/v)-coated dishes in EC-SFM, then fixed with 0.025% glutaraldehyde (v/v) and stored at -80 C in single dose aliquots containing 5×10^7 cells/mL in physiological saline for injection. Patients received intradermal injections of 1.5 mL vaccine in the upper arm weekly during the first month, and every 2 weeks subsequently, until disease progression	III	Results: Response to treatment: Among the 17 patients with at least one dose of vaccine, one patient had a partial response, four had progressive disease, all others stable disease at first follow-up. Median PFS was 5.5 mos Toxicity: Delayed-type hypersensitivity skin reactions developed at the injection site in 14 of 17 patients. No other adverse events were noted from the vaccination Authors' conclusions: HUVEC vaccine therapy is well tolerated with unlikely acquisition of resistance. However, radiological response was low (5.9%) despite the median OS comparing favorably with other salvage therapies. More study is warranted Comments and Conclusions: A prospective, nonrandomized trial without control in a small cohort warrants Class III designation
Chang et al. (2011)	Study description: Open label, Single arm phase I/II clinical trial investigating the adverse and therapeutic effects of a postoperative autologous dendritic cell tumor vaccine in patients with malignant glioma Patient population: 17 patients enrolled, 6 adult patients with progressive GBM Treatment regimen: After recovery from cytoreductive craniotomy, DC vaccines exposed to autologous glioma cells were given according to study's vaccine protocol	III	Results: OS: 36 m Toxicity: 1 patient with Grade III Lymphopenia, Authors' conclusions: Our results also suggest the possible benefit of our DC-tumor vaccine preparation and treatment protocol for adjuvant therapy of post-surgical residual GBM Comments and Conclusions: Classified as Class III due to its open label, nonrandomized, dose-escalation design without a control arm and small patient population

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Terasaki et al. (2011)	Study description: Prospective, Phase I trial of HLA-A24 patients receiving ITK-1 peptide vaccine for progressive GBM Patient population: 12 adult patients with positive humoral responses to at least four of 14 HLA-A24-restricted candidate peptides (ITK-1) with progressive supratentorial GBM (multicenter, open-label, dose-escalation design) Treatment regimen: 100 + genes encoding cancer antigens (nonmutated proteins) involved in cellular proliferation but not frequently expressed in normal cells were identified, with 14 peptides selected from this cohort for the ITK-1 vaccine. Of these, the four peptides showing the highest IgG titers were selected for vaccination in each patient. Patients then received peptides weekly for up to six times by subcutaneous injection into the upper back region at three different dose settings (1, 3, and 5 mg/peptide). Dose escalation was allowed after evaluation of safety. Each cycle lasted six weeks, with cycles repeated if no serious adverse events until disease progression	III	Results: Median OS: 10.5 mos Response to treatment: following resist criteria, one patient had PR, seven had SD and four had PD Toxicity: Grade 1 or 2 skin inflammatory reactions at injection sites occurred in all patients with no grade 3 SAE reported. However, the highest dose escalation of 5 mg/peptide was skipped because of injection site reactions at this dose noted in another advanced prostate cancer trial performed simultaneously Authors' conclusions: Personalized vaccination with ITK-1 peptide in patients who are HLA-A24 positive with GBM may be worthwhile for future clinical trials due to its safety and potential to boost the immune system Comments and Conclusions: A small, single-arm phase 1 study warrants Class III designation
Clavreul et al. (2010)	Study description: open, non-randomized, phase I study to evaluate the safety and feasibility of vaccination with Autologous tumor cells (ATC) and infusion of GM-CSF by a programmable pump in the treatment of progressive malignant gliomas Patient population: 6 adult patients with progressive glioblastoma, isolated from 9 patients with progressive high-grade glioma Treatment regimen: Patients underwent surgical resection at recurrence, tumor collected at surgery was then expanded in vitro, irradiated at 45 Gy, and then frozen. The cells were then thawed and administered between 2.0 and 5.0 × 10^6 ATC in 600 uL of physiological serum subcutaneously. Recombinant GM-CSF was then infused at the site of cell inoculation. Two vaccine protocols included 1) four SC vaccinations with ATC every 7 days in the abdomen and continuous infusion of GM-CSF (10 ug/24 h) for 28 days or 2) four SC vaccinations with ATC every 21 days close to cervical lymph nodes with GM-CSF infusion for 3 days before and 14 days after each vaccination	III	Results: OS: 8.6 m Authors' conclusions: This clinical trial shows that induction of a peripheral antitumor immune response is possible in glioma patients but not sufficient to preclude disease progression Comments and Conclusions: Classified as Class III due to its open label, nonrandomized, design without a control arm and small patient population

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Hau et al. (2007)	Study description: Prospective phase I/trial of treatment with TGF-beta2 inhibitor AP 12,009 employing patient-derived malignant glioma cells as well as peripheral blood mononuclear cells (PBMCs) Patient population: 24 HGG pts Treatment regimen: Perforated part of catheter was inserted into the largest, solid, contrast enhancing area of the tumor, avoiding ventricles, cysts, prior surgical resection cavities, blood vessels and eloquent brain areas. The first two patients, the catheter was passed through the skin, but was later modified to allow multiple cycle application. AP 12,009 was infused over the implanted port system continuously for 4 days or 7 days depending on treatment group	III	Results: Prolonged survival compared to literature data, although not primarily designed as an efficacy evaluation Toxicity: No infections related to the implanted catheter, and no treatment-related deaths or life-threatening toxicity. 7 of 24 patients experienced had an AE, with 2 Grade 3 and no Grade 4 Authors' conclusions: The major endpoints of safety and tolerability have been achieved Comments and Conclusions: This was not an efficacy trial, and as a phase 1 trial in a small cohort of nonrandomized patients, it was designated as class III
Carpentier et al. (2006)	Study description: Phase 1 trial was designed as an open-label, nonrandomized study Patient population: 24 patients enrolled, 9 at first recurrence, 8 at second recurrence, 7 at third recurrence Treatment regimen: groups of 3–6 patients were treated with escalating doses of CpG-28	III	Results: Median Survival: 7.2 m PFS-6: 4.5%, 1yS: 28% Toxicity: 1 dose limiting toxicity, 4 neurologic deterioration, 7 Grade III lymphopenia, 2 Grade III ALT elevation, 1 Grade III Hyponatremia Authors' conclusions: this study demonstrated that local treatment with CpG ODNs in patients with progressive glioblastoma is feasible and well tolerated at doses up to 20 mg Comments and Conclusions: Classified as Class III due to its open label, nonrandomized, dose-escalation design without a control arm and small patient population
Fakhrai et al. (2006)	Study description: Prospective phase I trial or whole-cell vaccine comprising autologous tumor cells genetically modified by a transforming growth factor-beta2 (TGF-beta2) antisense vector Patient population: 6 patients with progressive GBM Treatment regimen: Patients received 2–7 subcutaneous injections of $5\times10\text{^}6 - 2\times10\text{^}7$ autologous tumor cells per injection. TGF-b2 secretion by the tumor cells used to vaccinate patients was inhibited by 53–98%	III	Results: The overall median survival was 68 weeks. Median survival of the responding patients was 78 weeks, compared to a historic value of 47 weeks for glioma patients treated conventionally Toxicity: There were no Grade 3 or higher toxicities, with common problems including delayed type hypersensitivity reactions at site of second and subsequent vaccinations and Grade 2 or less flu-like symptoms of musculoskeletal aches, pains and fatigue Authors' conclusions: There were indications of humoral and cellular immunity induced by the vaccine. These findings support further clinical evaluation Comments and Conclusions: A single center, nonrandomized small series with no control arm warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Yamanaka et al. (2005)	Study description: Phase I/II trial of dendritic cell therapy in malignant glioma Patient population: 24 adult patients (18 with progressive GBM) Treatment regimen: The patient's peripheral blood dendritic cells were generated with GM-CSF plus IL4 with or without OK-432 and pulsed with autologous tumor lysate. Dendritic cells were injected intradermally or both intratumorally and intradermally every three weeks	III	Results: Median OS: 464.5 days (15.5 mos) Response to treatment: Of the GBM patients, 6 had SD, 3 had a minor response, 1 had PR, and 8 had PD Toxicity: There were no serious adverse effects and no clinical or radiological evidence of autoimmune reactions in any patients. There was mild erythema at the cervical injection site in seven cases, and a mild headache lasting a few days in one patient Authors' conclusions: Dendritic cell vaccination of patients with glioma seems to be safe and not associated with autoimmunity Comments and Conclusions: A phase I/II trial in a small cohort of patients with no control warrants Class III designation
Dillman et al. (2004)	Study description: Prospective phase I trial of intralesional lymphokine-activated killer (LAK) cells following surgery Patient population: 40 pts with progressive GBM Treatment regimen: At time of surgery, patients received autologous LAK cells into the tumor cavity	III	Results: At a median follow-up of 2.3 years, median survival post-LAK was 9.0 months; 1-year survival was 34% Toxicity: One patient developed a superficial surgical wound infection resolving with antibiotics, one patient who died within 1 mo of treatment from status epilepticus Authors' conclusions: Treatment is safe and feasible. Median survival rates are higher than reported in most published series of those who undergo reoperation for progressive GBM Comments and Conclusions: This study was Class III as a prospective phase I trial without control in a small cohort
Tsuboi et al. (2003)	Study description: Phase I trial of ex vivo expanded autologous tumor-specific T lymphocytes (ATTLs) for progressive malignant glioma Patient population: 7 adult patients with progressive glioblastoma were included in the cohort Treatment regimen: Target tumor tissue taken at first operation were submitted for routine primary culture. 3 weeks from separation of PBMC to induction of ATTLs was necessary, followed by once weekly injections of ATTLs in a 2-mL suspension via Ommaya reservoir into the cavity created by the inital surgery (intrathecal in one case)	III	Results: Median OS of the 7 patients with GBM: 4 mos Response to treatment: There were 3 cases of PR, 3 SD and one PD of the 7 patients with glioblastoma Toxicity: eported as "minor side effects" without further explanation Authors' conclusions: Results suggest that local administration of AATLs is effective in progressive malignant gliomas, although its antitumor effect may be temporary Comments and Conclusions: A phase 1 trial in a small cohort without controls warrants Class III designation

Table 6 (continued)

Author (year)	Description of study	Data class	Conclusions
Plautz et al. (1998)	Study description: Prospective phase I trial of systemic adoptive immunotherapy Patient population: Adult patients (n = 10) with grade III or IV malignant astrocytoma and good performance status and no evidence of immunocompromise Treatment regimen: Irradiated tumor cells (17–56 × 10^6 tumor cells) suspended in 0.6 mL phosphate-buffered saline containing 250 ug granulocyte macrophage-colony stimulating factor were injected intradermally on the anterior upper thigh bilaterally and GM-CSF (125 ug) was injected intradermally into each inoculation site daily for an additional three days. Inguinal lymph nodes draining the vaccine site were surgically removed 7 days after vaccination, T cells were extracted and activated, and then reinjected IV two days after oral cyclophosphamide (10 mg/kg)	III	Results: Median OS: 11.3 mos Response to treatment: Among the seven patients with progressive glioblastoma, there were two partial responses (one 7 mos, one over 13 mos) with the remaining patients having progressive disease Toxicity: There were no Grade 3 or 4 toxicities. Among the ten patients studied, there were 2 Grade I toxicities and 9 Grade II toxicities Authors' conclusions: These clinical observations warrant further trials to determine whether this approach can provide therapeutic benefits and improve survival Comments and Conclusions: A phase I trial in 10 patients without control warrants Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *PE* pulmonary embolism, *ALT* alanine aminotransferase, *AST* aspartate aminotransferace

mOS 9.9 months with HSPPC-96. They concluded the findings were comparable to the best outcomes with BEV, however they did not have a direct comparison and data were designated Class III [86]. Fenstermaker et al. performed a phase I trial with SurVaxM in specific HLA subtypes. PFS was 4.1 months and mOS was 20.2 months with 7 patients surviving beyond 12 months, concluding the vaccine was safe and induced an immune response in progressive GBM patients after failure of standard therapy [95]. This was designated Class III for small sample size and a lack of a control group. Teresaki et al. used individualized peptide vaccinations, achieving a mOS 10.5 months with seven patients showing stability of disease. Authors determined the vaccinations may have potential immune system boosting effects and could be worthy of further evaluation [108]. Tsuboi et al. evaluated the Wilms tumor 1 (WT1) peptide vaccination in 9 progressive glioblastoma patients that completed the study. Median OS was 5.8 months and the authors determined this was a safe treatment regimen, but did not comment on efficacy [109]. All peptide vaccination studies were given Class III designation.

In the only Class I designated study in vaccine trials, and imumunotherapy, Narita et al. prospectively evaluated 88 progressive glioblastoma with HLA-A24 positive patients given personalized peptide vaccines. Median OS was 8.4 months and the trial met neither the primary endpoints or secondary endpoints of OS, 1 year survival rate, antitumor responses, PFS, or PFS6, thus deeming the treatment of no significant benefit [99].

Immune checkpoint inhibitors

Cloughesy et al.'s randomized pilot study of pembrolizumab (inhibitor of PD-1) evaluated 35 patients with surgically resectable progressive glioblastoma. Sixteen patients underwent neoadjujvant and adjuvant treatment while 19 patients received adjuvant therapy only. Median OS in the neoadjuvant group was 13.7 months and 7.5 months in the adjuvant group. Median PFS-6 was 3.3 months in neoadjuvant, 2.4 months in the adjuvant group. The authors concluded PD-1 monoclonal blockade showed a significant OS and PFS benefit in the neoadjuvant group [91]. These data were deemed Class III since, despite being a multi-institutional, randomized design with a large patient population, it was pilot by design. Lukas et al. studied atezolizumab, an anti-PDL1 agent, in 16 patients and found the drug to be well tolerated with mOS of 4.2 months, but did not comment on efficacy [97]. This was designated Class III as a dose-escalation trial. In another class III study, Reiss et al. found that heavily pretreated patients with high grade gliomas had low response rates to pembrolizumab [101].

Three studies utilized nivolumab. Chamberlain et al.'s study of nivolumab, an immune checkpoint inhibitor targeting PD-1, was evaluated retrospectively after progression on BEV. They found mOS from treatment initiation was 3.5 months with PFS 2 months, concluding there was minimal benefit with nivolumab after disease progression on BEV [88]. Schalper et al. also studied nivolumab in resectable glioblastoma as both neoadjuvant and adjuvant therapy, finding no obvious benefit [103]. Mantica et al. reviewed nivolumab and found the treatment was safe and a small subset of patients experienced disease stabilization [98]. All of these studies were considered Class III as two were retrospective and one was a small series without a control.

Other immunotherapy

Clavreul et al.'s Phase I non-randomized study of Autologous Tumor Cells (ATC) with GM-CSF by subcutaneous programmable pump delivery in 6 patients with progressive glioblastoma was performed after resection at recurrence. Median OS was 8.6 months and the authors concluded there was an immune response induced in patients but not enough to delay or prevent disease progression [90]. This was in a small group of patients without control and designated as Class III evidence.

Dillman et al. prospectively evaluated intralesional lymphokine-activated killer cells (LAKs) in 40 patients after surgery. Median OS was 9 months with a 12-month survival of 34%. The authors concluded that median survival rates were higher than other published series for patients undergoing repeat resection [93]. As it was a relatively small study without a control group, this was deemed Class III.

Hau et al. evaluated AP12009, a TGFb2 inhibitor with patient derived glioma cells and peripheral blood mononuclear cells. In 19 patients undergoing direct tumor delivery, results showed a median OS of 10.3 months, although this was not a primary end point of the safety study. The authors concluded the treatment was safe and well tolerated [96]. This warrants Class III designation.

Carpentier et al.'s study evaluated 24 patients treated at either their first, second, or third recurrence with escalating doses of CpG-28. Median OS was 7.2 months and PFS6 4.5%- and 12-month survival 28%. Authors felt the treatment was well tolerated, and as a phase I trial without randomization and a small patient population, this was designated Class III evidence [87].

Convection enhanced delivery

Desjardins et al. evaluated intratumoral convection enhanced delivery of recombinant polio-rhinovirus chimera in 61 patients as a dose escalation and dose expansion trial. Median OS reached a plateau of 21% at 24 months which was sustained at 36 months and the authors concluded the treatment was safe and the survival rate was higher than among historical controls and warranted further evaluation [92]. This was deemed Class III as it lacked a control group and was a phase I dose-escalation trial.

Synthesis

The prior guidelines did not discuss immunotherapeutic regimens for progressive glioblastoma. In this update, we reviewed the studies on convection enhanced delivery, varying T-Cell and autologous lymphocyte or mononuclear cell studies, intratumoral agent delivery, vaccinations, and immune checkpoint inhibitors. The highest-level data were in a class I study showing no obvious benefit of a personalized peptide vaccine and a class III designated study showing a significant survival benefit in the neoadjuvant and adjuvant administration of pembrolizumab, increasing 6.2 months over the adjuvant only treatment group. The remainder of studies were Class III designations and of little benefit in guiding treatment suggestions as they were mostly early, Phase I safety and tolerability trials pending further efficacy study. This precludes the ability to make a recommendation for or against immunotherapy, suggesting the modality still warrants further evaluation. As such it is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies of immunotherapy.

Question 7 In adults with progressive glioblastoma is the use of immunotherapy in combination with cytotoxic agents superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendations: In the previously published guidelines on the role of targeted therapies in management of progressive glioblastoma in adults, immunotherapeutic agents in combination with cytotoxic treatments were not reviewed.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Study selection and characteristics of the updated search

The initial search strategy included 904 candidate articles. A total of 31 articles qualified for full text review. From these, 2 articles were included in the final review for Question 7 and are included in Table 7 [112, 113].

Table 7 The role of immunotherapy combined with cytotoxic therapy

Author (year)	Description of study	Data class	Conclusions
Akasaki (2016)	Study description: Single institution, Phase I/II trial of safety and efficacy of TMZ + immunotherapy with fusions of dendritic cells and glioma cells in progressive and newly diagnosed glioblastoma Patient population: Adult patients with glioblastoma of which 10 were progressive and 22 were newly diagnosed. Review of the 10 patients' pathology indicated Glioblastoma in 7, Anaplastic Astrocytoma for 2, and Anaplastic Oligodendroglioma in 1 Treatment regimen: Group R (progressive, n = 10) previously underwent Surgical resection followed by TMZ Chemotherapy and Radiation. At recurrence, TMZ was given at 150-200 mg/m2/day for 5 days of each 28 day treatment cycle. FCs suspended in .5 cc normal saline were inoculated intradermally 2 weeks after first maintenance dose of TMZ and repeated at least 3 times in each cycle. After 3rd inoculation, FC-inoculation was repeated every 6–12 months barring progressive disease	III	Results: OS: 18 m, stratified for dose of FC inoculation: < 1 × 10^6 12.6 m, 1–2 × 10^6 18.2, > 2 × 10^6 16.1 m Toxicity: Injection site Reaction Grade 1: 4, Lymphopenia/Leukopenia G1: 5, Lymphopenia/leukopenia G2: 2, no adverse events necessitated halting treatment, no correlation to number of inocluated FCs Authors' conclusions: TMZ + FC immunotherapy may have a capability to enhance the TMZ-based standard adjuvant therapy for patients with GBM and may have a synergistic effect in progressive GBM with acquired chemotherapeutic resistance Comments and conclusions: A single institution, small nonrandomized study warrants Class III designation
Hunn et al. (2015)	Study description: Prospective phase I trial of TMZ plus monocyte-derived dendritic cells (DC) pulsed with autologous tumor cells Patient population: 14 pts with progressive GBM, 9 of whom completed the trial Treatment regimen: Following leukapheresis to harvest PBMC, craniotomy for tumor resection occurred. Three weeks later, patients received a priming course of three rounds of dendritic cell (DC)-based vaccination intradermally at 2-week intervals, dosing 4 × 10^6 DC. One week after 3rd vaccine, patients began TMZ 150–200 mg/m^2 orally for 5 days every 28-day cycle for up to 6 cycles. Booster vaccine of 1 × 10^6 DC was administered 2 weeks after each cycle of TMZ	III	Results: Nine of 14 patients completed the initial phase of priming vaccinations and two cycles of TMZ, one had radionecrosis, one rapidly progressed, and in 3 the yield of DC vaccine was insufficient to proceed. 2 had radiological responses. 6 mo PFS 22% Toxicity: There were no grade 4 toxicities, premature withdrawals due to treatment-related toxicity, or AE directly attributable to vaccination Authors' conclusions: The combined treatment was safe and well-tolerated but feasibility in the progressive setting was marginal. Evidence of immune responses in a few patients broadly correlated with better clinical outcome Comments and conclusions: A phase 1 trial without control in a small cohort warrants Class III designation

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy

In a Phase I trial of temozolomide with monocyte derived dendritic cells pulsed with autologous tumor cells in 14 patients, only 9 of which were included in study results, PFS6 was 22%. Hunn et al. concluded this strategy was safe and well tolerated, but the feasibility was marginal and of limited benefit [112]. Akasaki et al. performed a Phase I/II trial evaluating TMZ with dendritic cell pulsed with glioma cells in both newly diagnosed and progressive glioblastoma. In the seven progressive glioblastoma cases, results showed a mOS of 18 months, with 1×10^6 DC dose yielding 12.6 month mOS, the $1–2 \times 10^6$ dose an 18.2 month survival, and the $> 2 \times 10^6$ dose a 16.1 month survival. Ultimately, authors concluded this immunotherapy may work synergistically with TMZ in progressive glioblastoma patients with acquired TMZ resistance [113]. As these were both small studies with nonrandomized cohorts lacking control groups, these were both designated Class III.

Synthesis

As an effect of a small number of studies with Class III data and limited patient populations and efficacy results, we

cannot make a recommendation at this time. It would be difficult to evaluate the effect without further data and larger studies with randomized designs with control groups, otherwise one cannot delineate whether effects are synergistic or related to either the cytotoxic or immunotherapy component of the treatment regimen. Thus, there is insufficient evidence on which to base a recommendation regarding this question. Again, it is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies of immunotherapy in combination with cytotoxic agents.

Question 8 In adults with progressive glioblastoma is the use of immunotherapy in combination with bevacizumab superior to standard salvage cytotoxic chemotherapy as measured by progression free survival and overall survival?

Prior Recommendations: In the previously published guidelines on the role of targeted therapies in the management of progressive glioblastoma in adults, immunotherapeutic agents combined with bevacizumab were not reviewed.

Recommendation

There is insufficient evidence to support a recommendation regarding this question.

Study selection and characteristics of the updated search

The initial search strategy included 904 candidate articles. A total of 31 articles qualified for full text review. From these, 1 article met inclusion criteria for inclusion in the final review for Question 8 and is included in Table 8 [114].

Bota et al. evaluated ER1671 and BEV against BEV monotherapy (placebo) in 9 patients, 5 in the active treatment group and 4 in placebo [114]. ERC1671 consisted of ERC-D (inactivated or irradiated whole tumor cells and lysates from allogeneic and autologous glioblastoma patients in combination with an immune system primer), cyclophosphamide, and GM-CSF. PFS was 7.3 months in the treatment group and 5.4 months in the placebo group. The authors concluded, based on interim results, that there was a meaningful survival benefit with minimal additional toxicity when adding ERC1671, GM-CSF, and cyclophosphamide treatment to BEV. However, the small size of each cohort limits this interpretation and thus this study yields class III data.

Table 8 The role of immunotherapy combined with bevacizumab

Author (year)	Description of study	Data class	Conclusions
Bota (2018)	Study description: Double blinded, randomized, Phase II trial comparing survival in patients with progressive glioblastoma receiving ER1671 and Bevacizumab vs bevacizumab and placebo Patient population: 9 patients with progressive GBM, older than 18, enrolled, 5 in the active treatment group 4 in placebo Treatment regimen: ERC1671 regimen consists of ERC-D (inactivated/irradiated whole tumor cells and lysates form allogeneic and autologous GBM patients in combination with immune system priming agents) and cyclophosphamide and GM-CSF. Dosing is with immune priming from Day 2–5 with Bevacizumab on Days 1 and 15, with vaccinations given Days 6, 9, 12, 15, 18 and repeated every 28 days until disease progression or intolerance	III	Results: PFS: 7.3 m in treatment group, 5.4 m in placebo Toxicity: no Grade 4–5 adverse reaction, 9 reported headaches (Grade III) Authors' conclusions: In summary, preliminary analysis of interim results from our study indicates that the addition of ERC1671/GMCSF/cyclophosphamide to bevacizumab resulted in a clinically meaningful survival benefit with minimal additional toxicity. The study is ongoing with the anticipated addition of two other sites Comments and Conclusions: While this is a double-blinded randomized trial, the limited sample size and exclusion criteria limit the conclusions to Class III data

BEV bevacizumab, *OS* overall survival, *PFS* progression free survival, *PFS6* six month progression free survival, *RR* response rate, *PD* progressive disease, *SD* stable disease, *CR* complete response, *PR* partial response, *AE* adverse event, *TMZ* temozolomide, *GBM* glioblastoma, *RT* radiation therapy, *HTN* hypertension, *CHF* congestive heart failure, *VTE* venous thromboembolism, *PE* pulmonary embolism

Synthesis

As there were no combination immunotherapy studies discussed in the prior guidelines, this single study does not provide enough high-level evidence to make a recommendation. Although designated Class III with interim results showing a potentially meaningful benefit over placebo when combining autologous and allogeneic tumor lysates as a vaccination combined with BEV treatment, no recommendations for this question are warranted until larger, randomized studies provide further results. It is suggested that when available, and patients meet inclusion criteria, they be enrolled in properly designed studies of immunotherapy in combination with bevacizumab or other targeted agents.

Discussion

Treatment for progressive glioblastoma has not significantly changed since our prior guidelines were released, and there has not been a significant change in median overall or progression free survival. Each of our questions were formulated to assess the contribution made by targeted therapies and immunotherapy in the treatment of patients with progressive glioblastoma.

In regard to Question 1, bevacizumab monotherapy was determined to be effective when compared to standard salvage cytotoxic chemotherapy based on improvements in imaging response and progression free survival at six months, although it did not create any significant improvement in median overall survival in progressive glioblastoma patients. Therefore, our recommendation remains unchanged from the prior guidelines released in 2014.

Question 2 sought to address BEV in combination with cytotoxic therapies as a superior treatment regimen to standard salvage cytotoxic therapy. Based on the new available data since 2014, this was found to have no clear survival benefit. More importantly, coupling that lack of evidence with the plethora of information on elevated toxicity in patients receiving BEV in combination with cytotoxic agents, the recommendation was ultimately made Level III against combination therapy. The most important study for this designation with Wick et al., Class I data, with 63.6% of patients suffering a grade 3 to 5 toxic event.

We then evaluated BEV with other targeted agents in Question 3. Three studies providing data that could answer this question included a phase I dose escalation trial and two small nonrandomized studies. There wasn't evidence of high enough power or quality to develop a recommendation, thus further studies need to be performed to further elucidate the potential of this type of regimen.

Question 4 revolved around targeted therapies in relation to standard salvage cytotoxic treatment in progressive glioblastoma. The highest class data evaluated was Class II, including Brown et al. in their evaluation of cediranib with gorafenib with only a trend toward improved survival, and Wick et al. discussing CD95 pathway inhibition with reirradiation. The remainder of studies did not provide enough evidence of quality to provide a recommendation for or against targeted therapies alone. As such, no recommendation could be made aside from requesting further studies be performed.

When combining targeted with cytotoxic therapy, we also were unable to provide a recommendation. The highest class evidence was Class I, where Batchelor et al. studied cediranib and did not find PFS prolongation in monotherapy or in combination with lomustine [80]. Two class II studies also did not find any survival benefit [78, 79].

Immunotherapeutics were a new addition to this set of recommendations. Ultimately, all groups studied under the question of immunotherapy as monotherapy, in combination with targeted agents, or in combination with BEV (questions 5–8) did not reveal sufficient data to provide any recommendations. The highest class designations were a class I study where Narita et al.'s Phase III trial of a personalized peptide vaccine found no benefit, and a class II study by Cloughesy et al. where they discovered a benefit in mOS with neoadjuvant administration of pembrolizumab [91, 99]. Immune checkpoint inhibitors remain of potential interest, albeit present data does not allow us to provide a recommendation.

Key issues for future research

Targeted and immunotherapies have generated a significant amount of interest and early research into the treatment of recurrent glioblastoma. Unfortunately, there remains insufficient evidence for the recommended use of many of these agents. However, there were some intriguing findings from this review, specifically the potential benefit of treatment with immune checkpoint inhibition prior to and after surgical resection for progressive glioblastoma. This should generate further studies surrounding immunotherapeutics either as monotherapy, in conjunction with resection, or as combination therapies. Additional well designed, larger, randomized controlled clinical trials may provide additional information on this topic.

Conclusion

This set of recommendations does not substantially affect the current targeted and immunotherapy regimens being offered to patients with progressive glioblastoma. Ideally, clinical trials should include more patients to better evaluate the safety and survival benefits provided. We did make a

Level III recommendation against bevacizumab in combination with cytotoxic agents due to the elevated toxicity and lack of benefit in survival, as well as a Level III supporting the use of bevacizumab monotherapy. However, this is not a significant deviation from the previously published guideline on this topic.

To restate, this should not ultimately change the treatment strategies offered by neuro-oncologic specialists in terms of standard treatment regimens. However, there were some intriguing findings, specifically the potential benefit of treatment with immune checkpoint inhibition prior to and after surgical resection for progressive glioblastoma. This should generate further interesting studies surrounding immunotherapeutics either as monotherapy, in conjunction with resection, or as combination therapies.

Ultimately, several limitations exist within our analysis of the literature as well as within the general study designs that prevent our ability to make high-level recommendations. Our search was limited to completed trials with accessible, published data. Our exclusion criteria were strict, resulting in some trials with potentially positive findings and data being excluded due to survival data mixing in pediatric patients and/or WHO Grade III astrocytomas or gliosarcoma. However, this allowed us to restrict our analysis to pay very strict attention to and make recommendations for treatment of adult patients with progressive glioblastoma. On the other hand, we were limited in making strong recommendations as many of the trials were statistically underpowered, lacked control groups, sometimes lacked standardization, or have not yet proceeded beyond initial Phase I and Phase II evaluations. In the future, it may be possible that recommendations on these topics will be strengthened due to creation of larger, randomized, multicenter trials addressing the topics of the smaller studies used as evidence in this document.

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Disclaimer of liability This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Declarations

Conflict of interest All Guideline Task Force members were required to disclose all potential COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this series of articles.

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