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# Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of chemotherapeutic management and antiangiogenic treatment of newly diagnosed glioblastoma in adults

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TOPIC REVIEW

# Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of chemotherapeutic management and antiangiogenic treatment of newly diagnosed glioblastoma in adults

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## Abstract

***Question*** What is the role of temozolomide in the management of adult patients (aged 65 and under) with newly diagnosed glioblastoma?

**Target population** These recommendations apply to adult patients diagnosed with newly diagnosed glioblastoma.

**Recommendation** Level I: Concurrent and post-irradiation Temozolomide (TMZ) in combination with radiotherapy and post-radiotherapy as described by Stupp et al. is recommended to improve both PFS and OS in adult patients with newly diagnosed GBM. There is no evidence that alterations in the dosing regimen have additional beneficial effect.

***Question*** Is there benefit to adjuvant temozolomide treatment in elderly patients (> 65 years old?).

**Target population** These recommendations apply to adult patients diagnosed with newly diagnosed glioblastoma.

**Recommendation** Level III: Adjuvant TMZ treatment is suggested as a treatment option to improve PFS and OS in adult patients (over 70 years of age) with newly diagnosed GBM.

***Question*** What is the role of local regional chemotherapy with BCNU biodegradable polymeric wafers in adult patients with newly diagnosed glioblastoma?

**Target population** These recommendations apply to adult patients diagnosed with newly diagnosed glioblastoma.

**Recommendation** Level III: There is insufficient evidence for the use of BCNU wafers following resection in patients with newly diagnosed glioblastoma who undergo the Stupp protocol after surgery. Further studies of higher quality are suggested to understand the role of BCNU wafer and other locoregional therapy in the setting of Stupp Protocol.

***Question*** What is the role of bevacizumab in the adult patient with newly diagnosed glioblastoma?

**Target population** These recommendations apply to adult patients diagnosed with newly diagnosed glioblastoma.

**Recommendation** Level I: Bevacizumab in general is not recommended in the initial treatment of adult patients with newly diagnosed GBM. It continues to be strongly recommended that patients with newly diagnosed GBM be enrolled in properly designed clinical trials to assess the benefit of novel chemotherapeutic agents compared to standard therapy.

**Keywords** GBM · Chemotherapy · Brain tumors · Bevacizumab · Temozolomide · Gliomas

## Rationale

Surgery is recommended for newly diagnosed brain tumors to provide a pathological diagnosis, and when safe, to maximally resect the tumor. Whether patients undergo a gross total resection, subtotal resection, or biopsy, chemotherapy is usually initiated afterwards. While the previous guideline reviewed the data through 2008 [1], additional studies continue to define the role of chemotherapy and periodic review is required to review the role of chemotherapeutic options

Navid Redjal and Brian V. Nahed have contributed equally as co-first authors.

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in the management of adult patients with newly diagnosed glioblastoma in order to provide updated recommendations.

## Objectives

The purpose of this update is to assess the literature since the last set of clinical guidelines for chemotherapy in the management of newly diagnosed glioblastoma in adult patients. We seek to review new evidence and update the recommendations in regards to chemotherapy.

## 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 an update of the guidelines for management of newly diagnosed glioblastoma. The writers represent a multi-disciplinary panel of clinical experts encompassing neurosurgery, neurooncology, and radiation oncology. Together, they were recruited to develop this update on the evidence-based practice guidelines for newly diagnosed glioblastoma (GBM) in adults. The methodology and findings of the previous guidelines were reviewed, and additional questions were developed to incorporate recent literature addressing practice patterns in management of GBM patients.

### Literature review and eligibility criteria

The following electronic databases were searched from January 1, 2008 to December 31, 2018: PubMed, Embase, and Cochrane Database of Systematic Reviews using relevant MeSH and non-MeSH terms, including "GBM", "GBM multiforme", "GBM", "Newly-diagnosed", "newly diagnosed", and "clinical trial."

To be included in the guideline, a publication had to meet the following criteria:

#### Inclusion criteria

- Peer-reviewed publications
- Clinical studies in patients with newly diagnosed glioblastoma/high grade glioma
- Each study reporting on at least five or more subjects
- Adult patients (> 18 years of age). Studies with mixed adult and child populations were included if the adult cohorts could be isolated and analyzed separately
- Publications written in English

The search criteria were developed and performed by two independent reviewers. Citations were independently reviewed and included if they met the a priori criteria for relevance. No discrepancies in study eligibility were noted. Corresponding full-text PDFs were obtained for all citations meeting the criteria, and reviewed. Data was extracted by the first reviewer and verified by another, all of which were compiled into evidence tables. The tables and data were reviewed by all of the authors. Articles not meeting the selection criteria were removed.

### Data collection process

Our search criteria yielded a total of 271 publications, which were reviewed by two authors independently. Among these, 148 studies met the eligibility criteria and were further screened. 89/148 studies met all outlined selection criteria and specifically focused on chemotherapy for GBM.

Those abstracts that met with the selection criteria mentioned above were retrieved in full text form. The adherence to the selection criteria were confirmed. Corresponding full-text PDFs were obtained for all citations meeting the criteria, and reviewed. Data was extracted by the first reviewer and verified by another, all of which were compiled into evidence tables. The tables and data were reviewed by all of the authors. Articles not meeting the selection criteria were removed.

## Scientific foundation

### Classification of evidence and recommendation levels

Each reviewer independently determined the strength of the evidence, classified the level of evidence according to the criteria described in the Introduction section. Differences in classification of evidence and level of recommendations between the two reviewers were discussed between the reviewers to reach an agreement. If an agreement could not be reached the other three authors were asked to review the evidence and recommendations to allow the group to reach a consensus. Difference in level of recommendations were discussed amongst the reviewers and if a consensus could not be made discussed with the authors. For each article, a level of recommendation was achieved. Level I was reserved for well-designed, prospective, randomized and controlled studies with clear mechanisms to limit bias. Level II recommendations described studies that were randomized and controlled studies, but with design flaws leading to potential bias and limiting the paper's conclusions, non-randomized

cohort studies, and case–control studies. Level III recommendations were reserved for single surgeon, single institutional case series, comparative studies with historical control, and randomized studies with significant flaws related to studies with limited power and compromised statistical analysis. Additional information on study classification and recommendation development can be found at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

### Summary of prior recommendations

In the previously published guidelines on the chemotherapeutic management of newly diagnosed GBM [1], the role of concurrent and post-irradiation temozolomide reached level I recommendations based upon a single class I study [2]. BCNU-impregnated biodegradable polymers were recommended as level II based upon two studies. The addition of temozolomide to radiation therapy for patients older than 70 with a Karnofsky performance status above 50 received a level III recommendation [1].

### Assessment for risk of bias

Our search generated a list of abstracts, which were screened, and those articles that addressed our identified questions underwent full independent review by the authors. Reviewers were critical in their assessment, specifically in regard to trial design, such as randomization of treatment, blindedness, prospective character, etc., size of study population, baseline characteristics between study groups which could account for survivorship bias, selection bias, and appropriate statistical analyses of reported data.

## Results of literature review

### Temozolomide in patients with newly diagnosed GBM

Twelve studies examining the use of temozolomide for the treatment of newly diagnosed GBM (GBM) were eligible and were included in this analysis (Table 1).

#### Should patients with newly diagnosed GBM undergo temozolomide as adjuvant therapy?

In a phase III randomized controlled trial [2], Stupp et al. established level 1 evidence for the use of concurrent and post-irradiation temozolomide (TMZ) for the treatment of GBM. Since the previous guidelines publication in 2008 [1], no further large randomized controlled clinical studies have been done to address the role of chemotherapy in GBM. A small class II study by Karacetin et al. [3] showed statistically significant improvement in PFS and OS in GBM patients with concurrent/adjuvant TMZ with RT compared to RT only.

#### Does MGMT promoter methylation status predict benefit to adjuvant TMZ treatment?

We identified a total of six studies [4–9] that examined the role of MGMT methylation status with respect to response to TMZ treatment. All studies found that patients with newly diagnosed GBM with methylated MGMT promoter status had better outcomes with TMZ treatment compared to patients with MGMT promoter unmethylated tumors. Park et al. [4] found that only MGMT promoter-methylated patients benefited (improved PFS and OS) from adjuvant TMZ treatment compared to MGMT promoter-unmethylated patients. Further, patients with MGMT methylated tumors who underwent concurrent TMZ and radiation had significant improvement in PFS and overall OS compared to patients with MGMT methylated tumors receiving post-irradiation TMZ (OS 41 months vs. 17 months and PFS 24 months vs 3 months) [4]. This finding suggests that most treatment benefit from TMZ in MGMT promoter methylated tumors occurs during concomitant TMZ/RT treatment. In another study, Barbagallo et al. [5] found a direct correlation of median survival with MGMT promoter methylation status. Gilbert et al. [6], in a randomized controlled clinical trial, examined the benefit of dose dense adjuvant TMZ and again noted an association of MGMT promoter methylation with improved OS and PFS with the use of standard TMZ treatment. Weiler et al. [9] provided further evidence that MGMT promoter methylation status is an important predictive factor in response to TMZ treatment in a study investigating different dosing regimens for TMZ. Examining the role of TMZ therapy in elderly patients with GBM, Perez-Larraya et al. [7] found that MGMT promoter methylation was associated with improved response to TMZ therapy, consistent with the findings from other studies. Finally, in a more recent study examining standard TMZ treatment in combination with bevacizumab therapy, Gilbert et al. [8] confirmed the value of MGMT promoter methylation status as a positive prognostic factor, which was associated with significant improvement in PFS and OS. Although these studies were not specifically designed to compare treatment based on MGMT promoter methylation status, they all strongly suggest that methylation of the MGMT promoter in GBM is associated with improved outcome after TMZ treatment as compared to tumors with unmethylated MGMT promoter.

**Table 1** Temozolomide in patients with newly diagnosed GBM

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Bhandari et al. (2017) | *Study description* single institution, prospective randomized study to assess the impact of six versus 12 cycles of adjuvant Temozolomide (TMZ) on Overall Survival (OS) in newly diagnosed postoperative patients of Glioblastoma Multiforme (GBM)<br>*Patient population* 40 postoperative patients of GBM between age 18–65 years and Karnofsky Performance Score (KPS) ≥ 70 were included<br>*Treatment regimen*<br>all patient received radiation (60 Gy in 30 fractions over six weeks) with concomitant TMZ (75 mg/m$^2$/day) and were randomized to adjuvant therapy with either:<br>- six cycles (C-TMZ arm) (n = 20)<br>- 12 cycles (E-TMZ arm) of TMZ (n = 20)<br>(TMZ 150–200 mg/m$^2$ for five days, repeated four weekly) | II | ***Results***<br>*Median PFS*<br>C-TMZ: 12.8 months<br>E-TMZ: 16.8 months<br>(p = 0.069)<br>*Median OS*<br>C-TMZ: 15.4 months<br>E-TMZ: 23.8 months<br>(p = 0.044)<br>***Toxicity***<br>"Overall, 5% and 15% patients respectively in C-TMZ and E-TMZ arm had haematological toxicity ≥ 3 in grade"<br>***Author's Conclusions***<br>"Our study showed that E-TMZ is well tolerated and leads to a significant increase in PFS as well as OS in newly diagnosed patients of GBM. Further prospective randomized studies are needed to validate the findings of our study"<br>***Comments and conclusions***<br>Classified as Class II because is a prospective randomized trial. This study provides evidence that extended TMZ can have improved PFS and OS. The study is limited since it did not assess MGMT methylation status which is a known important predictive factor in response to TMZ treatment |
| Blumenthal et al. (2017) | *Study description* retrospective analysis of four multicenter randomized trials for newly diagnosed GBM patients assessing PFS and OS in patients who were treated with 6 cycles and those who continued beyond 6 cycles of adjuvant TMZ<br>*Patient population* 624 newly diagnosed GBM patients qualified for analysis<br>*Treatment regimen*<br>TMZ until progression or up to 12 cycles (> 6C) = 291 pts<br>TMZ discontinue after 6 cycles (6C) = 333 pts | III | ***Results***<br>*Median PFS:*<br>TMZ 6C: 10.4 months (95% CI: 8.7–11.9)<br>TMZ > 6C: 12.2 months (95% CI: 9.4–14.0)<br>"Adjusted for prognostic factors, treatment with more than 6 cycles of TMZ was associated with a somewhat improved progression-free survival (hazard ratio [HR] 0.80 [0.65–0.98], P = .03), in particular for patients with methylated MGMT (n = 342, HR 0.65 [0.50–0.85], P < .01)"<br>*Median OS:*<br>TMZ 6C: 24.9 months (95% CI: 19.9–28.7)<br>TMZ > 6C: 27.0 months (95% CI: 21.54–30.9)<br>"OS was not affected by the number of TMZ cycles (HR = 0.92 [0.71–1.19], P = .52), including the MGMT methylated subgroup (HR = 0.89 [0.63–1.26], P = .51)"<br>***Author's conclusions***<br>"Continuing TMZ beyond 6 cycles was not shown to increase overall survival for newly diagnosed GBM"<br>***Comments and conclusions***<br>Classified as Class III because this is a retrospective pooled study. This study provides evidence that extended TMZ can have improved PFS, however, there was no support for improved OS. The study is limited given its retrospective nature and lack of specific toxicity data |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Gramatzkiet al. (2017) | *Study description* retrospective single-center cohort study of GBM patients examining the effects of prolonged TMZ maintenance on progression-free survival (PFS) and overall survival (OS)<br>*Patient population* 142 newly diagnosed GBM patients qualified for analysis<br>*Treatment regimen*<br>patient received TMZ/RT → TMZ and completed 6 cycles or ≥ 6 cycles of maintenance chemotherapy without progression<br>Adjuvant TMZ<br>7 or more cycles = 61 pts<br>6 cycles = 81pts | III | ***Results***<br>*Median PFS:*<br>Extended TMZ (> 6 cycles): 20.5 months (95% CI 17.7–23.3)<br>Standard TMZ (6 cycles): 17.2 months (CI 10.2–24.2)<br>(p = 0.035)<br>"However, there was no significant association of prolonged TMZ chemotherapy with PFS (hazard ratio [HR] = 0.8, 95% CI 0.4–1.6, p = 0.559) or OS (HR = 1.6, 95% CI 0.8–3.3, p = 0.218) adjusted for age, extent of resection, Karnofsky performance score, presence of residual tumor, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, or isocitrate dehydrogenase (IDH) mutation status"<br>*Median OS*<br>Extended TMZ (> 6 cycles): 32.6 months (95% CI 28.9–36.4)<br>Standard TMZ (6 cycles): 33.2 months (95% CI 25.3–41.0)<br>(p = 0.126)<br>***Author's conclusions***<br>"These data may not support the practice of prolonging maintenance TMZ chemotherapy beyond 6 cycles"<br>***Comments and conclusions***<br>Classified as Class III because this is a retrospective single-center cohort study. This study does not provide evidence that extended TMZ can improve PFS when adjusted for age, extent of resection, Karnofsky performance score, presence of residual tumor, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, or isocitrate dehydrogenase (IDH) mutation status. This is another study that does not show support for improved OS with extended TMZ. Again, this is another study which is limited given its retrospective nature |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Skardellyet al. (2017) | *Study description* retrospective single-center cohort study of GBM patients examining the effects of prolonged TMZ maintenance on progression-free survival (PFS) and overall survival (OS)<br>*Patient population* 107 newly diagnosed GBM patients qualified for analysis who were treated with radiation therapy with concomitant and adjuvant TMZ<br>*Treatment regimen*<br>Adjuvant TMZ groups:<br>Group A - stopped TMZ maintenance therapy within the first six cycles (n = 32)<br>Group B - completed six TMZ maintenance cycles,<br>(n = 32)<br>Group C - continued with TMZ therapy beyond six cycles<br>(n = 43)<br>Patients with progression during the first six TMZ maintenance cycles were excluded | III | ***Results***<br>*Median PFS:*<br>Group A: 8.1 months (95% CI 6.1–12.4)<br>Group B: 13.7 months (95% CI 10.6–17.5)<br>Group C: 20.9 months (95% CI 15.2–43.5)<br>At first progression, response rates of TMZ/lomustine rechallenge were 47% in group B and 13% in group C<br>*Median OS*<br>Group A: 12.7 months (95% CI 10.3–16.8)<br>Group B: 25.2 months (95% CI 17.7–55.5)<br>Group C: 28.6 months (95% CI 24.4-open)<br>"multivariate Cox regression for patients in group C compared with group B that accounted for imbalances of other risk factors showed no different relative risk (RR) for OS (RR 0.77, p = .46)"<br>***Author's conclusions***<br>"Our data do not support a general extension of TMZ maintenance therapy beyond six cycles"<br>"We compared the effect of more than six cycles of TMZ in comparison with exactly six cycles on overall survival (OS) and progression-free survival (PFS) by multivariate analysis and found a benefit in PFS but not OS"<br>***Comments and conclusions***<br>Classified as Class III because this is a retrospective single-center cohort study. This study provides evidence that extended TMZ can have improved PFS, however, there was no support for improved OS. Again, this is another study which is limited given in its retrospective nature and lack of specific toxicity data |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Hanet al. (2015) | *Study description* single institution, retrospective assessment focused on the effect of timing of initiation of concurrent radiation and chemotherapy after surgery on outcome of patients with glioblastoma (GBM)<br>*Patient population* newly diagnosed GBM patients who were enrolled from 2004 to 2010 in 4 clinical trials consisting of radiation plus temozolomide and an experimental agent (n = 198)<br>*Treatment regimen*<br>The interval to initiation of therapy was determined from the time of surgical resection<br>Chemoradiation < 30 days from surgery: 100pts<br>Biopsy: 26<br>STR: 40<br>GTR: 33<br>Chemoradiation 30–34 days from surgery: 48pts<br>Biopsy: 2<br>STR: 26<br>GTR: 19<br>Chemoradiation > 34 days from surgery: 50pts<br>Biopsy: 5<br>STR: 29<br>GTR: 15<br>Radiation: ~ 60 Gy (30 fractions of 1.8–2 Gy)<br>Chemotherapy: TMZ- Stupp protocol<br>Clinical trials:<br>Enzastaurin + RT + TMZ (phase I): 12pts<br>Enzastaurin + RT + TMZ (phase II): 66pts<br>Ertolinib + RT + TMZ: 66pts<br>Ertolinib + bevacizumab + RT + TMZ: 59pts | III | ***Results***<br>Median wait time between surgery and initiation of concurrent chemoradiation was 29.5 days (range, 7–56 days)<br>After adjusting for protocol and baseline prognostic variables including extent of resection by multivariate analysis<br>-A short delay in chemoradiation administration (at 30–34 days) was predictive of prolonged OS (hazard ratio [HR]: 0.63, P = .03) and prolonged PFS (HR: 0.68, P = .06) compared with early initiation of concurrent chemoradiation (< 30 days)<br>-A longer delay to chemoradiation (> 34 days) was not associated with improved OS ((HR: 0.94, P = .77) or PFS (HR: 0.91, P = .63) compared with early initiation (< 30 days)<br>***Toxicity***<br>Not reported<br>***Author's conclusions***<br>"A short delay in the start of concurrent chemoradiation is beyond the classic paradigm of 4 weeks post-resection and may be associated with prolonged OS and PFS……. However, due to the retrospective nature of our analysis, there is a significant potential for confounding: the treating physicians may have tendencies to rush more fragile-appearing patients into adjuvant therapy, thus patients with shorter waiting times would have included those patients with a greater number of poor prognostic factors, such as older age, worse KPS, or less than gross total resection achieved at the time of surgery"<br>***Comments and conclusions***<br>Classified as Class III because is a purely retrospective review. Although, this retrospective study which uses data from prior clinical trials has significant limitations, it does highlight with some statistical significance the importance of timing of chemoradiation after surgery. Early (< 30 days) chemoradiation does not appear to be beneficial nor does a longer delay (> 34 days). In their analysis, authors show that a short delay (30–34 days) is predictive prolonged PFS and OS as compared to early chemoradiation |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Sunet al. (2015) | *Study description* retrospective study using the TCGA database to assess the effect of time from surgery to initiation of concurrent radiation and TMZ chemotherapy on survival in patients with newly diagnosed GBM<br>*Patient population* newly diagnosed GBM patients identified from TCGA database who underwent concurrent radiation and TMZ chemotherapy after 2005 (n = 218)<br>*Treatment regimen*<br>Surgery:<br>Data not available<br>"Radiotherapy was delivered to all patients at a median dose of 60 Gy. All patients received concurrent temozolomide chemotherapy, and additional chemotherapy was given at tumor recurrence to 74 patients."<br>Delay in treatment groups<br>Delay to therapy was defined as the time from surgery to the initiation of radiotherapy<br>"The median delay was 27 days. For statistical analysis, patients were stratified by length of delay to therapy relative to the median time to therapy. "<br>"Additionally, data were analyzed by grouping patients into quartiles of delay to therapy, with the first quartile including all patients with delays up to 20 days, the second quartile including 21–27 days, the third quartile including 28–35 days, and the fourth quartile including 36 days or longer"<br>Patients with a delay to therapy longer or shorter than the median demonstrated no differences in age, male to female ratio, KPS score, or use of additional chemotherapy at tumor recurrence | III | ***Results***<br>*Median PFS:*<br>delay to initiation of therapy (≤27 days): 7.2 months<br>delay to initiation of therapy (>27 days): 7.8 months<br>(p = 0.840)<br>delay to initiation of therapy (≤20 days): 5.4 months<br>delay to initiation of therapy (≥36 days): 7.4 months<br>(p = 0.667)<br>*Median OS*<br>delay to initiation of therapy (≤27 days): 15.9 months<br>delay to initiation of therapy (>27 days): 14.9 months<br>(p = 0.180)<br>delay to initiation of therapy (≤20 days): 16 months<br>delay to initiation of therapy (≥36 days): 14.2 months<br>(p = 0.124)<br>delay to initiation of therapy (≤42 days): 15.9 months<br>delay to initiation of therapy (>42 days): 12.9 months<br>(p = 0.022)<br>***Toxicity***<br>No data reported<br>***Author's conclusions***<br>"Modest delay in initiation of postoperative chemotherapy and radiation does not appear to be associated with worse PFS or OS in patients with newly diagnosed glioblastoma, while significant delay longer than 6 weeks may be associated with worse OS"<br>***Comments and conclusions***<br>Classified as Class II because is a purely retrospective study. Study does not show any significant effect on PFS or OS with a delay in initiation of treatment unless longer than 6 weeks. Significant limitations of study include inability to "control for extent of resection, tumor location, or tumor size…….extent of initial temozolomide chemotherapy received or additional experimental therapy due to enrollment in clinical trials" |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Barbagalloet al. (2014) | *Study description* Retrospective study comparing long-term treatment of TMZ (> 6 cycles) to standard treatment (6 cycles) for newly diagnosed glioblastoma multiforme (GBM) patients<br>*Patient population* matched cohort analysis of newly diagnosed GBM patients:<br>Group A (TMZ > 6 cycles): received more than 6 cycles of TMZ chemotherapy (n = 19)<br>Group B (TMZ = 6 cycles): received a maximum of 6 cycles of TMZ chemotherapy (n = 18)<br>*Treatment regimen*<br>*Surgery*<br>All patients with radiographic GTR except STR in 1pt in group A and 1 pt in group B<br>TMZ treatment:<br>Initiation of therapy on day 2 or 3 postoperatively-dose of 150 mg/m$^2$ for 5 days of a 28-day cycle for both groups. Following this first TMZ cycle, all patients received radiation therapy and concurrent TMZ administration dosed according to the Stupp protocol<br>Group A: adjuvant TMZ therapy- patients received 150 mg/m$^2$ for 5 days every 28 days for more than 6 cycles (up to 101 cycles)<br>Group B: adjuvant TMZ therapy- patients received 150 mg/m$^2$ for 5 days every 28 days for no more than 6 cycles | III | ***Results***<br>*Median PFS:*<br>Group A (TMZ > 6 cycles): 20 months<br>Group B (TMZ = 6 cycles): 4 months<br>(p = 0.0002)<br>*Median OS*<br>Group A (TMZ > 6 cycles): 28 months<br>Group B (TMZ = 6 cycles): 8 months<br>(p = 0.0001)<br>***Toxicity***<br>Data not provided but authors noted "No cumulative toxicity was observed in either group studied. In Group A patients, who received more than 6 cycles of TMZ, only minor side effects were observed and these were not clinically significant, such as platelet reduction in 2 patients and white cell reduction in 2 patients. These side effects did not require treatment intervention, and TMZ administration was not interrupted"<br>***Author's conclusions***<br>"This study describes the longest experience so far reported with TMZ in patients with newly diagnosed glioblastomas, with as many as 101 cycles, who were treated using GTR. Statistically significant data confirm that median survival correlates with MGMT promoter methylation status as well as with the number of TMZ cycles administered. Long-term TMZ therapy appears feasible and safe"<br>***Comments and conclusions***<br>Classified as Class III because is a purely retrospective study. Study has significant limitations including significant important differences in Group A and B which include MGMT status (significantly more patients with MGMT promoter methylation in group A) and age (significantly more younger patients in group A) which makes it difficult to determine benefit of long-term TMZ therapy given these factors have known effect on PFS and OS. Further, a positive selection bias for patients to continue on monthly TMZ beyond 6 cycles is likely to play a role. Only a prospective randomized design may be able to address this concern |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Gilbertet al. (2013) | *Study description* single institution, prospective randomized study assessment of whether dose-dense TMZ improves OS or PFS in newly diagnosed GBM patients<br>*Patient population* newly diagnosed GBM patients with KPS > 60 (n = 833)<br>*Treatment regimen*<br>all patient received fractionated RT (60 Gy total dose) with concomitant oral temozolomide (75 mg/m(2)/day × 7 days/ week, for 6 weeks)<br>Adjuvant TMZ:<br>Standard treatment TMZ group (n = 411): 150 mg/m$^2$ for 5 consecutive days of a 28-day cycle, and TMZ was increased for subsequent cycles to 200 mg/m$^2$ if no treatment-related adverse events greater than grade 2 were noted. Treatment was planned for six cycles with the potential to extend treatment to a total of 12 cycles<br>Dose-dense TMZ group (n = 422): 75 mg/m$^2$ for 21 consecutive days of a 28-day cycle, which was increased for subsequent cycles to 100 mg/m$^2$ if no treatment-related adverse events greater than grade 2 were noted. As with the standard dose arm, six cycles were planned with the potential to extend to a total of 12 cycles | II | ***Results***<br>*Median PFS:*<br>Standard treatment TMZ group: 5.5 months<br>Dose-dense TMZ group: 6.7 months<br>(p = 0.06)<br>*Median OS*<br>Standard treatment TMZ group: 16.6 months<br>Dose-dense TMZ group: 14.9 months<br>(p = 0.63)<br>MGMT methylation status- Median OS<br>MGMT methylated: 21.2 months<br>MGMT unmethylated: 14 months<br>(p < 0.001)<br>MGMT methylation status- Median PFS<br>MGMT methylated: 8.7 months<br>MGMT unmethylated: 5.7 months<br>(p < 0.001)<br>***Toxicity***<br>Grade 3 or 4 toxicity (mostly lymphopenia and fatigue):<br>Standard treatment TMZ group: 34%<br>Dose-dense TMZ group: 54%<br>(p < 0.001)<br>***Author's conclusions***<br>"This study did not demonstrate improved efficacy for DD temozolomide for newly diagnosed GBM, regardless of methylation status. However, it did confirm the prognostic significance of MGMT methylation"<br>***Comments and conclusions***<br>Classified as Class II because is a prospective randomized trial (not reported to be blinded). A well-designed randomized trial that did not demonstrate any significant benefit in PFS or OS from use of dose-dense adjuvant TMZ therapy compared to standard therapy. Also of note, the dose-dense strategy was found to have statistically increased percentage of patient with Grade 3 or 4 toxicities. The study again reaffirms the association of MGMT methylation with improved OS and PFS with use of standard treatment |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Parket al. (2013) | *Study description* retrospective analysis focusing on two prospective patient groups: RT followed by adjuvant TMZ (RT- > TMZ) and concomitant RT and TMZ followed by adjuvant TMZ (CCRT-TMZ) from SCNOG/KROG study a phase III trial evaluating the effects of neoadjuvant chemotherapy with nimustine-cisplatin when used in conjunction with radiotherapy plus adjuvant temozolomide in patients with newly diagnosed glioblastoma patients<br>*Patient population* newly diagnosed GBM patients with KPS > 70 (n = 75)<br>RT- > TMZ group: 25pts (with known MGMT promoter methylation status)<br>CCRT-TMZ group: 50 pts selected with a 2:1 matching ratio to each patient of the RT- > TMZ group was applied considering the age, extent of resection, MGMT promoter methylation status and postsurgical performance status<br>*Treatment regimen*<br>RT- > TMZ group: fractionated RT (60 Gy total dose) followed by temozolomide monotherapy (150–200 mg/m(2)/day × 5 days every 28 days for 6 cycles)<br>*Surgery*<br>> 95% resection: 10 (40%)<br>< 95% resection: 15 (60%)<br>Biopsy: 4 (28%)<br>MGMT promoter methylation:<br>Methylated: 7 (28%)<br>Unmethylated: 18 (72%)<br>CCRT-TMZ group: fractionated RT (60 Gy total dose) with concomitant oral temozolomide (75 mg/m$^2$/day × 7 days/ week, for 42 consecutive days) followed by temozolomide monotherapy (150–200 mg/m$^2$/day × 5 days every 28 days for 6 cycles)<br>*Surgery*<br>> 95% resection: 20 (40%)<br>< 95% resection: 30 (60%)<br>Biopsy: 12 (20%)<br>MGMT promoter methylation:<br>Methylated: 14 (28%)<br>Unmethylated: 36 (72%) | III | ***Results***<br>*Median PFS:*<br>With MGMT promoter: Methylated<br>RT- > TMZ: 3 months<br>CCRT-TMZ: 24 months<br>(p = 0.02)<br>With MGMT promoter: Unmethylated<br>RT- > TMZ: 6 months<br>CCRT-TMZ: 6 months<br>(p = 0.19)<br>*Median OS*<br>With MGMT promoter: Methylated<br>RT- > TMZ: 17 months<br>CCRT-TMZ: 41 months<br>(p = 0.02)<br>With MGMT promoter: Unmethylated<br>RT- > TMZ: 17 months<br>CCRT-TMZ: 18 months<br>(p = 0.53)<br>***Toxicity***<br>Grade 3 or 4 toxicities<br>RT- > TMZ: 4 (16%)<br>CCRT-TMZ: 7 (14%)<br>***Author's conclusions***<br>"In conclusion, we can claim that the concomitant use of temozolomide with radiotherapy is a crucial step in the standard treatment for glioblastoma patients with MGMT promoter methylation. For glioblastoma patients with an unmethylated MGMT promoter, the value of temozolomide usage is questionable, either concurrently or as an adjuvant after radiotherapy"<br>***Comments and conclusions***<br>Classified as Class III because is a retrospective analysis of a prior well designed prospective study. Although, there are several limitations as authors mention in present study ("patient groups were highly selected", small number of patients, "proportion of MGMT promoter-methylated patients [being smaller (28%) than that reported for the general GBM pts (45%)], the study does show significant evidence that treatment with concomitant TMZ does show significant improvement in PFS and OS in patients with methylated MGMT promoter GBMs |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Roldán et al. (2012) | *Study description* Retrospective population study comparing extended adjuvant TMZ treatment (> 6 cycles) to standard treatment (6 cycles) for newly diagnosed glioblastoma multiforme (GBM) patients<br>*Patient population* newly diagnosed GBM patients (n = 273)<br>Of these patients, 52pts received concurrent TMZ + RT followed by adjuvant TMZ<br>Adjuvant TMZ for 6 cycles (n = 23)<br>Adjuvant TMZ for > 6 cycles (n = 29)<br>*Treatment regimen*<br>Per Stupp protocol<br>Adjuvant TMZ for > 6 cycles (n = 29):<br>Debulking: 76%<br>Biopsy: 24%<br>MGMT promoter statues<br>Methylated: 63%<br>Unmethylated: 37%<br>Adjuvant TMZ for 6 cycles (n = 23):<br>Debulking: 76%<br>Biopsy: 24%<br>MGMT promoter statues<br>Methylated: 47%<br>Unmethylated: 53% | III | ***Results***<br>*Median OS*<br>Adjuvant TMZ for > 6 cycles: 16.5 months<br>Adjuvant TMZ for 6 cycles: 24.6 months<br>(p = 0.031)<br>Median PFS not provided but authors noted "in multivariate analysis for PFS, concurrent<br>chemoradiotherapy, MGMT promoter methylation and receiving more than six cycles of monthly chemotherapy were independent prognostic factors"<br>***Toxicity***<br>Data not provided but authors noted "Extended adjuvant therapy was not associated with increased toxicity"<br>***Author's conclusions***<br>"These data suggest extended adjuvant temozolomide (i.e., more than six cycles) should be considered in patients with newly diagnosed GBM"<br>***Comments and conclusions***<br>Classified as Class III because is a purely retrospective study. Study has significant limitations including authors noting "confounding factor" that at treatment progression second line therapies were used which are not controlled for which include "VP16 (Etoposide), CCNU (Lomustine), palliative care or inclusion in trials for recurrent GBM." Also, GTR and STR were combined into the same group of "Debulking" underscoring importance of extent of resection |
| (Karacetinet al. (2011) | *Study description* single institution, prospective randomized study assessment on the efficacy and safety of radiotherapy (RT) with concomitant and subsequent temozolomide in comparison to RT alone in the treatment of patients with newly diagnosed glioblastoma multiforme (GBM) after surgery<br>*Patient population* newly diagnosed GBM patients with KPS > 80 (n = 40)<br>*Treatment regimen*<br>RT + TMZ group: 20pts<br>Fractionated RT (60 Gy total dose) with concomitant oral temozolomide (75 mg/m$^2$/day × 7 days/ week, for 6 weeks) followed by temozolomide monotherapy (200 mg/m$^2$/day × 5 days every 28 days for 6 cycles)<br>Surgery:<br>GTR: 8<br>STR: 8<br>Biopsy: 4<br>RT group: 20 pts<br>Surgery:<br>GTR: 14<br>STR: 3<br>Biopsy: 3<br>Fractionated RT (60 Gy in 30 fractions) | II | ***Results***<br>*Median PFS:*<br>RT + TMZ: 13 months<br>RT only: 5 months<br>(p = 0.0001)<br>*Median OS*<br>RT + TMZ: 19 months<br>RT only: 11.5 months<br>(p = 0.0264)<br>***Toxicity***<br>RT + TMZ: grade 3 hematologic toxicity in 6 patients<br>***Author's conclusions***<br>"These data show that the combination of temozolomide, concomitant and subsequent to RT seems more effective than RT alone in patients with newly diagnosed GBM and that multimodality treatment is safe and well tolerated"<br>***Comments and conclusions***<br>Classified as Class II because is a prospective randomized trial (not reported to be blinded). Another study which shows statistically significant improvement in PFS and OS with concomitant/adjuvant TMZ with RT compared to RT only |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Weileret al. (2010) | *Study description* single institution, prospective randomized phase II trial to evaluate the toxicity and efficacy of chemoradiotherapy with temozolomide (TMZ) administered in an intensified 1-week on/1-week off schedule plus indomethacin for treatment of patients with newly diagnosed glioblastoma multiforme (GBM),<br>*Patient population* newly diagnosed GBM patients with KPS > 60 (n = 41)<br>*Treatment regimen*<br>TMZ was administered orally before and after RT in<br>a weekly alternating schedule starting at 150 mg/m$^2$ on Days 1–7 of 14-day cycles. If the beginning of RT coincided with Days 1–7 of any cycle (''week on TMZ''), the entire cycle was completed first before low-dose TMZ at 50 mg/m$^2$ was initiated. If the beginning of RT coincided with Days 8–14 (''week off TMZ''), concomitant low-dose TMZ at 50 mg/m$^2$ was started only after completion of the current week off TMZ<br>-The dose of concomitant TMZ was chosen to be lower (50 mg/m$^2$) than the standard dose (75 mg/m$^2$)<br>-At 4 weeks after RT, the weekly alternating TMZ regimen was continued, starting at 150 mg/m$^2$. No maximal number of cycles was defined. Dose adjustments of adjuvant TMZ were done according to weekly hemograms after every second cycle | II | ***Results***<br>1-year survival rate: 73.2% (95% confidence interval, 56.8–84.2%)<br>*Median PFS:*<br>Total: 7.6 months (95% confidence interval, 6.2–10.4)<br>Methylated MGMT: 15.8 months (95% confidence interval, 8.4–21.5)<br>Unmethylated MGMT: 6.2 months (95% confidence interval, 5.8–7.7)<br>*Median OS*<br>Total:15.9 months (95% confidence interval, 15.0–23.8)<br>Methylated MGMT: 21.5 months (95% confidence interval, 19–NA)<br>Unmethylated MGMT: 15 months (95% confidence interval, 11.5–23.8)<br>***Toxicity***<br>"Grade 4 hematologic toxicity was observed in 15 patients (36.6%)"<br>"Treatment-related nonhematologic Grade 4–5 toxicity was reported for 2 patients (4.9%)"<br>***Author's conclusions***<br>"The dose-dense regimen of TMZ administered in a 1-week on/1-week off schedule resulted in acceptable nonhematologic toxicity. Compared with data from EORTC/NCIC trial, patients with an unmethylated MGMT gene promoter appeared not to benefit from intensifying the TMZ schedule regarding the median PFS and OS. In contrast, data are promising for patients with a methylated MGMT promoter"<br>***Comments and conclusions***<br>Classified as Class II because is a prospective randomized trial. This study again provides evidence that MGMT methylation status is an important predictive factor in response to TMZ treatment. Although significant limitations exist, when the current 1-week on/1-week off schedule is compared to historical data from the EORTC/NCIC trial, the current regimen shows improvement in PFS in methylated MGMT promoter GBM patients |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Clarkeet al. (2009) | *Study description* single institution, prospective randomized phase II trial to evaluate between dose-dense or metronomic temozolomide for treatment of patient with newly diagnosed glioblastoma multiforme (GBM),<br>*Patient population* newly diagnosed GBM patients with KPS > 60 (n = 85)<br>*Treatment regimen*<br>all patient received fractionated RT (60 Gy total dose) with concomitant oral temozolomide (75 mg/m(2)/day × 7 days/ week, for 6 weeks)<br>Adjuvant TMZ:<br>Dose-dense TMZ group (n = 42): 150 mg/m$^2$ daily from days 1–7 and 15–21 of each cycle<br>*Surgery*<br>GTR: 43%<br>STR: 33%<br>Biopsy:24%<br>Metronomic TMZ group(n = 43): 50 mg/m$^2$ daily from days 1–28 of each cycle<br>*Surgery*<br>GTR: 39%<br>STR: 39%<br>Biopsy:22%<br>Maintenance doses of 13-c/s-retinoic acid were then administered until tumor progression | I | ***Results***<br>*Median OS*<br>Dose-dense TMZ group: 17.1 months (95% CI, 14.0 to 28.1 months)<br>Metronomic TMZ group: 15.1 months (95% CI, 12.3 to 18.9 months)<br>Of note: "When analysis was restricted to the 59 patients who actually received adjuvant chemotherapy as planned, median OS was 17.8 months (95% CI, 14.0 to not reached) for the dose-dense group and 16.3 months (95% CI, 13.3 to 18.9) for the metronomic group"<br>*Median PFS:*<br>Dose-dense TMZ group: 6.6 months (95% CI, 4.2 to 7.8 months)<br>Metronomic TMZ group: 5.0 months (95% CI, 4 to 6.7 months)<br>"Pseudoprogression was observed in 37% of assessable patients and may have had an impact on estimates of progression-free survival"<br>***Toxicity***<br>Grade 3 or 4 toxicities- dose-dense TMZ group (31/42) and metronomic TMZ group (28/43). "Both adjuvant regimens were well tolerated, and no unexpected<br>toxicities or rates of toxicity were observed"<br>***Author's conclusions***<br>"Both dose-dense and metronomic temozolomide regimens were well tolerated with modest toxicity. The dose-dense regimen appears promising, with 1-year survival of 80%"<br>***Comments and conclusions***<br>Classified as Class II because is a prospective randomized trial (not reported to be blinded). As the authors note, the purpose of the study was not designed to compare the two treatment strategies but rather compare to the historical control from the EORTC/NCIC phase III trial. Interestingly, the dose-dense TMZ group was shown to have median survival of 15.4 months in the unmethylated MGMT promoter GBM pts (compared to historical control of 12.7 months) indicating possible benefit of this treatment strategy. The study did show that both treatment strategies were tolerated in the majority of patients without significant toxicity |

**Table 1** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Sheret al. (2008) | *Study description* single institution, retrospective assessment on the efficacy of concomitant temozolomide in patients treated by concurrent and adjuvant TMZ versus adjuvant TMZ alone in the setting of newly diagnosed GBM<br>*Patient population* newly diagnosed GBM patients (n = 107)<br>*Treatment regimen*<br>RT with adjuvant TMZ-only: 21pts<br>fractionated RT (~60 Gy total dose) followed by temozolomide monotherapy (200 mg/m(2)/day × 5 days every 28 days for 6 cycles)<br>RT + concurrent/adjuvant TMZ: 22 pts<br>fractionated RT (~60 Gy total dose) with concomitant oral temozolomide (75 mg/m(2)/day × 7 days/ week, for 6 weeks) followed by temozolomide monotherapy (200 mg/m(2)/day × 5 days every 28 days for 6 cycles)<br>Surgery- RT with adjuvant TMZ-only:<br>biopsy: 29%<br>STR: 38%<br>GTR: 33%<br>Surgery- RT + concurrent/adjuvant TMZ:<br>biopsy: 23%<br>STR: 54%<br>GTR: 23% | III | ***Results***<br>*Median PFS:*<br>RT with adjuvant TMZ-only: 8.6 months<br>RT + concurrent/adjuvant TMZ: 9.7 months<br>(p = 0.22)<br>*Median OS*<br>RT with adjuvant TMZ-only: 15.6 months<br>RT + concurrent/adjuvant TMZ:: 25.5 months<br>(p < .05)<br>***Toxicity***<br>"there was no significant difference in the number of patients with grade 2 or higher toxicities (P = 0.54, Fisher's exact test)"<br>***Author's conclusions***<br>"In this highly selected cohort, we have shown that treatment with concurrent and adjuvant temozolomide was associated with a significant increase in overall survival compared to adjuvant temozolomide alone on univariate analysis. After adjustment for RPA class, this relationship maintained borderline significance"<br>***Comments and conclusions***<br>Classified as Class II because is a retrospective study. Another study which shows statistically significant improvement in OS with RT + concomitant/adjuvant TMZ compared to RT with adjuvant TMZ-only |

#### Is there benefit of adjuvant TMZ treatment in elderly patients (> 70 years of age)?

Two Class III studies [7, 10] examined the role of adjuvant TMZ for treatment of elderly patients with newly diagnosed GBM (Table 2). In a multicenter, prospective non-randomized phase II study of patients age 70 years or older with newly diagnosed GBM and postoperative KPS < 70, Perez-Larraya et al. [7] showed that these patients can tolerate TMZ treatment with improvement in PFS, OS, and functional status compared to reported supportive care data. In this study, MGMT promoter methylation was shown to indicate better response to TMZ therapy. In a retrospective study, Behm et al. [10] found statistically significant improvement in OS in elderly patients > 70 years of age with combined radiation and concomitant/adjuvant TMZ. Similar to previous findings in studies prior to 2008 [11–14], these studies indicate that treatment of elderly patients with adjuvant TMZ results in significant improvement in outcomes.

#### Synthesis

There is class I evidence that concurrent and post-irradiation temozolomide in combination with radiotherapy and post-radiotherapy as described by Stupp et al. is recommended to improve both PFS and OS in adult patients with newly diagnosed GBM.

Although the above studies were not specifically designed to compare treatment based on MGMT promoter methylation status, they all strongly suggest that methylation of the MGMT promoter in GBM is associated with improved outcome after TMZ treatment as compared to tumors with unmethylated MGMT promoter.

There is class III evidence that adjuvant TMZ treatment is recommended as a treatment option to improve PFS and OS in adult patients (over 70 years of age) with newly diagnosed GBM.

### Timing of temozolomide in patients with newly diagnosed GBM?

#### When should temozolomide treatment be initiated after initial diagnosis of GBM?

Two Class III studies [15, 16] examined the effect of timing of initiation of concomitant TMZ/RT after diagnosis. In a single institution, retrospective assessment, Han et al. [15] found neither early (< 30 days) nor delayed (> 34 days) chemoradiation as beneficial. In their analysis, they showed that a short delay (30–34 days) is predictive of prolonged PFS and OS as compared to earlier or delayed chemoradiation. Sun et al. [16], in another retrospective study, found no significant effect on PFS or OS with a delay in initiation of treatment unless treatment was delayed by more than 6 weeks. Although these retrospective studies have significant limitations, they are consistent with previous studies [17–19] which have not shown any significant benefit of starting chemoradiation sooner than 4 weeks.

#### Does prolonged or non-standard temozolomide dosing regimens provide benefit compared to standard temozolomide dosing?

One class II study [20] and five class III studies [5, 21–24] examined the benefit of extended adjuvant TMZ treatment (> 6 cycles) compared to standard adjuvant therapy (6 cycles). In a prospective non-blinded randomized study, Bhandari et al. [20], examined the impact of six versus 12 cycles of adjuvant TMZ on OS in newly diagnosed postoperative patients. They found that that extended TMZ was well tolerated and lead to an increase in PFS (12.8 months vs. 16.8 months, p = 0.069) as well as OS (15.4 months vs. 23.8 months, p = 0.044) in newly diagnosed patients of GBM. They noted that the study was limited in the small number of patients (n = 40, 20 in each group) and lack of listing MGMT methylation status which is known prognosticator for response to TMZ therapy. In a retrospective matched cohort analysis of GBM patients treated with TMZ, Barbagallo et al. [5] examined two groups of patients: Group A, in which patients had greater than 6 cycles of adjuvant TMZ treatment (up to 101 cycles), and Group B, where patients did not receive more than 6 cycles of adjuvant TMZ treatment. The authors report that the median survival correlated with the number of TMZ cycles administered, however, this conclusion can be challenged based on significant limitations in the study design given important differences in the two groups. First, there were significantly more patients with MGMT promoter methylation in group A and the age of patients was significantly younger in group A compared to group B. Furthermore, a positive selection bias for patients to continue on monthly TMZ beyond 6 cycles was likely to play a role. Another retrospective study by Roldan et al. [21], also suggested improved median survival in patients receiving more than 6 cycles of TMZ compared to standard therapy of 6 cycles; however, the study had similar limitations in deriving this conclusion given that both groups had significant differences including that the extended adjuvant TMZ group had more patients with a methylated MGMT promoter than the group receiving standard therapy. In a larger study (n = 624) by Blumenthal et. al [22], which was a retrospective analysis of four multicenter randomized trials for newly diagnosed GBM patients, continuing TMZ beyond 6 cycles had some improvement in PFS, but did not show to increase overall survival after adjusting for prognostic factors. Similarly, in a retrospective single-center cohort study, Skardelly et al. [23] again did not find any evidence

**Table 2** Adjuvant TMZ treatment in elderly patients

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Behmet al. (2013) | *Study description* single institution, retrospective assessment focused on comparing GBM patients above the age of 65 treated with radiation alone or with concomitant and adjuvant chemoradiotherapy (TMZ)<br>*Patient population* GBM patients (n = 293)<br>Pts age > 65: 139pts<br>*Treatment regimen*<br>Radiation: ~ 60 Gy (30 fractions of 1.8–2 Gy)<br>Chemotherapy: TMZ- Stupp protocol<br>In patients > 65:<br>Radiation only: 59<br>Radiation + TMZ: 80<br>Surgery in age > 65 with RT alone:<br>GTR- 73%<br>Partial- 14%<br>Biopsy- 14%<br>Surgery in age > 65 with combined RT + TMZ<br>GTR- 56%<br>Partial- 11%<br>Biopsy- 13%<br>Radiation: ~ 60 Gy (30 fractions of 1.8–2 Gy)<br>Chemotherapy: TMZ- Stupp protocol | III | ***Results***<br>*Median overall survival*<br>In all pts:<br>TMZ + RT: 13.5 months<br>RT only: 4.8 months<br>(p < .0001)<br>In matched analysis of elderly pts (age > 65):<br>*Median overall survival*<br>TMZ + RT: 8.7 months<br>RT only: 3.6 months<br>(p < .0001)<br>***Toxicity***<br>Termination of temozolomide due to toxicity in 8 patients greater than 70 years of age. All of these experienced a prolonged low platelet count of less than 100<br>***Author's conclusions***<br>"Retrospective matched pair analysis gives class 2b evidence for prolonged survival due to concomitant and adjuvant temozolomide in elderly glioblastoma patients. Until prospective data for combined radiochemotherapy in elderly patients will be available concomitant and adjuvant temozolomide therapy should not be withheld"<br>***Comments and conclusions***<br>Classified as Class III because is a retrospective review. Study shows statistically significant improvement in OS in elderly patients > 65 years of age with combined radiation and concomitant/adjuvant TMZ. Of note, the authors point out that "besides survival and toxicity the patients quality of life and self- dependence must be kept in mind. As a limitation of this study, these data could not be provided retrospectively" |

**Table 2** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Pérez-Larrayaet al. (2011) | *Study description* Multicenter, prospective non-randomized phase II study of patients age 70 years or older with newly diagnosed GBM and postop KPS < 70<br>*Patient population* patients age 70 years or older with newly diagnosed GBM and postop KPS < 70 (n = 70)<br>*Treatment regimen*<br>Surgery: 65 underwent biopsy, 5 partial resection, 1 GTR<br>Chemotherapy:<br>Up to 12 cycles of temozolomide within first month after diagnostic biopsy or resection. The first dose was 150 mg/m$^2$ for 5 consecutive days every 28 days, with dose escalation up to 200 mg/m$^2$ at the second cycle in the absence of hematologic toxic effect<br>No radiation given to any patient | III | ***Results***<br>*Median PFS* 16 weeks<br>MGMT promoter methylation indicated longer PFS (26 weeks vs 11 weeks, p = 0.03)<br>*Median overall survival* 25 weeks<br>MGMT promoter methylation indicated longer OS (31 weeks vs 19 weeks, p = 0.03)<br>23 pts improved KPS by 10 or more points<br>***Toxicity***<br>Grade 3 to 4 neutropenia and thrombocytopenia occurred in 13% and 14% of patients respectively<br>***Author's conclusions***<br>"Temozolomide has an acceptable tolerance in elderly patients with GBM and KPS less than 70. It is associated with improvement of functional status in 33% of patients and appears to increase survival compared with supportive care alone, especially in patients with methylated MGMT promoter"<br>***Comments and conclusions***<br>Classified as Class III because study is nonrandomized prospective study. Study shows that newly diagnosed GBM patients with KPS < 70 who are over the age of 70 can tolerate TMZ treatment with improvement in PFS, OS, and functional status compared to reported supportive care data. MGMT promoter methylation was shown to indicate better response to TMZ therapy, in line with numerous other studies |

of improvement in overall survival with some improvement in PFS. Furthermore, Gramatzki et al. [24] after adjusting for age, extent of resection, KPS, presence of residual tumor, MGMT promoter methylation status, or IDH mutation status, not only did not find any benefit in OS, but, also they did not see any improvement in PFS. Ultimately, these studies do not provide sufficient evidence for extended adjuvant TMZ treatment. Future prospective trials will be required to better understand the effects of extended adjuvant TMZ treatment.

Three class II studies [6, 9, 25] investigated non-standard TMZ dosing regimens including dose dense and metronomic TMZ dosing strategies. In a prospective randomized phase II trial, Clarke et al. [25] compared post-irradiation adjuvant dose-dense TMZ (150 mg/m$^2$ daily from days 1–7 and 15–21 of each cycle) and a metronomic TMZ regimen (50 mg/m$^2$ daily from days 1–28 of each cycle) and found that either treatment was relatively well tolerated with the dose dense regimen trending towards better outcomes. They noted that the purpose of the study was not designed to compare the two treatment strategies but rather compare their treatment regimens to the historical control from the EORTC/NCIC phase III trial. Interestingly, the dose-dense TMZ group was shown to have a median survival of 15.4 months in unmethylated MGMT promoter GBM patients (compared to historical controls of 12.7 months), indicating a possible benefit of this treatment strategy. In another well designed randomized controlled trial, Gilbert et al. [6] did not demonstrate any significant benefit in PFS or OS from the use of dose-dense adjuvant TMZ therapy compared to standard therapy. Also of note, the dose-dense strategy was found to have statistically increased percentage of patient with Grade 3 or 4 toxicities. Weiler et al. [9] in a different dose-dense regimen, where TMZ was administered orally before and after RT in a weekly alternating schedule (50 mg/m$^2$ during RT and 150 mg/m$^2$ after RT with no maximal number of cycles defined) showed that this dose dense regimen showed some improvement in PFS in methylated MGMT promoter GBM patients compared to historical data from the EORTC/NCIC trial. Significant limitations in comparing the findings of this study with the historical data of the EORTC/NCIC trial include that this study's patients were also all treated with indomethacin, the median KPS was 90, and the median number of cycles treated with adjuvant therapy

was 6.5 (compared to median of 3 cycles in the EORTC/NCIC trial). The above studies did not show any significant evidence that alternative TMZ dosing strategies can lead to better outcomes compared to the standard Stupp protocol.

#### Synthesis

The above studies in regards to timing of TMZ treatment do not provide any significant evidence that alternative TMZ dosing strategies can lead to better outcomes compared to the standard Stupp protocol. In regards to the initiation of TMZ treatment, the retrospective studies above did not show any significant benefit of starting chemoradiation sooner than 4 weeks. Furthermore, the above studies do not provide sufficient evidence for extended adjuvant TMZ treatment or that alternative TMZ dosing strategies can lead to better outcomes compared to the standard Stupp protocol.

## Adjuvant therapy in patients with newly diagnosed GBM?

### Should temozolomide be given concomitantly with radiation therapy?

Two class III studies [4, 26] met the eligibility criteria for examining the role of concomitant TMZ therapy during radiation. In a retrospective analysis focusing on two prospective patient groups (RT followed by adjuvant TMZ and concomitant RT with TMZ followed by adjuvant TMZ) from a larger phase III clinical trial, Park et al. [4] found evidence that treatment with concomitant TMZ during radiation showed significant improvement in PFS and OS in patients with methylated MGMT promoter GBMs compared to treatment with post-irradiation TMZ only (PFS 24 months to 3 months and OS 41 months to 17 months, respectively). Interestingly, there was no significant difference in PFS or OS in patients with unmethylated MGMT promoter GBMs, indicating that the potential benefit of concomitant TMZ during radiation is only applicable to methylated MGMT tumors. In another retrospective study, Sher et al. [26] showed statistically significant improvement in OS with RT + concomitant TMZ + adjuvant TMZ compared to RT with adjuvant TMZ-only (OS 25.5 months compared 15.6 months, respectively). Unfortunately, this study did not test for MGMT methylation status, possibly accounting for the lack of significant differences in PFS between both groups. Although these studies have clear limitations, they highlight the important role of concomitant TMZ during RT, especially for methylated MGMT tumors in the overall benefit of adjuvant TMZ.

### What is the role for local regional chemotherapy with BCNU biodegradable wafers in patients with newly diagnosed GBM?

Seven Class III studies [27–33] met our inclusion criteria which examined the use of BCNU biodegradable wafers (Gliadel wafers) as local therapy for patients with GBMs (Table 3). Affronti et al. [27] in single institution retrospective study comparing outcomes of newly diagnosed GBM patients receiving surgical resection with and without carmustine (BCNU) wafers followed by RT and concurrent TMZ plus rotational chemotherapy (temozolomide, carmustine, irinotecan) showed no statistically significant benefit in the use of BCNU wafers in addition to finding that this group had increased grade 3/4 toxicity (31% BCNU wafer group and 16 in the non-BCNU wafer group). They noted, however, though that the BCNU wafer group had better outcomes than the historical EORTC/NCIC data from the Stupp et al. paper [2], however this finding may be confounded by differences in the extent of resection in both studies. Specifically, patients in the BCNU wafter study had either gross total or subtotal resections, whereas 17% of patients in the EORTC/NCIC study underwent biopsy only. De Bonis et al. [28] found no substantial improvement in survival when adding loco-regional chemotherapy with BCNU wafers to standard therapy and found increased risk for adverse events. Furthermore, in a prospective non-randomized single arm study, Salmaggi et al. [29] found no significant improvement in survival with possibly slight improvement in PFS in newly diagnosed GBM patients treated with BCNU wafers in combination with 6-month metronomic temozolomide and radiation therapy. In another study examining newly diagnosed GBM patients aged > 65 years who underwent surgical resection with and without carmustine (BCNU) wafers, Chaichana et al. [30] showed statistically significant improvement in survival in patients older than 65 years old who underwent surgical resection with BCNU wafer placement compared to those that did not undergo BCNU wafer placement at surgical resection. However, the findings of this study is limited in terms of understanding efficacy with only 6/45 patients receiving temozolomide in either group. Similarly in a study by Noel et al. [31], the differences in the BCNU wafer treated group and the non-BCNU wafer treated group limits any significant conclusions made by the authors of this study. In this single institution, retrospective assessment of treatment of WHO Grade III or IV glioma patients who received surgical resection with and without BCNU wafers, the authors observed a trend, although not statistically significant, in improvement in outcome with treatment of patients with local regional therapy with BCNU, temozolomide, and radiotherapy. This trend in improvement in overall survival in GBM patients is difficult to claim given that 5 patients in the no-BCNU wafer group had biopsy

**Table 3** Local regional chemotherapy with BCNU biodegradable wafers in patients with newly diagnosed GBM

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Akiyamaet al. (2018) | *Study description* single institution, retrospective assessment of therapy for newly diagnosed GBM patients who received surgical resection with carmustine (BCNU) wafers and bevacizumab or without BCNU wafer and without bevacizumab<br>*Patient population* newly diagnosed GBM patients (n = 54) treated with resection and standard radiochemotherapy with (TMZ,Stupp Regimen)<br>Groups:<br>1. BCNU wafer and bevacizumab treated between 2013–2016 n = 29;<br>2. no BCNU wafer and no bevacizumab treated between 2010–2012 n = 25<br>There were no significant differences in age, sex, Karnofsky Performance Status on admission, isocitrate dehydrogenase 1/2 mutation ratio, or resection rate between the combined and standard therapy groups | III | ***Results***<br>Progression-free survival<br>BCNU wafer + bevacizumab group: 16.8 months<br>No BCNU wafer and no bevacizumab group: 7.3 months<br>(p = 0.009)<br>*Median overall survival*<br>BCNU wafer + bevacizumab group: 24.2 months<br>No BCNU wafer and no bevacizumab group: 15.3 months<br>(p = 0.027)<br>***Toxicity***<br>Overall, the incidence of adverse events leading to discontinuation of the study drug was similar between the treatment groups, except for infection, which was more common in the combined treatment group and required repeat surgery<br>***Author's conclusions***<br>"The combined therapy showed higher efficacy compared with standard therapy in patients with GBM. Therefore, combined therapy seems to be effective with an acceptable toxicity profile"<br>***Comments and conclusions***<br>Classified as Class III because study is a retrospective study. The study and its conclusions have significant limitations. The patients that are being compared are from two separate treatment eras 2010–2012 and 2013–2016 which limits direct comparisons of results. The combination of BCNU wafers with bevacizumab is compared to treatment with neither BCNU wafers and bevacizumab, which limits direct comparison of either treatment. The patients who had the combined treatment had increased rate of repeat surgery which also limits direct comparison of results |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Rouxet al. (2017) | *Study description* Single center retrospective study including 340 consecutive adult patients with a newly diagnosed supratentorial glioblastoma who underwent surgical resection with (n = 123) or without (n = 217) BCNU wafer implantation as first-line oncological treatment<br>*Patient population* newly diagnosed GBM patients (n = 340) treated with resection Groups:<br>1. BCNU wafer n = 123;<br>2. no BCNU wafer n = 217 | III | ***Results***<br>Progression free survival<br>BCNU wafer + subtotal/total resection (> 90%): 11.9 months (95%CI 8.1–12.5)<br>subtotal/total resection: 10.0 months (95% CI 7.0–11.5)<br>BCNU wafer + partial resection (< 90%): 9.0 months (95% CI 7.0–12.0)<br>Partial resection: 6.5 months (95% CI 5.0–7.9)<br>Overall Survival<br>BCNU wafer + subtotal/total resection (> 90%): 22.5 months (95% CI 21.0–31.0)<br>subtotal/total resection: 20.5 months (95% CI 17.0–33.0)<br>BCNU wafer + partial resection (< 90%): 18.0 months (95% CI 16.0–25.5)<br>Partial resection: 12.0 months (95% CI 9.0–15.0)<br>Adjusted Hazard Ratio (aHR)<br>BCNU wafer implantation PFS 0.74 [95% CI 0.55–0.99], p = 0.043<br>OS 0.69 [95% CI 0.49–0.96], p = 0.029<br>Subtotal and total resection PFS 0.70 [95% CI 0.54–0.91], p = 0.009<br>OS 0.52 [95% CI 0.38–0.70], p < 0.001<br>Standard combined chemoradiotherapy PFS 0.40 [95% CI 0.29–0.55], p < 0.001<br>OS 0.58 [95% CI 0.42–0.81], p = 0.002<br>***Toxicity***<br>"Carmustine wafer implantation and extent of resection did not significantly increase postoperative complications, including postoperative infections (p = 0.269, and p = 0.446, respectively. Carmustine wafer implantation and extent of resection did not significantly increase adverse events during adjuvant oncological therapies (p = 0.968, and p = 0.571, respectively)"<br>***Author's conclusions***<br>"Carmustine wafer implantation in combination with maximal resection, followed by standard combined chemoradiotherapy is safe, efficient, and well-tolerated in newly diagnosed supratentorial glioblastomas in adults<br>***Comments and conclusions***<br>Classified as Class III because study is a retrospective study. The study and its conclusions have significant limitations. As the authors note, the study was retrospective and the patients were not randomly assigned, which can "induce bias in the patient selection". The authors also note that certain biomarkers such as MGMT methylation were not assessed in the dataset and, therefore, differences in groups cannot be definitively attributed to therapy given the known benefit of MGMT methylation. The study does highlight the benefit of extent of resection and combined chemoradiation |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Salmaggiet al. (2013) | *Study description* Single institution prospective study of carmustine (BCNU) wafers in combination with 6-month metronomic temozolomide and radiation therapy in newly diagnosed glioblastoma patients<br>*Patient population* GBM patients (n = 35)<br>-newly diagnosed GBM patients<br>- KPS > 70<br>*Treatment regimen*<br>Surgery: newly diagnosed GBM patients (GTR 25/35)<br>Radiation: total of ~ 60 Gy<br>Chemotherapy: Temozolomide | III | ***Results***<br>Progression-free survival<br>Median time to tumor progression was 12.5 months<br>*Median overall survival*<br>Median survival was 17.8 months<br>The only factor significantly associated with longer survival was gross total tumor removal<br>***Toxicity***<br>7 pts needed to stop temozolomide therapy due to toxicity (causes included Grade 4 thrombocytopenia, leukopenia, liver toxicity, nephrotoxicity), 1 pt died from Legionella pneumonia,1 pt treated for presumed brain abscess, 4 cases of DVT/PE<br>***Author's conclusions***<br>"PFS at 12 months in this study compares favorably with data present in the literature concerning single-treatment modalities, although the results for survival are less convincing"<br>***Comments and conclusions***<br>Classified as Class III because study is a prospective nonrandomized single arm study. Study showed no significant improvement in survival with possibly slight improvement in PFS |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| De Boniset al. (2012) | *Study description* single institution, retrospective assessment of therapy for newly diagnosed and recurrent GBM patients who received surgical resection with and without carmustine (BCNU) wafers<br>*Patient population* GBM patients (n = 165)- newly diagnosed GBM patients (n = 77, BCNU wafer treated n = 19) and recurrent GBM patients (n = 88, BCNU wafer treated n = 28)<br>*Treatment regimen*<br>Surgery: newly diagnosed GBM patients (GTR 42/77); recurrent GBM patients (GTR 66/88)<br>Radiation and Chemotherapy:<br>newly diagnosed GBM patients<br>Radiation: total of ~ 60 Gy<br>Chemotherapy: Temozolomide<br>Recurrent GBM patients: previously had undergone chemo-radiation<br>*13 newly diagnosed GBM pts and 8 recurrent GBM pts did not receive standard chemotherapy (surgery alone or different chemo regimen) | III | ***Results***<br>*Median overall survival*<br>Newly diagnosed GBM pts<br>BCNU wafer group: 14 months (95% CI 8–18 months)<br>No BCNU wafer group: 11 months (95% CI 8–14 months)<br>Recurrent GBM pts<br>BCNU wafer group: 6 months (95% CI 4–8 months)<br>No BCNU wafer group: 9 months (95% CI 7–11 months)<br>The only factor significantly associated with longer survival was gross total tumor removal<br>***Toxicity***<br>Patients with a higher number of wafers implanted and patients with recurrent tumors were significantly at risk for adverse effects. Patients with eight Gliadel wafers implanted had a threefold increased risk of adverse effects and a 5.6-fold increased risk of implantation site-related adverse effects, and patients with recurrent tumor had a 2.8-fold increased risk of adverse effects and a 9.3-fold increased risk of implantation site-related adverse effects<br>***Author's conclusions***<br>"Adding Gliadel to standard treatment did not significantly improve the outcome. The toxicity after Gliadel use was significantly higher, both for patients with newly diagnosed and patients with recurrent glioblastoma"<br>***Comments and conclusions***<br>Classified as Class III because study is a retrospective nonrandomized review. Study showed no significant improvement in survival with increased risk for adverse events |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Noëlet al. (2012) | *Study description* single institution, retrospective assessment of therapy WHO Grade III or IV glioma pts who received surgical resection with and without carmustine (BCNU) wafers<br>*Patient population* WHO Grade III or IV glioma pts (n = 65)<br>-BCNU wafer treated n = 28<br>-20pts with GBM<br>-8pts with WHO grade III glioma<br>- non BCNU wafer treated n = 37<br>-16pts with GBM<br>-20pts with WHO Grade III<br>*Treatment regimen*<br>Surgery: Three groups:<br>macroscopically complete resection in 19 cases (31%)<br>-BCNU wafer group- 10 pts<br>-No BCNU wafer group- 9 pts<br>macroscopically incomplete resection in 36 cases (59%);<br>-BCNU wafer group- 15 pts<br>-No BCNU wafer group- 21 pts<br>large resection biopsy in 6 cases (10%)<br>-BCNU wafer group- 1 pt<br>-No BCNU wafer group- 5 pts<br>4 tumor resections could not be classified<br>Radiation and Chemotherapy:<br>Stupp protocol (60 Gy radiation with TMZ)<br>Radiation:<br>Dose = 60 Gy<br>-BCNU wafer group- 24 pts<br>-No BCNU wafer group- 30 pts<br>Dose < 60 Gy<br>-BCNU wafer group- 4 pts<br>-No BCNU wafer group- 7 pts<br>Chemotherapy:<br>Post RT TMZ<br>-BCNU wafer group- 24 pts<br>-No BCNU wafer group- 32 pts<br>No post RT TMZ<br>-BCNU wafer group- 4 pts<br>-No BCNU wafer group- 5 pts | III | ***Results***<br>Median relapse-free survival<br>BCNU wafer group: 12.9 months<br>No BCNU wafer group: 14 months<br>(p = 0.89)<br>*Median overall survival*<br>BCNU wafer group: 20.6 months<br>No BCNU wafer group: 20.8 months<br>GBM subset<br>BCNU wafer group: 20.8 months<br>No BCNU wafer group: 13.8 months<br>(p = 0.067)<br>***Toxicity***<br>Four cases of Grade 3 thrombocytopenia occurred, all in the BCNU wafer group<br>***Author's conclusions***<br>"Adding Gliadel to treatment described by Stupp et al. does not clearly improve the outcome of patients; however, a trend in OS appeared for patients with glioblastoma in favor of the triple association Gliadel, temozolomide, and radiotherapy. To date, implantation of Gliadel wafers in the operative site does not appear to be justified if the patient may benefit from temozolomide treatment at a later time point"<br>***Comments and conclusions***<br>Classified as Class III because study is a retrospective study. A trend in possible improvement in overall survival in GBM pts needs to take in consideration that 5pts in the no-BCNU wafer group only had biopsy while only 1pt in the BCNU wafer group underwent biopsy. In univariate analysis quality of surgical removal (p = 0.03) was prognostic factor of OS |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Chaichanaet al. (2011) | *Study description* single institution, retrospective assessment of therapy for newly diagnosed GBM patients aged 65 years and older who received surgical resection with and without carmustine (BCNU) wafers<br>*Patient population* GBM patients aged 65 years and older (n = 133) with (BCNU wafer treated n = 57)<br>45 of the patients with BCNU wafer implantation were matched with 45 pts without BCNU wafer implantation (matching factors- age, KPS, eloquent cortex involvement, extent of resection, postop radiation, postop temozolomide)<br>*Treatment regimen*<br>Surgery: GTR (38/45) pts<br>Radiation and Chemotherapy:<br>newly diagnosed GBM patients<br>Chemotherapy:<br>Only 6/45 pts received temozolomide<br>Radiation:<br>Only 40/45 received radiation therapy | III | ***Results***<br>*Median overall survival*<br>BCNU wafer group: 8.7 months<br>No BCNU wafer group: 5.5 months<br>(p = 0.007)<br>Subset of pts older than 70 years<br>BCNU wafer group: 9.1 months<br>No BCNU wafer group: 4.8 months<br>(p = 0.007)<br>***Toxicity***<br>Similar peri-operative morbidity in both groups including:<br>1/45 pts developing cerebral edema and 2/45 pts developing surgical site infection in BCNU wafer implantation group<br>0/45 pts developing cerebral edema and 1/45 pts developing surgical site infection in non-BCNU wafer implantation group<br>***Author's conclusions***<br>"The present study provides several useful insights for older patients with GBM. First, the use of carmustine wafers in these patients does not increase peri-operative morbidity and mortality. Second, the use of carmustine wafers is nearly as efficacious in prolonging survival for older patients with GBM as it is with younger patients with GBM"<br>***Comments and conclusions***<br>Classified as Class III because study is a retrospective case–control study. Study showed statistically significant improvement in survival in patients older than 65 years old who underwent surgical resection with BCNU wafer placement, however, study is limited in terms of understanding efficacy with only 6/45 pts receiving temozolomide in either group |

**Table 3** (continued)

| Author (Year) | Description of Study | Data Class | Conclusions |
|---|---|---|---|
| Affrontiet al. (2009) | *Study description* single institution, retrospective assessment of therapy for newly diagnosed GBM patients who received surgical resection with and without carmustine (BCNU) wafers followed by RT and concurrent TMZ plus rotational chemotherapy<br>*Patient population* GBM patients (n = 85). 36 in BCNU wafer group and 49 with no BCNU wafer implantation<br>*Treatment regimen*<br>Surgery at initial diagnosis: all pts (GTR 65% in no BCNU wafer group, 69% in BCNU wafer group)<br>Radiation and Chemotherapy: all pts<br>Radiation: total of 60 Gy<br>Chemotherapy-concurrent temozolomide plus rotational multiagent chemotherapy (temozolomide, carmustine, irinotecan) | III | ***Results***<br>*Median overall survival*<br>BCNU wafer group: 89.5 weeks<br>No BCNU wafer group: 72.7 week<br>BCNU wafer group: 1 year survival: 81%; 2 year survival: 47%<br>No BCNU wafer group: 1 year survival: 69%; 2 year survival: 29%<br>BCNU wafer was not an independent predictor (P = 0.110) of survival after adjustment for RPA class<br>The proportion of patients in the BCNU wafer cohort who lived longer than predicted based upon Stupp regimen results was significantly greater than 0.5 (P < 0.006); similar results based upon the RTOG trial data were observed (P < 0.001)<br>***Toxicity***<br>Grade 3 and 4 hematologic toxicity: 31% in BCNU wafer group and 16% in no BCNU wafer group<br>***Author's conclusions***<br>"Although not statistically significant, these data suggest that the inclusion of carmustine wafers in a treatment regimen involving rotational chemotherapy may be of benefit"<br>***Comments and conclusions***<br>Classified as Class III because is a retrospective review. The small sample size and hence low power may have contributed to the lack of statistical significance |

only while 1 patient in the BCNU wafer group underwent biopsy only. This difference makes it difficult to conclude a positive trend in outcome with the use of BCNU wafers especially given their own univariate analysis of the quality of surgical removal ($p = 0.03$) which was a prognostic factor in overall survival. In another single institution, retrospective study by Akiyama et al. [32], therapy for newly diagnosed GBM patients who received surgical resection with BCNU wafers and bevacizumab or without BCNU wafer and without bevacizumab was examined. The study showed that patients who underwent BCNU wafer + bevacizumab group compared to no BCNU wafer and no bevacizumab group had significant benefit in PFS and OS (16.8 months vs. 7.3 months, $p = 0.009$; and 24.2 months vs. 15.3 months, $p = 0.027$). The study and its conclusions have significant limitations. The patients that are being compared are from two separate treatment eras 2010–2012 (no BCNU wafer) and 2013–2016 (BCNU wafer) which limits direct comparisons of results. The combination of BCNU wafers with bevacizumab is compared to treatment with neither BCNU wafers and bevacizumab, which limits direct comparison of either treatment. Roux et. al [33] also found benefit and relative safety of BCNU wafer compared to standard therapy without wafer, however, again this study was single institution retrospective study with potential selection bias.

In the prior guidelines publication in 2008 [1], the recommendation for the use of BCNU biodegradable wafers referenced two prospective studies [34, 35] which were randomized placebo controlled trials examining the efficacy of BCNU wafers in an era prior to the establishment of systemic TMZ as standard therapy. Both studies suggested a benefit from using BCNU wafers as locoregional chemotherapy.

The previous guideline detailed level II recommendations for the use BCNU wafers. Since then, concomitant temozolomide and radiation therapy (Stupp Protocol) has become the standard of care supported by level I evidence. The seven level III studies have not provided sufficient evidence that demonstrates significant improvement in overall survival or progression free survival to support the use of BCNU wafers. Additional studies of higher quality are required to understand the role of BCNU wafer and other locoregional therapy in the setting of Stupp Protocol are necessary.

### What is the role of adjuvant bevacizumab (Avastin) in patients with newly diagnosed GBM?

Two Class I studies [8, 36] and 9 Class III studies [37–45] met our inclusion criteria to examine the benefit of adjuvant bevacizumab use in patients with GBM (Table 4). Both Class I studies (16,35) found no overall survival benefit in patients treated with adjuvant bevacizumab. In a multicenter, prospective randomized double-blind phase III trial examining the efficacy of bevacizumab added to standard therapy with RT/TMZ for the treatment of newly diagnosed GBM, Chinot et al. [36] found that the addition of adjuvant bevacizumab did not result in any overall survival benefit (OS 16.8 months with bevacizumab and 16.7 with placebo). They also noted an increased rate of adverse events, but they did see a benefit in terms of increased PFS and maintenance of performance status before deterioration with use of bevacizumab across different subgroups. Similarly, in another multicenter prospective randomized double-blinded phase III trial, Gilbert et al. [8] found that adding bevacizumab to standard therapy of concurrent TMZ + radiotherapy + adjuvant monthly TMZ did not result in any overall survival benefit (OS 15.7 months with bevacizumab and 16.1 months with placebo). Although this study did show improved PFS with bevacizumab similar to the study by Chinot et al. [35], it differed significantly in assessment of functional outcome since patients in this study were found to have worsened quality of life in the bevacizumab group. Furthermore, in another study examining the results of two consecutive phase II trials of hypofractionated-intensity modulated radiotherapy (hypo-IMRT) and TMZ with or without bevacizumab, Carlson et al. [37] did not find any significant benefit in adding bevacizumab to hypo-IMRT/TMZ, in addition to having a significant increase in Grade III toxicities with bevacizumab. In another Class III study, Van Linde et al. [40], in a single institution prospective non-randomized phase II study, evaluated the safety and efficacy of bevacizumab in combination with TMZ and RT in newly diagnosed GBM patients and found no benefit of bevacizumab treatment in terms of OS as compared to historical data with standard therapy (of note, in this study patients only received bevacizumab during concomitant RT + TMZ and did not receive bevacizumab during adjuvant TMZ therapy). In another prospective non-randomized single-arm phase II study, Omuro et al. [42] evaluated the use of hypofractionated stereotactic radiotherapy (HFSRT) combined with concomitant/ adjuvant TMZ and bevacizumab in the treatment of patients with newly diagnosed GBM. This study did not reveal any significant benefit in OS with bevacizumab treatment as compared to historical data. The study also provided interesting results regarding to molecular data demonstrating that the expression level of pro-angiogenic genes had no prognostic value in determining response to bevacizumab therapy.

Other class III studies that met inclusion criteria indicated a possible improvement in outcome with the use of adjuvant bevacizumab when compared to historical controls, however, these studies had specific characteristics in the study population that would limit their broader applicability. Lai et al. [39] in a multicenter, prospective non-randomized single-arm phase II study evaluating the efficacy of bevacizumab in combination with TMZ and RT in the treatment of patients with newly diagnosed GBM, commented

**Table 4** Adjuvant bevacizumab in patients with newly diagnosed GBM

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Reyes-Boteroet al. (2018) | *Study description* Multicenter, prospective, nonrandomized, phase II trial evaluating the efficacy and safety of upfront temozolomide (TMZ) and bevacizumab (Bev) in patients aged ≥ 70 years and a KPS < 70<br>*Patient population* Older patients with impaired performance status (Patients aged ≥ 70 years with a KPS < 70) and biopsy-proven GBM (n = 66)<br>*Treatment regimen*<br>Treatment consisted of TMZ administered at 130–150 mg/m$^2$ per day for 5 days every 4 weeks plus Bev administered at 10 mg/kg every 2 weeks | | ***Results***<br>Median PFS: 15.3 weeks (95% CI, 12.9–19.3)<br>Median OS: 23.9 weeks (95% confidence interval [CI], 19–27.6)<br>"Twenty-two (33%) patients became transiently capable of self-care (i.e., KPS > 70). Cognition and quality of life significantly improved over time during treatment"<br>Toxicity:<br>Grade ≥ 3 hematological adverse events occurred in 13 (20%) patients<br>high blood pressure in 16 (24%)<br>venous thromboembolism in 3 (4.5%)<br>cerebral hemorrhage in 2 (3%)<br>intestinal perforation in 2 (3%)<br>***Author's conclusions***<br>"This study suggests that TMZ + Bev treatment is active in elderly patients with GBM with low KPS and has an acceptable tolerance level. "<br>"the estimated OS median of 24 weeks that we found appears higher that the 12 weeks of OS that we found in a similar patient population treated with supportive care alone (personal data, unpublished). However, it is comparable to the 25 weeks that we reported in similar patients receiving TMZ alone. Whether this combination is superior to TMZ alone remains to be demonstrated by a randomized study"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized single-arm phase II study. As the authors point out, the OS from the combination of TMZ + Bev is comparable to TMZ alone and, therefore, it is unclear if there is benefit from combination. The possible benefit of combination with Bev in quality of life needs to be assessed in a direct comparison to TMZ alone in randomized controlled study |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Hataet al. (2017) | *Study description* Single center retrospective case series evaluating the outcomes of newly diagnosed GBM patients treated after 2006 who were treated with and without bevacizumab (BEV)<br>*Patient population* Newly diagnosed GBM patients treated after 2006 (n = 69)<br>3 treatment groups:<br>1)Type I, partial removal with temozolomide (TMZ)/BEV and concurrent radiotherapy (CCRT) (n = 13)<br>2) Type II, partial removal with TMZ and CCRT (n = 19)<br>3) Type III, gross total removal with TMZ and CCRT. (n = 37)<br>*Treatment regimen*<br>BEV was administered intravenously at a dose of 10 mg/kg body weight every 2 weeks (commencing 28 days after craniotomy or 14 days after stereotactic biopsy), followed by subsequent cycles every 2 weeks as the add-on treatment for GBM patients receiving TMZ and CCRT. Maintenance treatment with BEV of the same dose commenced 4 weeks after the completion of CCRT and was performed in combination with maintenance treatment with TMZ<br>TMZ maintenance therapy was performed for a maximum of 24 cycles | III | ***Results***<br>Median PFS:<br>1)Type I pts- 10 months<br>2) Type II pts- 2.6 months<br>3) Type III pts- 8.5 months<br>"PFS of Type I patients was significantly higher than that of Type II patients (P = 0.014), but comparable to that of Type III patients"<br>Median OS:<br>1)Type I pts- 17.4 months<br>2) Type II pts- 9.8 months<br>3) Type III pts- not reported<br>"Differences in OS rates between Type I and Type II patients were less apparent (P = 0.075), although the median OS of Type I patients was ~ 8 months higher than that of Type II patients (17.4 vs 9.8 months, respectively)"<br>"The clinical deterioration rate during initial treatment was significantly (P = 0.024) lower in Type I than in Type II patients (7.7% vs 47.4%, respectively). Differences in OS rates between Type I and Type II patients with a poor performance status (PS) were significant (P = 0.017)"<br>Toxicity:<br>Grade II neutropenia and thrombocytopenia- 1patient<br>DVT- 2 patients<br>progressive brain atrophy—1 patient<br>Author's Conclusions<br>"Our findings suggest that add-on BEV can prevent early clinical deterioration of [partially resected]-GBM patients and contribute to a prolonged survival, especially for those with a poor PS"<br>***Comments and conclusions***<br>Classified as Class III because is a retrospective single center study. Again, this study provides further evidence that Bev does not improve overall survival. There is potential benefit to quality of life that needs to be further assessed in a larger multi-center randomized controlled study |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Carlsonet al. (2015) | *Study description* Two consecutive phase II trials of hypofractionated-intensity modulated radiotherapy (hypo-IMRT) and temozolomide (TMZ) were used to compare outcome from therapy with or without bevacizumab (BEV) in patients with newly diagnosed GBM<br>*Patient population* newly diagnosed GBM patients with KPS ≥ 60<br>In hypo-IMRT and TMZ (hypo-IMRT/TMZ alone) group: n = 26 (pts enrolled from 2008–2010)<br>In hypo-IMRT + TMZ + bevacizumab (hypo-IMRT/TMZ/BEV) group: n = 30 (pts enrolled from 2010–2013)<br>*Treatment regimen*<br>Surgery:<br>hypo-IMRT/TMZ:<br>Gross total resection: 11<br>Near total resection:12<br>Partial resection:1<br>Biopsy:2<br>hypo-IMRT/TMZ/BEV:<br>Gross total resection: 17<br>Near total resection: 5<br>Partial resection: 3<br>Biopsy: 5<br>All patients received postoperative hypo-IMRT to the surgical cavity and residual tumor plus margin to a total dose of 60 Gy and to the T2 abnormality with margin to 30 Gy, both in ten fractions<br>Concurrent TMZ (75 mg/m$^2$/day) was given to all patients for 28 consecutive days followed by adjuvant TMZ (150–200 mg/m$^2$/day). Patients enrolled on the hypo-IMRT/TMZ/BEV trial received concurrent and adjuvant BEV (10 mg/kg) on days 1 and 15 of each 28-day cycle<br>Of note: Mean KPS in hypo-IMRT/TMZ/BEV trial was 83 compared to the hypo-IMRT/TMZ alone which was 73 (p = 0.025); also the PTV1 treated was larger in hypo-IMRT/TMZ/BEV trial (127.7) as compared to the hypo-IMRT/TMZ (100) (p = 0.029) | III | ***Results***<br>*Median PFS:*<br>hypo-IMRT/TMZ: 9.4 months<br>hypo-IMRT/TMZ/BEV: 12.8 months<br>(p = 0.58)<br>*Median OS*<br>hypo-IMRT/TMZ: 16.3 months<br>hypo-IMRT/TMZ/BEV: 16.3 months<br>***Toxicity***<br>Grade III/IV toxicities:<br>hypo-IMRT/TMZ: 0%<br>hypo-IMRT/TMZ/BEV: 30% (9/30pts) – (fatigue, nausea, anorexia, wound dehiscence, as well as one instance of PE and one of stroke)<br>***Author's conclusions***<br>"Based on our two trial comparison, the addition of BEV does not improve OS in patients with GBM treated with hypo-IMRT to 60 Gy delivered in 6 Gy fractions over 2 weeks with concurrent and adjuvant TMZ"<br>***Comments and conclusions***<br>Classified as Class III because the study consisted of comparison of two non-randomized consecutive prospective trials. The study did not show any significant benefit in adding bevacizumab to hypo-IMRT/TMZ, in addition to having a significant increase in Grade III toxicities. Also of note, the two groups did have statistically significant differences in KPS and PTV1 limiting a direct comparison |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| van Lindeaet al. (2015) | *Study description* Single institution prospective non-randomized phase II study evaluating the safety of bevacizumab (BEV) in combination with TMZ and RT in the treatment of patients with newly diagnosed glioblastoma<br>*Patient population* newly diagnosed GBM patients (n = 19)<br>*Treatment regimen*<br>-Surgery:<br>Biopsy:6/19<br>Resection: 13/19<br>-Standard fractionated RT with total dose of 60 Gy in combination with daily TMZ 75 mg/m$^2$ and BEV 10 mg/kg on days 1, 14, and 28, followed by 6 monthly cycles of TMZ 150–200 mg/m$^2$ on days 1–5 of each 28-day cycle | III | ***Results***<br>Overall response rate: 26%<br>Median PFS: 9.6 months (95% CI: 4.3–14.4 months)<br>Median OS: 16 months (95% CI:8.1–26.3 months)<br>***Toxicity***<br>No grade III/IV toxicities during combination treatment<br>***Author's conclusions***<br>"Combination of bevacizumab with radiotherapy and TMZ is safe and feasible in patients with newly diagnosed GBM, but because of low response rates, this treatment strategy does not favor a neoadjuvant approach"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized phase II study. Of note, in this study patients only received BEV during concomitant RT + TMZ and did not receive any BEV treatment during adjuvant TMZ therapy. The study, although a limited sample size, does not show any benefit of BEV treatment for OS as compared to historical data with standard therapy (EORTC-NCIC trial) |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Chinotet al. (2014) | *Study description* Multi-center, prospective randomized double-blind phase III study examining the efficacy of the addition of bevacizumab to radiotherapy–temozolomide for the treatment of newly diagnosed GBM<br>*Patient population* (n = 921) newly diagnosed GBM patients with:<br>1. WHO performance status ≤ 2<br>2. use of stable or decreasing glucocorticoid doses within 5 days prior to randomization<br>3. adequate healing of craniotomy or cranial-biopsy site<br>4. Treatment had to be initiated between 29 and 48 days after most recent surgery<br>*Treatment regimen*<br>Patients were randomized to:<br>Bevacizumab + RT + TMZ group: n = 463<br>(intention-to-treat population)<br>Treatment protocol:<br>-IV bevacizumab (10 mg/kg of body weight every 2 weeks) or placebo, plus radiotherapy (2 Gy 5 days a week; maximum, 60 Gy) and oral TMZ (75 mg/m$^2$ of body-surface area per day) for 6 weeks<br>- after a 28-day treatment break, maintenance bevacizumab (10 mg/kg every 2 weeks) or placebo, plus temozolomide (150–200 mg/m$^2$ per day for 5 days each 28 day cycle), was continued for six cycles, followed by bevacizumab monotherapy (15 mg/kg every 3 weeks) or placebo until disease progression or unacceptable toxicity<br>*Surgery*<br>Biopsy: 9.5%<br>STR: 48.2%<br>GTR: 42.3%<br>Bevacizumab + RT + TMZ:<br>Biopsy: 13.1%<br>STR: 45.9%<br>GTR: 41% | I | ***Results***<br>*Median PFS:*<br>Bevacizumab + RT + TMZ: 10.6 months<br>(stratified HR for progression or death, 0.64; 95% confidence interval [CI], 0.55 to 0.74; P < 0.001)<br>*Median OS*<br>Bevacizumab + RT + TMZ: 16.8 months<br>(stratified HR for death, 0.88; 95% CI, 0.76 to 1.02; P = 0.10)<br>OS at 1 year:<br>Bevacizumab + RT + TMZ: 72.4%<br>(P = 0.049)<br>OS at 2 years:<br>Bevacizumab + RT + TMZ: 30.1%<br>(P = 0.24)<br>Survival without deterioration in performance status<br>Bevacizumab + RT + TMZ: 9.0 months<br>(HR for deterioration with bevacizumab, 0.65; 95% CI, 0.56 to 0.75; P < 0.001)<br>Time to deterioration in performance status was longer with bevacizumab than with placebo Bevacizumab + RT + TMZ: 14.2 months<br>(HR, 0.79; 95% CI, 0.65 to 0.96; P = 0.02)<br>Time to initiation of glucocorticoids<br>Bevacizumab + RT + TMZ: 12.3 months<br>(HR, 0.71; 95% CI, 0.57 to 0.88; P = 0.002)<br>***Toxicity***<br>Serious adverse events:<br>Bevacizumab + RT + TMZ: 38.8%<br>Grade 3 or higher adverse events:<br>Bevacizumab + RT + TMZ: 66.8%<br>"Serious adverse events observed more frequently in the bevacizumab group included bleeding, complications of wound healing, gastrointestinal perforation, and congestive heart failure"<br>***Author's conclusions***<br>"The addition of bevacizumab to radiotherapy–temozolomide did not improve survival in patients with glioblastoma. Improved progression-free survival and maintenance of baseline quality of life and performance status were observed with bevacizumab; however, the rate of adverse events was higher with bevacizumab than with placebo"<br>***Comments and conclusions***<br>Classified as Class I because is a multicenter prospective randomized double-blinded phase III trial. Study shows that adding bevacizumab to standard therapy of concomitant TMZ + radiotherapy + adjuvant TMZ does not result in overall survival benefit<br>Although an increased rate of adverse events was observed with the addition of bevacizumab, there was a notable benefit in terms of increased PFS and maintenance of performance status before deterioration with use of bevacizumab across different subgroups |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Gilbertet al. (2014) | *Study description* Multi-center, prospective randomized double-blind phase III study examining the efficacy of the addition of bevacizumab to radiotherapy–temozolomide for the treatment of newly diagnosed GBM<br>*Patient population* (n = 637) newly diagnosed GBM patients with:<br>1. KPS ≥ 70<br>2. use of stable or decreasing glucocorticoid doses within 5 days prior to randomization<br>*Treatment regimen*<br>Patients were randomized to:<br>Bevacizumab + RT + TMZ group: n = 320<br>Treatment protocol:<br>-Radiotherapy (2 Gy 5 days a week; maximum 60 Gy) and oral TMZ (75 mg/m$^2$ of body-surface area per day) for 6 weeks<br>- IV bevacizumab (10 mg/kg of body weight every 2 weeks) or placebo starting at week 4 of radiotherapy, until disease progression, severe treatment-related toxicity, or completion of adjuvant therapy (maximum number of doses, 24 over 12 cycles)<br>- 4 weeks from radiotherapy treatment, temozolomide maintenance therapy (150–200 mg/m$^2$ per day for 5 days on a 28 day cycle) and was continued for six cycles with the option of extension to a total of 12 cycles until the disease progressed or unacceptable toxic effects developed | I | ***Results***<br>*Median PFS:*<br>Bevacizumab + RT + TMZ: 10.7 months<br>(HR, 0.79; 95% confidence interval [CI], 0.66 to 0.94; P = 0.007)<br>*The p-value did not reach the prespecified threshold for significance (P < 0.004)*<br>*Median OS*<br>Bevacizumab + RT + TMZ: 15.7 months<br>(HR 1.13; 95% CI, 0.93 to 1.30; P = 0.21)<br>*Median OS*<br>Unmethylated MGMT: 14.3 months<br>Methylated MGMT: 23.2 months<br>(HR 2.10; 95% CI, 1.65 to 2.68; P < 0.001)<br>***Toxicity***<br>"Serious adverse events were more prevalent in the bevacizumab group than in the placebo group, including hypertension (4.2% vs. 0.9%), thromboembolic disease (7.7% vs. 4.7%), wound dehiscence (1.5% vs. 0.9%), fatigue (13.1% vs. 9.0%), visceral perforation (1.2% vs. 0.4%), and serious hemorrhage (1.5% vs. 0.9%). Serious neutropenia was more common in the bevacizumab group (10.0% vs. 5.1%), but thrombocytopenia was slightly less common (11.1% vs. 11.7%)"<br>***Author's conclusions***<br>"In conclusion, we did not observe an overall survival advantage with first-line use of bevacizumab in patients with newly diagnosed glioblastoma. Furthermore, higher rates of neurocognitive decline, increased symptom severity, and decline in health-related quality of life were found over time among patients who were treated with bevacizumab"<br>***Comments and conclusions***<br>Classified as Class I because is a multicenter prospective randomized double-blinded phase III trial. This study shows that adding bevacizumab to standard therapy of concurrent TMZ + radiotherapy + adjuvant monthly TMZ does not result in an overall survival benefit. Although this study does show improved PFS with bevacizumab similar to another phase III study (Chinotet al. (2014), it differs significantly from that study where patients treated with bevacizumab were noted to have longer periods of maintaining better functional status, whereas in the study by Gilbert et al. patients were found to have worsened quality of life in the bevacizumab group. The study also confirmed the value of MGMT promoter methylation as a positive prognostic factor, which was associated with significant improvement in PFS and OS |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Omuroet al. (2014) | *Study description* single institution, prospective non-randomized single-arm phase II study evaluating the use of hypofractionated stereotactic radiotherapy (HFSRT) combined with concomitant/ adjuvant TMZ and BEV in the treatment of patients with newly diagnosed glioblastoma<br>*Patient population* newly diagnosed GBM patients with KPS ≥ 70 who underwent surgical resection with tumor volume ≤ 60 cc (n = 40)<br>*Treatment regimen*<br>-hypofractionated stereotactic radiotherapy (HFSRT) delivered in six treatments over 2 weeks (total ~ 60 Gy); concomitant treatment with BEV 10 mg/kg i.v. on days 1 and 15, and TMZ 75 mg/m$^2$ given orally daily throughout HFSRT, for a total of 2 weeks<br>- approx, 3 weeks after HFSRT adjuvant TMZ was administered at 150–200 mg/m$^2$ on Days 1–5 of a 28-day cycle for 6 cycles, and BEV was administered on Days 1 and 15 of each cycle<br>Surgery:<br>Partial resection or Biopsy: 30/40 (75%)<br>GTR: 10/40 (25%) | III | ***Results***<br>Objective response rate (complete + partial): 87% (by Macdonald criteria) and 57% (by RANO)<br>Median PFS: 10 months (95%CI,8–11 months)<br>Median OS: 19 months (95% CI, 15–23 months)<br>TCGA transcriptional glioblastoma subclasses (n = 31 patients):<br>Proneural: 26%;- ORR (RANO): 14% (95% CI, 0–53%)<br>Mesenchymal: 42% ORR (RANO): 70% (95% CI, 0–53%)<br>Classical: 29%; ORR (RANO): 83% (95% CI, 0–53%)<br>Neural: 3%. ORR (RANO): N/A<br>"Patients with proneural tumors had lower response rate compared with other phenotypes (P = 0.009), and survived a median of 15 months, as compared with 21 months for other phenotypes (P = 0.56). "<br>"The expression levels of angiogenesis and hypoxia-related genes had no prognostic value"<br>***Toxicity***<br>1 pt developed irreversible grade 4 renal failure<br>1 pt developed grade 4 surgical wound infection<br>2 patients had grade 4 pulmonary embolism<br>1 pt experienced a late ischemic stroke<br>1 pt with a history of difficult to control seizures died suddenly during sleep on treatment<br>***Author's conclusions***<br>"In summary, we describe a new use for bevacizumab in newly diagnosed glioblastoma, capitalizing on the anti-permeability effects to develop a convenient hypofractionated radiotherapy schedule. In our hands, this regimen was found to be safe, associated with minimal detrimental effects on QoL, and with survival results comparable with other regimens"<br>"Analysis of advanced neuroimaging parameters suggests ADC and FDG-PET as potentially useful biomarkers, whereas tissue correlatives uncovered the poor prognosis associated with the proneural signature in non–IDH-1–mutated glioblastoma"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized single-arm phase II study. This study did not reveal any significant benefit in overall survival with BEV treatment as compared to historical data. However, the study does show that use of HFSRT, which can provide more convenient schedule for pts of 2 weeks of RT treatment rather than the standard 6 weeks, can be accomplished with use of BEV with similar outcomes compared to historical data (EORTC/NCIC trial). As the authors note though, given the study design, the "results are applicable to unifocal tumors, with a volume of 60 cc or less." The study also provides interesting results regarding molecular data collected where expression levels of angiogenic genes had no prognostic value in determining response to BEV therapy, in addition, to finding that the proneural TCGA transcriptional GBM subclass had a lower response rate and overall survival compared to the other groups |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Narayanaet al. (2012) | *Study description* single institution, prospective non-randomized single-arm phase II study evaluating the efficacy and the associated toxicity of bevacizumab (BEV) in combination with TMZ and RT in the treatment of patients with newly diagnosed glioblastoma<br>*Patient population* newly diagnosed GBM patients with KPS ≥ 70 who underwent surgical resection (n = 51)<br>*Treatment regimen*<br>-Standard RT with total dose of 60 Gy started within 30 days after surgery with concurrent TMZ (75 mg/m$^2$ for 42 days during RT)<br>-BEV was given every 2 weeks at 10 mg/kg starting with the first day of RT/TMZ<br>-adjuvant TMZ temozolomide was administered at 150 mg/m$^2$ on Days 1–7 of a 28-day cycle for 6 cycles, and BEV was administered on Days 8 and 22 of each cycle<br>Surgery:<br>Biopsy: 6/51 (12%)<br>STR: 9/51 (18%)<br>GTR: 36/51 (70%) | III | ***Results***<br>Median PFS: 13 months<br>Median OS: 23 months<br>"35 patients who experienced a relapse, 20 (57.1%) had diffuse recurrence, defined by the presence of contrast-enhancing disease and/or FLAIR changes in more than 2 lobes"<br>***Toxicity***<br>Grade III: 7 patients (13.7%)<br>Grade IV: 3 patients (5.9%) (thrombocytopenia, PE)<br>***Author's conclusions***<br>"The addition of bevacizumab to conventional therapy in newly diagnosed GBM appears to improve both PFS and OS in patients with newly diagnosed GBM, with acceptable morbidity. A shift toward diffuse relapse was noted in a significant number of patients. Ongoing Phase III clinical trials will show the true benefit of this antiangiogenic approach"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized single-arm phase II study. Although the study claims to have apparent improvement of PFS and OS with the addition of BEV as compared to the EORTC trial, the patient population presented here has substantial differences in the extent of resection (current study with reported 70% of patients with GTR compared to EORTC study with only 39%). Also of note, the authors find in this study that "57% of patients [had] a diffuse pattern of recurrence compared with a historical rate of around 10% in patients treated with conventional chemotherapy alone" |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Laiet al. (2011) | *Study description* Multicenter, prospective non-randomized single-arm phase II study evaluating the efficacy and the associated toxicity of bevacizumab (BEV) in combination with TMZ and RT in the treatment of patients with newly diagnosed glioblastoma<br>*Patient population* newly diagnosed GBM (including gliosarcoma) patients with KPS ≥ 60 who underwent surgical resection (n = 70)<br>*Treatment regimen*<br>-Standard RT with total dose of 60 Gy started within 3 to 6 weeks after surgery with concurrent TMZ (75 mg/m$^2$ for 42 days during RT)<br>-BEV was given every 2 weeks at 10 mg/kg starting with the first day of RT/TMZ<br>-After a 2-week minimum interval after the last daily TMZ dose, patients were treated with biweekly BEV and TMZ every 4 weeks at 150 to 200 mg/m$^2$/d for the first 5 days of every 28-day cycle until progression or for a maximum of 24 TMZ cycles (post-RT phase). For patients completing 24 cycles of TMZ, single-agent BEV was continued every 2 weeks until progression<br>Surgery:<br>Biopsy: 2/70 (3%)<br>STR: 40/70 (57%)<br>GTR: 28/70 (40%) | III | ***Results***<br>Median PFS: 13.6 months (95%CI, 11.1 to 16.5 months)<br>Median OS: 19.6 months (95%CI, 16.1 to 23.3 months)<br>***Toxicity***<br>Grade III/IV toxicities:<br>Wound infection: 6%<br>VTE/PE: 19%<br>Cerebrovascular ischemia: 9%<br>CNS hemorrhage: 3%<br>Fatigue: 20%<br>***Author's conclusions***<br>"In conclusion, we found that the addition of BEV to RT/TMZ firstline therapy was tolerable without apparent unanticipated toxicities. In general, nonhematologic toxicities were similar compared to use of BEV at recurrence with the exception of potentially greater incidence of arterial and venous thromboembolism. While we observed improved PFS, the apparent lack of benefit in OS compared to University of California, Los Angeles/KPLA patients salvaged with BEV awaits the results of ongoing large randomized studies"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized single-arm phase II study. The study provides important data regarding toxicity profile with use of BEV therapy showing specifically increase in thromboembolic events and wound healing complications. Although,the study provides some valuable information regarding PFS and OS, the study population is significantly different from the historical control groups since in the study group only 3% of patients underwent biopsy while in the UCLA/KPLA and EORTC-NCIC control groups 21% and 17% underwent biopsy. Also, comparison of overall survival in the study group and the UCLA/KPLA control is difficult to interpret given that over 50% of the control group received BEV as a salvage therapy at recurrence. Also of note, the study reported survival from the date of diagnosis while the EORT/NCIC trial reported from the date of enrollment which could add to perceived OS |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Vredenburghet al. (2011) | *Study description* single institution, prospective non-randomized single-arm phase II study evaluating the efficacy and safety of the addition of BEV to RT + TMZ, followed by BEV, TMZ, and irinotecan, for newly diagnosed glioblastoma patients<br>*Patient population* newly diagnosed GBM patients with KPS ≥ 60 who underwent surgical resection (n = 75)<br>*Treatment regimen*<br>-Standard RT with total dose of ~ 60 Gy started 2–6 weeks after surgery with concurrent TMZ (75 mg/m$^2$)<br>-BEV was given every 14 days at 10 mg/kg starting a minimum of 28 days from surgery<br>-adjuvant TMZ temozolomide was administered at 200 mg/m$^2$ on Days 1–5 of a 28-day cycle for 6–12 cycles, and BEV (10 mg/kg) was administered every 14 days. Irinotecan was dosed every 14 days at 125 mg/m$^2$ (for pts not on enzyme-inducing antiepileptic drug (EIAED) and dosed at 340 mg/m$^2$ for patients on an EIAED. Patients homozygous for the UGT 7/7 alleles received reduced dose irinotecan, those not on EIAEDs received 75 mg/m$^2$,and patients on EIAEDs received 275 mg/m$^2$ every 2 weeks<br>Surgery:<br>STR: 35/75 (47%)<br>GTR: 40/75 (53%) | III | ***Results***<br>Median PFS: 14.2 months (95% CI: 12–16)<br>Median OS: 21.2 months (95% CI: 17.2–25.4)<br>"Greater age, subtotal resection, and RPA class 4 were significant predictors of poorer overall survival"<br>***Toxicity***<br>6 pts (8%) developed grade 4 thrombocytopenia<br>4 patients (5%) developed grade 4 neutropenia<br>2 toxic deaths, 1 from neutropenic sepsis and 1 from a pulmonary embolism<br>"16 of the 70 patients (23%) who started adjuvant temozolomide, bevacizumab, and irinotecan terminated protocol treatment of toxicity, including 1 bowel perforation, likely attributable to the bevacizumab"<br>***Author's conclusions***<br>"The addition of bevacizumab to standard radiation therapy and temozolomide, followed<br>by bevacizumab, irinotecan, and temozolomide, for the treatment of newly diagnosed glioblastoma has moderate toxicity and may improve efficacy compared with historical controls. The results from phase III trials are required before the role of bevacizumab for newly diagnosed glioblastoma is established"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized single-arm phase II study. Although the study claims to have apparent improvement of PFS and OS with the addition of BEV as compared to the EORTC trial, the patient population presented here has substantial differences in the extent of resection (current study has no pts enrolled with biopsy compared with EORTC study which had 17% pts undergoing biopsy). The study highlights the significant toxicities of adjuvant TMZ + BEV + irinotecan |

**Table 4** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Laiet al. (2008) | *Study description* single institution, prospective non-randomized phase II study evaluating the safety and tolerability of bevacizumab (BEV) in combination with TMZ and RT in the up-front treatment of patients with newly diagnosed glioblastoma<br>*Patient population* newly diagnosed GBM patients with KPS > 60 who underwent surgical resection (n = 10)<br>*Treatment regimen*<br>-Standard RT with total dose of 60 Gy started within 3 to 5 weeks after surgery with concurrent TMZ (75 $mg/m^2$ for 42 days during RT)<br>-BEV was given every 2 weeks at 10 mg/kg starting with the first day of RT/TMZ<br>-After a 2-week interval upon completion of RT, the post-RT phase commenced with resumption of TMZ at 150 to 200 $mg/m^2$ for 5 days every 4 weeks and continuation of BEV every 2 weeks | III | ***Results***<br>Median PFS: not reported (they reported PFS as at least greater than 8.8 months since many pts had not progressed at end of study)<br>Median OS: not reported<br>***Toxicity***<br>Three serious adverse events seen in at least 20% of patients:<br>-myelotoxicity<br>-wound healing complications<br>-venous thromboembolic events<br>1pt developed optic neuropathy resulting in complete blindness<br>***Author's conclusions***<br>"The observed toxicities were acceptable to continue enrollment toward the overall target group of 70 patients. Preliminary efficacy analysis shows encouraging mean progression-free survival. At this time data are not sufficient to encourage routine off-label use of BEV combined with TMZ/RT in the setting of newly diagnosed glioblastoma without longer follow-up, enrollment of additional patients, and thorough efficacy assessment"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized trial. Although a small sample size, the study does point out important toxicities (myelotoxicity, wound healing, venous thromboembolic events) which need to be closely monitored for during BEV therapy |

on improved PFS and OS compared to historical control of the EORTC-NCIC data, however, their study population was significantly different from the historical control groups since in their study group only 3% of patients underwent biopsy while in the EORTC-NCIC group 17% underwent biopsy as compared to subtotal or gross total resection. Also, comparison of overall survival in the study group and the UCLA/KPLA control group is difficult to interpret given that over 50% of the UCLA/KPLA control group received bevacizumab as a salvage therapy at recurrence. Also of note, the EORTC/NCIC trial reported survival from the date of enrollment while this study reported survival from the date of diagnosis which could add to perceived OS. The study did provide important data regarding toxicity profile with use of bevacizumab therapy showing specifically increase in thromboembolic events and wound healing complications. Similarly, Narayana et al. [41] in a prospective non-randomized single-arm phase II study concluded that there was apparent improvement of PFS and OS with the addition of bevacizumab to standard therapy as compared to the EORTC-NCIC trial, however, again the patient population presented here has substantial differences in the extent of resection (current study with reported 70% of patients with GTR compared to EORTC-NCIC study with only 39%). Likewise, in another prospective non-randomized single-arm phase II study evaluating the efficacy and safety of the addition of bevacizumab to RT + TMZ, followed by bevacizumab, TMZ, and irinotecan for newly diagnosed GBM patients. Vredenburgh et al. [43] asserted that there was an apparent improvement of PFS and OS with the addition of bevacizumab as compared to the EORTC trial, but, again the patient population presented here had substantial differences in the extent of resection (current study has no patients enrolled with biopsy compared with EORTC study which had 17% patients undergoing biopsy). Additionally, the study found significant toxicities of adjuvant TMZ + bevacizumab + irinotecan. Taking into consideration all the above studies, upfront use of bevacizumab is likely to improve PFS but has so far not been shown to extent OS in GBM patients. Moreover, conflicting data exists regarding the exact benefit of adjuvant bevacizumab in terms of quality of life. Another prospective nonrandomized single-arm phase II study by Reyes-Botero et. al [44] evaluated the efficacy and safety of upfront temozolomide (TMZ) and bevacizumab in patients aged ≥ 70 years and a KPS < 70 and found the combination to be well tolerated with potential to improve quality of life. Similarly, Hata et. al [45] found possible benefit in quality of life when adding bevacizumab to partially resected tumors in combination with combined chemoradiation. Again, these studies provide further support to performing a randomized controlled trial to assess benefit of bevacizumab on quality of life for GBM patients.

### Is there a role for chemotherapy agents other than TMZ for the treatment of GBM?

A number of studies have examined the use of several chemotherapy agents other than TMZ for the treatment of GBM (Table 5). Studies that met our inclusion criteria examined the role of irinotecan, nitrosurea based chemotherapy agents (carmustine, nimustine), cisplatin, procarbazine, and gemcitabine. One Class I study [46] and two Class III studies [47, 48] examined the role of irinotecan in the treatment of GBM. In multi-center, prospective randomized phase II study examining the efficacy of bevacizumab combined with irinotecan (Bev-Iri) versus bevacizumab combined with temozolomide (Bev-Tem) before, during and after radiotherapy in newly diagnosed GBM patients, Hofland et al. [46] found that Bev-Iri did not provide any significant benefit when compared to Bev-Tem. This study did not show any benefit of Bev-Iri to Bev-Tem in terms of response rate and PFS. By interpreting the results of this study, one needs to consider that there were no study patients who underwent GTR as per protocol and concurrent chemoradiation was delayed compared to the standard Stupp et al. protocol. Furthermore, in a prospective study of RT and irinotecan followed by BCNU plus irinotecan in newly diagnosed GBM patients, Jaeckle et al. [47] did not find any benefit of this treatment regimen compared to standard Stupp protocol, in addition to finding that this combination was less well tolerated. Similarly, in a prospective trial evaluating the efficacy and safety of TMZ in combination with irinotecan before radiotherapy in patients with newly diagnosed GBM, Quinn et al. [29] did not show any benefit of combining TMZ with irinotecan compared to TMZ alone, their data suggest that this combination was found to be more toxic and poorly tolerated. They explained that the results were difficult to interpret and to compare with other studies as the majority of patients (81%) only underwent a biopsy. Moreover, 52% of patients (22/42) discontinued therapy after 1 or 2 cycles of treatment (due to disease progression or adverse events) and went on to immediate radiotherapy + TMZ, further limiting the interpretation of the study results. These studies did not show any benefit of irinotecan therapy compared to standard therapy with TMZ, in addition to some increased toxicity in many cases.

Two Class II studies [49, 50] and two Class III studies [51, 52] examined the role of nitrosurea based chemotherapies (nimustine (ACNU), carmustine (BCNU)) in the treatment of GBM. In a multicenter prospective randomized phase III study examining the efficacy of chemotherapy with nimustine (ACNU)- cisplatin (CDDP) when used in conjunction with radiotherapy plus adjuvant temozolomide in patients with newly diagnosed GBM, Kim et al. [49] found significant toxicity with neoadjuvant ACNU-CDDP treatment. Although, there appeared to be some survival benefit

**Table 5** Chemotherapy agents other than TMZ for the treatment of GBM

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Hoflandet al. (2014) | *Study description* Multi-center, prospective randomized phase II study examining the efficacy of neoadjuvant bevacizumab combined with irinotecan (Bev-Iri) versus bevacizumab combined with temozolomide (Bev-Tem) before, during and after radiotherapy in newly diagnosed GBM<br>*Patient population* (n = 63) newly diagnosed GBM patients with:<br>1. ECOG performance status ≤ 2<br>2. Residual contrast enhancing tumor ≥ 1 cm on the baseline MR scan (done ≤ 14 days prior to therapy)<br>3. No prior therapy for GBM except resection or biopsy<br>*Treatment regimen*<br>Treatment was not started until ≥ 4 weeks from the initial surgery or primary biopsy<br>Patients were randomized to:<br>1. Bevacizumab-irinotecan (Bev-Iri) or bevacizumab-temozolomide (Bev-Tem) for eight weeks,<br>2. Followed by radiotherapy (fractionated RT 60 Gy total dose) and concomitant Bev-Iri or Bev-Tem<br>3. Followed by adjuvant Bev-Iri or Bev-Tem for another eight weeks<br>Bevacizumab 10 mg/kg was administered every two weeks for the full duration of the study (before, during and after radiotherapy) in both treatment arms<br>-Bevacizumab combined with temozolomide (Bev-Tem):<br>TMZ 200 mg/m$^2$ was given daily for five days followed by 23 days off, before and after the radiotherapy. During the radiotherapy, a dose of temozolomide of 75 mg/m 2 was given daily<br>-Bevacizumab combined with irinotecan (Bev-Iri):<br>Irinotecan was similarly administered every two weeks for the full duration of the study: "Patients on enzyme inducing anti-epileptic drugs (EIAID) received a dose of 340 mg/m 2 while patients not on EIAIDs received a dose of 125 mg/m"<br>*Surgery*<br>(Bev-Tem)<br>STR: 30<br>Biopsy: 2<br>(Bev-Iri)<br>STR: 28<br>Biopsy: 3 | I | ***Results***<br>Response to therapy (modified MacDonald criteria): no new lesions, no use of corticosteroids and no decrease in clinical status<br>1.CR (complete response): disappearance of all contrast enhancing disease and T2-changes<br>No complete responses in either group<br>2. PR (partial response): decrease ≥ 50% in contrast enhancing disease, no increase in T2<br>Bev-Tem: 32% (95% CI 17–51%)<br>Bev-Iri: 23% (95% CI 9–44%)<br>3. mPR (minor partial response): decrease of 25–50% contrast enhancing lesions<br>Bev-Tem: 35.5% (95% CI 19–55%)<br>Bev-Iri: 27% (95% CI 12–48%)<br>4. PD (progressive disease): Increase ≥ 25% of contrast enhancing lesions, and/or the appearance of new contrast enhancing lesions, and/or a significant increase in dose of corticosteroids and/or significant clinical deterioration<br>Bev-Tem: 13% (95% CI 4–29%)<br>Bev-Iri: 19%(95% CI 8–38%)<br>*Response rate*<br>Bev-Tem: 32% (95% CI 15–51%)<br>Bev-Iri: 23% (95% CI 9–44%)<br>*Median PFS*<br>Bev-Tem: 7.7 months (95% CI 5.1–10.2 months)<br>Bev-Iri: 7.3 months (95% CI 5.0–9.3 months)<br>*Median OS*<br>Bev-Tem: 11.8 months (95% CI 8.2–15.3 months)<br>Bev-Iri: 15.1 months (95% CI 9.6–20.6 months)<br>***Toxicity***<br>Grade III/IV non-hematological toxicities:<br>Bev-Tem: 12 events<br>Bev-Iri:11 events<br>Grade III/IV/V hematological toxicities:<br>Bev-Tem: 22 events of grade III/IV with one case of fatal febrile neutropenia (grade V toxicity)<br>Bev-Iri:8 events<br>***Author's conclusions***<br>"Only the Bev-Tem arm met the pre-specified level of activity of interest. Our results did not indicate any benefit from Bev-Iri in first-line therapy as opposed to Bev-Tem in terms of response rate and PFS"<br>***Comments and conclusions***<br>Classified as Class I because is a multicenter prospective randomized trial. Study suggests that Bev-Iri does not provide any significant benefit when compared to Bev-Tem. The results of the study, as authors note, need to take into consideration that no patients who were part of this study underwent GTR as per study protocol. Also of note, in this study concurrent chemoradiation was delayed compared to the standard Stupp protocol |

**Table 5** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Wanget al. (2014) | *Study description* single institution, retrospective comparison of outcome of GBM pts with at least near-total resection (NTR) treated with initial radiation and TMZ or ACNU-based (ACNU plus teniposide or cisplatin) chemotherapy<br>*Patient population* newly diagnosed GBM patients with at least near-total resection (NTR + GTR) who received both chemotherapy and radiation as initial therapy (n = 135)<br>ACNU based group (n = 34)<br>TMZ group (n = 101)<br>Near-total resection (NTR) defined as thin rim enhancement of the resection cavity only (resection margins at the level of tumor border) on the early MRI (within 72 h from surgery)<br>*Treatment regimen*<br>Surgery:<br>ACNU based group:<br>GTR: 40.6%<br>NTR: 59.4%<br>TMZ group:<br>GTR: 44.1%<br>NTR: 55.9%<br>All patients received fractionated RT total dose 60 Gy<br>ACNU based group (82 ACNU plusVM26, 19 ACNU plus CDDP):<br>*ACNU-based chemotherapy was initiated after completion of RT*<br>ACNU (90 mg/m$^2$, day 1) plusVM26 (60 mg/m$^2$,days 1–3) or ACNU (90 mg/m$^2$/day) plus CDDP (40 mg/m$^2$/day) infused continuously for 3 days (both schemes at 6-week intervals). A total of 6 cycles were administered unless the patient showed progressive disease during treatment or unacceptable toxicity or refused further treatment. Hematologic,<br>TMZ group:<br>*Patients received the concurrent chemo- radiotherapy* TMZ (75 mg/m$^2$, oral) was given from the first until the last day of RT, 4 weeks off, maintenance therapy at a dose of 150 to 200 mg/m$^2$ daily for 5 days every 28-day cycle. TMZvwas administered 6 cycles or continued up to 12 months if tolerated by the patient | III | ***Results***<br>*Median PFS*<br>ACNU based group: 10.1 months<br>TMZ group: 17.7 months<br>(p = 0.039)<br>*Median OS*<br>ACNU based group: 15.4 months<br>TMZ group: 26.3<br>(p = 0.011)<br>***Toxicity***<br>ACNU based group: 30.7% of pts did not complete therapy because of prolonged hematological toxicity (persistent leukopenia) and in nine (8.2%) because of severe nonhematological toxicity (fatigue, lethargy, vomiting, etc.)<br>TMZ group: 8.8% of pts did not complete treatment (two with leukopenia and one with vomiting)<br>***Author's conclusions***<br>"Our data suggest that the survival benefit of TMZ therapy is superior to that of an ACNU-based regimen in patients with extensive tumor resection, also shows greater tolerability"<br>***Comments and conclusions***<br>Classified as Class III because is a retrospective study. Unfortunately, the results of the study are very difficult to interpret given the patients in ACNU-based group started therapy after completion of RT and therefore did not have any concomitant chemotherapy with radiation as the TMZ group. Also, greater than 40% of pts could not complete ACNU based treatment given significant toxicity. The authors note that while in a subgroup analysis of pts who were able to complete at least 4 cycles of ACNU-based therapy "a modest improvement in survival occurred in this ACNU subgroup, the efficacy was still inferior to that in the TMZ cohort" |

**Table 5** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Shibuiet al. (2013) | *Study description* Multi-center, prospective randomized phase II/III study examining the efficacy of nimustine (ACNU) + procarbazine (PCZ) compared to ACNU alone for GBM and anaplastic astrocytoma (AA)<br>*Patient population* (n = 111) newly diagnosed GBM and AA patients with ECOG ≤ 3<br>*Treatment regimen*<br>ACNU alone (n = 55: 40 GBM and 15 AA):<br>1. fractionated RT (~ 60 Gy) concomitant with 80 mg/m$^2$ of ACNU was administered intravenously on days 1 and 36 during RT<br>2. Adjuvant therapy consisting of 80 mg/m$^2$ of ACNU alone started 56 days from the final administration of ACNU and was given every 8 weeks, for up to 12 cycles<br>ACNU/PCZ (n = 56: 41 GBM and 15 AA):<br>1. fractionated RT (~ 60 Gy) concomitant with 80 mg/m$^2$ of oral PCZ was administered daily from days 1 to 10 and days 36 to 45, and given together with intravenous ACNU (80 mg/m$^2$) on days 8 and 43<br>2. Adjuvant therapy consisting ACNU + PCZ- PCZ 80 mg/ m$^2$ orally on days 1–10, ACNU: 80 mg/m$^2$ intravenously on day 8 was given every 8 weeks, for up to 12 cycles<br>*Surgery*<br>ACNU alone:<br>GTR: 32.7%<br>STR: 54.5%<br>Biopsy: 12.7%<br>ACNU/PCZ<br>GTR: 37.5%<br>STR: 46.4%<br>Biopsy: 16.1% | II | ***Results***<br>*Median PFS*<br>Intention to treat (ITT) pts:<br>ACNU alone: 8.6 months<br>ACNU/PCZ: 6.9 months<br>*Median PFS of the GBM subgroup*<br>ACNU alone: 6.2 months<br>ACNU/PCZ: 6.3 months<br>*Median OS*<br>Intention to treat (ITT) pts:<br>ACNU alone: 27.4 months<br>ACNU/PCZ: 22.4 months<br>(p = 0.75)<br>*Median OS of the GBM subgroup*<br>ACNU alone: 19 months<br>ACNU/PCZ: 19.5 months<br>***Toxicity***<br>"Grade 3/4 hematologic adverse events occurred in more than 40% of patients in both arms, and 27% of patients discontinued treatment because of adverse events"<br>***Author's conclusions***<br>"The addition of PCZ to ACNU was not beneficial, in comparison with ACNU alone, for patients with newly diagnosed AA and GBM<br>***Comments and conclusions***<br>Classified as Class II because is a multicenter prospective randomized trial (not blinded). Study shows no benefit in PFS or OS when combining PCZ with ACNU during radiotherapy treatment |

**Table 5** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Kimet al. (2011) | *Study description* Multi-center, prospective randomized phase III study examining the efficacy of chemotherapy with nimustine (ACNU)- cisplatin (CDDP) when used in conjunction with radiotherapy plus adjuvant temozolomide in patients with newly diagnosed glioblastoma<br>*Patient population* (n = 82) newly diagnosed GBM patients with KPS ≥ 70 (8 did not meet inclusion criteria; n = 76 for analysis; a total of 35 pts were suitable for the "per protocol" set (17 in control group, 18 in treatment group)<br>*Treatment regimen*<br>Patients were randomized to:<br>Control group:<br>1. fractionated RT 60 Gy total dose<br>2. 4 weeks after RT, patients received up to 6 cycles of adjuvant oral temozolomide (150–200 mg/m$^2$) for 5 days every 28 days.<br>Treatment group(ACNU-CDDP):<br>1. two cycles of ACNU-CDDP neoadjuvant chemotherapy- ACNU (40 mg/m$^2$/day) and CDDP (40 mg/m$^2$/day) was administered by continuous infusion for 72 h and was repeated after 6 weeks<br>2. RT was initiated 6 weeks after the last cycle of ACNU-CDDP (fractionated RT 60 Gy total dose)<br>3. 4 weeks after RT, patients received up to 6 cycles of adjuvant oral temozolomide (150–200 mg/m$^2$) for 5 days every 28 days.<br>*Surgery*<br>Control group:<br>GTR: 40.5%<br>STR: 28.6%<br>Biopsy: 31.0%<br>Treatment group (ACNU-CDDP)<br>GTR: 32.5%<br>STR: 55%<br>Biopsy: 12.5% | II | ***Results***<br>*Median PFS*<br>Intention to treat (ITT) pts:<br>Control group: 5.1 months<br>Treatment group (ACNU-CDDP): 6.6 months<br>(p = 0.8)<br>Per protocol (PP) pts:<br>Control group: 8.2 months<br>Treatment group (ACNU-CDDP): 9.6 months<br>(p = 0.3)<br>*Median OS*<br>Intention to treat (ITT) pts:<br>Control group: 18.9 months<br>Treatment group (ACNU-CDDP): 28.4 months<br>(p = 0.2)<br>Per protocol (PP) pts:<br>Control group: 19 months<br>Treatment group (ACNU-CDDP): NA (since 88.9% pts censored)<br>(p < 0.001)<br>***Toxicity***<br>Grade III/IV/V hematologic adverse effects:<br>Treatment group (ACNU-CDDP): 65.8% of pts including three who experienced neutropenic fever and one patient who died from sepsis<br>Control group: 2.6% of pts<br>***Author's conclusions***<br>"The high frequency of serious hematological toxicity with ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy and adjuvant temozolomide limits its usage as primary treatment for glioblastoma"<br>***Comments and conclusions***<br>Classified as Class II because is a multicenter prospective randomized trial (not blinded). Study shows significant toxicity with neoadjuvant ACNU-CDDP treatment. Although, there appears to be some survival benefit when comparing treatment to RT followed by adjuvant TMZ, the study lacks comparison to the standard Stupp protocol |

**Table 5** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Metroet al. (2010) | *Study description* single institution, prospective phase II study of gemcitabine with radiotherapy (RT) as first line treatment for newly diagnosed GBM patients<br>*Patient population* newly diagnosed GBM patients with KPS > 70 (n = 23) who underwent either surgical subtotal resection or biopsy<br>*Treatment regimen*<br>Surgery:<br>STR: 17<br>Biopsy: 6<br>-Fractionated RT (60 Gy total dose)<br>-From 24 to 72 h before the 1st day of RT, patients started concomitant gemcitabine given IV at dose of 175 mg/m$^2$ weekly for 6 weeks, covering the whole period of radiotherapy<br>-No later than 6 weeks after the end of the experimental treatment of chemoradiotherapy, irrespective of<br>tumor response, patients were treated with oral temozolomide 150–200 mg/m$^2$ for 5 days every 28 days until disease progression or unacceptable toxicity | III | ***Results***<br>Response to treatment: 4/23 pts (per modified MacDonald criteria)<br>Stable disease: 14/23<br>MGMT promoter methylated pts- disease control was reported to be 91% (10/11pts)<br>MGMT promoter unmethylated pts- disease control was reported to be 77.5% (7/9pts)<br>Median PFS: 6.8 months (95% CI 6.1–7.6)<br>Median OS: 10.1 months (95% CI 8.7–11.6)<br>***Toxicity***<br>Grade 3 neutropenia in 2pts and transaminitis in 2 pts<br>***Author's conclusions***<br>"Concomitant radiotherapy–gemcitabine is active and well tolerated in newly diagnosed glioblastoma multiforme. Activity is observed both in tumors with methylated and unmethylated MGMT promoter"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized trial. Results are difficult to compare to standard Stupp protocol given as authors note there are no patients with gross total surgical resection. Additionally, all patients do receive adjuvant TMZ. However, they do note that there is some response to concomitant RT with gemcitabine in unmethylated MGMT promoter GBMs, although patient number is small, they suggest that this might be a patient population that might benefit from an alternative regimen |
| Jaeckleet al. (2010) | *Study description* Multicenter, prospective phase II study of RT and irinotecan, followed by BCNU plus irinotecan in newly diagnosed GBM patients<br>*Patient population* newly diagnosed GBM patients with ECOG ≤ 2 (n = 56)<br>*Treatment regimen*<br>Surgery:<br>GTR: 32%<br>STR: 45%<br>Biopsy: 23%<br>-Fractionated RT (50 Gy total dose)<br>-MTD for patients receiving:<br>1. Enzyme-inducing anticonvulsants (EIAC):<br>-irinotecan 400 mg/m$^2$/week on Days 1, 8, 22 and 29 during RT, followed by BCNU 100 mg/m$^2$ Day 1, and irinotecan, 400 mg/m$^2$ on Days 1, 8, 22 and 29, every 6 weeks<br>2. non-EIAC patients<br>-irinotecan 125 mg/m$^2$/week on Days 1, 8, 22 and 29 during RT, followed by BCNU 100 mg/m$^2$ Day 1 and irinotecan 75 mg/m$^2$ Days1,8,22 and 29, every 6 weeks<br>UGT1A1*28 genotyping (6/6, wild type; 6/7, heterozygote; 7/7, dual variant allele) was performed on tumor tis- sues obtained at initial surgery | III | ***Results***<br>Median PFS: 3.9 months (95% CI: 3.2–5.1)<br>PFS at 6 months: 28.6% (95% CI: 18.9–43.2)<br>Median OS: 10.8 months (95% CI 7.7–14.9)<br>OS at 12 months: 44.6% (95% CI: 33.3–59.8)<br>***Toxicity***<br>"Patients went off treatment due to adverse events (7%), refusal (11%), progressive disease (48%), death (9%), and other (9%); 16% completed protocol treatment"<br>***Author's conclusions***<br>"We conclude that in treatment of patients with newly diagnosed GBM, concomitant RT and irinotecan and adjuvant irinotecan plus BCNU does not show greater efficacy than prior NCCTG regimens or current TMZ- containing regimens, and is more toxic. We did not observe clinically relevant radio-sensitizing effects"<br>"Non-EIAC patients with UGT1A1*28 variant alleles appear particularly sensitive to toxicity from irinotecan"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized trial. Results do not show any benefit of concomitant RT and irinotecan and adjuvant irinotecan plus BCNU compared to standard Stupp protocol and appear to be more toxic |

**Table 5** (continued)

| Author (year) | Description of study | Data class | Conclusions |
|---|---|---|---|
| Quinnet al. (2009) | *Study description* single institution, prospective non-randomized phase II study evaluating the efficacy and safety of TMZ in combination with irinotecan (CPT-11) before radiotherapy in patients with newly diagnosed GBM<br>*Patient population* newly diagnosed GBM patients with KPS > 70 who underwent either surgical subtotal resection or biopsy (n = 42)<br>*Treatment regimen*<br>Surgery:<br>STR: 8<br>Biopsy: 34<br>-Patients received TMZ at a dose of 200 mg/m$^2$/day on days 1–5 and CPT-11 on days 1, 8, 22, and 29, with a dose adjustment for enzyme-inducing antiepileptic drug (EIAEDs) use | III | ***Results***<br>Response to treatment: (per modified MacDonald criteria)<br>Partial response (PR): 19% of patients<br>Median PFS: 3.1 months<br>Median OS: 13.8 months<br>***Toxicity***<br>Grade 3/4 adverse events: 36% of patients; 2 patients died, one of intracranial hemorrhage and one of treatment-related renal failure<br>***Author's conclusions***<br>"Although TMZ plus CPT-11 is at least comparable in efficacy toTMZalone, this combination appears more toxic and poorly tolerated"<br>***Comments and conclusions***<br>Classified as Class III because is a prospective nonrandomized trial. Results from this study are difficult to evaluate and compare with other studies as 81% of patients only had a biopsy. Moreover, 52% of pts (22/42) discontinued therapy after 1 or 2 cycles of treatment (due to disease progression or adverse events) and went on to immediate radiotherapy + TMZ, further limiting the interpretation of the study results |
| Vinja-muriet al. (2009) | *Study description* single institution, retrospective comparison of outcome of GBM pts treated with initial radiation and chemotherapy of TMZ or BCNU<br>*Patient population* newly diagnosed GBM patients who received both chemotherapy and radiation as initial therapy(n = 81);<br>BCNU treated (n = 49)<br>TMZ treated (n = 32)<br>*Treatment regimen*<br>Surgery included biopsy or subtotal resection:<br>Tumor size mean reported:<br>BCNU treated group: 4.5 cm<br>TMZ treated group: 4.0 cm<br>(P = 0.20)<br>All patients received fractionated RT total dose 60 Gy<br>BCNU group:<br>200 mg/m$^2$ intravenously every 8 weeks for a maximum of eight cycles, beginning as close to the start of radiotherapy as possible. Some elderly patients the initial dose of BCNU was reduced to 150 mg/m$^2$. Two patients, who were entered on an ECOG clinical trial, received BCNU as 80 mg/m$^2$ intravenous daily for 3 days every 8 weeks<br>TMZ group:<br>75 mg/m$^2$ orally daily 7 days a week from the first until the last day of radiotherapy. After a rest period of about 3 weeks the drug was restarted either at 150 or 200 mg/m$^2$ orally daily for 5 days every 28 days. The TMZ was continued up to 2 years if tolerated by the patient | III | ***Results***<br>*Median PFS*<br>BCNU group: 7.7 months<br>TMZ group: 5.2 months<br>(p = 0.8)<br>*Median OS*<br>BCNU group:11.5 months<br>TMZ group: 15.9 months<br>(p < 0.02)<br>In subgroup analysis of pts who underwent different salvage therapies, the authors noted that the median OS of theTMZ patients who did not receive the salvage therapy of bevacizumab + irinotecan (n = 22) was 11 months<br>***Toxicity***<br>BCNU group: 13/49 (27%) toxicity caused treatment to be stopped<br>TMZ group: 2/32 (6%) treatment stopped because of toxicity (one due to thrombocytopenia and one to fatigue)<br>***Author's conclusions***<br>"These data suggest that the superior OS of the TMZ-treated GBM patients was not due to better tumor control by TMZ but was possibly related to the newer salvage therapy that was available to them"<br>***Comments and conclusions***<br>Classified as Class III because is a purely retrospective study. Although, this study has significant limitations (non-randomized, tumor size larger in BCNU group, pts were treated in earlier years in BCNU group which could have made the outcome worse, not all pts in BCNU group received concomitant chemotherapy with radiation), the authors do elucidate the importance of examining salvage therapy and outcome |

when comparing treatment to RT followed by adjuvant TMZ, the study lacked comparison to the standard Stupp protocol where patients were also treated with concomitant TMZ during radiation. Regardless, the study found serious toxicity with the ACNU-CDDP regimen, which further challenges its possible benefit. In another multicenter prospective randomized trial, Shibui et al. [50] found no benefit in PFS or OS when examining the efficacy of nimustine (ACNU) + procarbazine (PCZ) compared to ACNU alone for GBM and anaplastic astrocytoma. The authors noted that their study "was terminated early because temozolomide was newly approved in Japan." Additionally, in a retrospective comparison of outcome of GBM patients treated with initial radiation and chemotherapy of TMZ or BCNU, Vinjamure et al. [51] found that TMZ treated GBM patients had better overall outcomes compared to BCNU treated patients, but they commented that this was due to newer salvage therapies in the era of TMZ treatment. This study had significant limitations such as non-randomized patients, tumor sizes were significantly larger in BCNU group, patients were treated in earlier years in BCNU group, and that not all patients in BCNU group received concomitant chemotherapy with radiation. Similarly, the results from another retrospective study comparing outcomes of GBM patients with at least near-total resection treated with initial radiation and TMZ or ACNU-based (ACNU plus teniposide or cisplatin) chemotherapy [52] are difficult to interpret given significant differences in treatment regimes. For example, the patients in ACNU-based group started therapy after completion of RT and, therefore, did not have any concomitant chemotherapy with radiation as the TMZ group. Also, greater than 40% of patients could not complete ACNU based treatment given significant toxicity. The authors note that while in a subgroup analysis of patients who were able to complete at least 4 cycles of ACNU-based therapy "a modest improvement in survival occurred in this ACNU subgroup, the efficacy was still inferior to that in the TMZ cohort." Overall, these studies do not support the use of nitrosurea based chemotherapies such as BCNU or ACNU over standard treatment with TMZ.

One class III study [53] examined the effect of gemcitabine in the treatment of GBM. In this single institution, prospective phase II study of gemcitabine with radiotherapy (RT) as first line treatment for newly diagnosed GBM patients followed by adjuvant TMZ, Metro et al. [53] noted that there is some response to concomitant RT with gemcitabine but these results are difficult to compare to standard Stupp protocol given that no patients in this group had undergone gross total surgical resection. Also, given all the patients do receive adjuvant TMZ it is difficult to identify treatment with gemcitabine as cause of specific outcomes. Given small number of patients and lack of control group, the study did not provide any significant evidence that concomitant gemcitabine during RT has any benefit over standard therapy with TMZ.

### Synthesis

In terms of adjuvant therapy for newly diagnosed GBM, there is class III evidence that highlights the important benefit of concomitant radiation with TMZ, especially for methylated MGMT tumors.

In regards to local regional chemotherapy with BCNU biodegradable wafers, the previous guidelines detailed level II recommendations, however, this recommendation was based on prior class I evidence where no systemic chemotherapy was used and/or TMZ had not been established as standard of care. In the current era, a number of level III studies have demonstrated no significant improvement in overall survival or progression free survival to support the use of BCNU wafers. Additional studies of higher quality are required to understand the role of BCNU wafer and other locoregional therapy in the setting of Stupp Protocol is necessary.

With respect to upfront use of bevacizumab, a number of studies have shown improved PFS but no improvement in OS in GBM patients. Moreover, conflicting data exists regarding the exact benefit of adjuvant bevacizumab in terms of quality of life requiring further rigorously designed clinical studies.

Furthermore, the above studies have not shown any convincing evidence that alternative chemotherapy regimens had any benefit over standard treatment with TMZ.

## Conclusions and key issues for future investigation

Chemotherapy is essential in the management of newly diagnosed GBM. The use of temozolomide is supported by level I recommendations for patients with newly diagnosed GBM as previously shown by Stupp et al. and reported in the previous guidelines [2]. Although, many studies have identified the methylation of the MGMT promoter as a positive predictor for TMZ treatment in patients with newly diagnosed GBM, prospective randomized controlled trials with and without concurrent RT in methylated and non-methylated MGMT promoter GBM groups would help better elucidate and emphasize the benefit of TMZ treatment for these particular subsets of patients. Currently, while recognizing their limitations, the existing publications can be used to consider treatment options, but more importantly, to frame the important questions for future clinical trials.

Prospective randomized controlled trials in specific subsets of patients (i.e. by age group, molecular profile, extent of resection, previous treatment) would help define optimal

timing and treatment regimens. Furthermore, given the poor prognosis of patients with GBMs, future clinical trials need to emphasize and prospectively consider quality of life measures in addition to PFS and OS. As additional clinical trials bring forth new chemotherapeutic and specific targeted options, the role of TMZ + concurrent RT followed by adjuvant TMZ treatment will need to be examined as standard therapy compared to new treatment regimens.

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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.

## Compliance with ethical standards

**Conflict of interest** The Update on Newly Diagnosed Glioblastoma Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

| Author | Conflicts |
|---|---|
| Navid Redjal | None |
| Brian Nahed | Research Funding: NIH, American Cancer Society<br>Co-founder and consultant React Neuro |
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## References

1. Fadul CE, Wen PY, Kim L, Olson JJ (2008) Cytotoxic chemotherapeutic management of newly diagnosed glioblastoma multiforme. J Neurooncol 89:339–357. https://doi.org/10.1007/s11060-008-9615-4
2. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. https://doi.org/10.1056/NEJMoa043330
3. Karacetin D, Okten B, Yalcin B, Incekara O (2011) Concomitant temozolomide and radiotherapy versus radiotherapy alone for treatment of newly diagnosed glioblastoma multiforme. J BUON 16:133–137
4. Park CK, Lee SH, Kim TM et al (2013) The value of temozolomide in combination with radiotherapy during standard treatment for newly diagnosed glioblastoma. J Neurooncol 112:277–283. https://doi.org/10.1007/s11060-013-1060-3
5. Barbagallo GMV, Paratore S, Caltabiano R et al (2014) Long-term therapy with temozolomide is a feasible option for newly diagnosed glioblastoma: a single-institution experience with as many as 101 temozolomide cycles. Neurosurg Focus 37:E4. https://doi.org/10.3171/2014.9.FOCUS14502
6. Gilbert MR, Wang M, Aldape KD et al (2013) Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol 31:4085–4091. https://doi.org/10.1200/JCO.2013.49.6968
7. Pérez-Larraya JG, Ducray F, Chinot O et al (2011) Temozolomide in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial. J Clin Oncol 29:3050–3055. https://doi.org/10.1200/JCO.2011.34.8086
8. Gilbert MR, Dignam JJ, Armstrong TSTS et al (2014) A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370:699–708. https://doi.org/10.1056/NEJMoa1308573
9. Weiler M, Hartmann C, Wiewrodt D et al (2010) Chemoradiotherapy of newly diagnosed glioblastoma with intensified temozolomide. Int J Radiat Oncol Biol Phys 77:670–676. https://doi.org/10.1016/j.ijrobp.2009.05.031
10. Behm T, Horowski A, Schneider S et al (2013) Concomitant and adjuvant temozolomide of newly diagnosed glioblastoma in elderly patients. Clin Neurol Neurosurg 115:2142–2146. https://doi.org/10.1016/j.clineuro.2013.08.002
11. Brandes AA, Vastola F, Basso U et al (2003) A prospective study on glioblastoma in the elderly. Cancer 97:657–662. https://doi.org/10.1002/cncr.11097
12. Glantz M, Chamberlain M, Liu Q et al (2003) Temozolomide as an alternative to irradiation for elderly patients with newly diagnosed malignant gliomas. Cancer 97:2262–2266. https://doi.org/10.1002/cncr.11323
13. Chinot OL, Barrle M, Frauger E et al (2004) Phase II study of temozolomide without radiotherapy in newly diagnosed glioblastoma multiforme in an elderly populations. Cancer 100:2208–2214. https://doi.org/10.1002/cncr.20224
14. Keime-Guibert F, Chinot O, Taillandier L et al (2007) Radiotherapy for glioblastoma in the elderly. N Engl J Med 356:1527–1535. https://doi.org/10.1056/NEJMoa065901

15. Han SJ, Rutledge WC, Molinaro AM et al (2015) The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. Neurosurgery 77:248–253. https://doi.org/10.1227/NEU.0000000000000766
16. Sun MZ, Oh T, Ivan ME et al (2015) Survival impact of time to initiation of chemoradiotherapy after resection of newly diagnosed glioblastoma. J Neurosurg 122:1144–1150. https://doi.org/10.3171/2014.9.JNS14193
17. Blumenthal DT, Won M, Mehta MP et al (2009) Short delay in initiation of radiotherapy may not affect outcome of patients with glioblastoma: a secondary analysis from the radiation therapy oncology group database. J Clin Oncol 27:733–739. https://doi.org/10.1200/jco.2008.18.9035
18. Seidlitz A, Siepmann T, Löck S et al (2015) Impact of waiting time after surgery and overall time of postoperative radiochemotherapy on treatment outcome in glioblastoma multiforme. Radiat Oncol 10:172. https://doi.org/10.1186/s13014-015-0478-5
19. Noel G, Huchet A, Feuvret L et al (2012) Waiting times before initiation of radiotherapy might not affect outcomes for patients with glioblastoma: a French retrospective analysis of patients treated in the era of concomitant temozolomide and radiotherapy. J Neurooncol 109:167–175. https://doi.org/10.1007/s11060-012-0883-7
20. Bhandari M, Gandhi AK, Devnani B, et al (2017) Comparative study of adjuvant temozolomide six cycles versus extended 12 cycles in newly diagnosed glioblastoma multiforme. J Clin Diagn Res 11:XC04–XC08. https://doi.org/10.7860/JCDR/2017/27611.9945
21. Roldán Urgoiti GB, Singh AD, Easaw JC (2012) Extended adjuvant temozolomide for treatment of newly diagnosed glioblastoma multiforme. J Neurooncol 108:173–177. https://doi.org/10.1007/s11060-012-0826-3
22. Blumenthal DT, Gorlia T, Gilbert MR et al (2017) Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. Neuro Oncol 19:1119–1126. https://doi.org/10.1093/neuonc/nox025
23. Skardelly M, Dangel E, Gohde J et al (2017) Prolonged temozolomide maintenance therapy in newly diagnosed glioblastoma. Oncologist 22:570–575. https://doi.org/10.1634/theoncologist.2016-0347
24. Gramatzki D, Kickingereder P, Hentschel B et al (2017) Limited role for extended maintenance temozolomide for newly diagnosed glioblastoma. Neurology 88:1422–1430. https://doi.org/10.1212/WNL.0000000000003809
25. Clarke JL, Iwamoto FM, Sul J et al (2009) Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma. J Clin Oncol 27:3861–3867. https://doi.org/10.1200/JCO.2008.20.7944
26. Sher DJ, Henson JW, Avutu B et al (2008) The added value of concurrently administered temozolomide versus adjuvant temozolomide alone in newly diagnosed glioblastoma. J Neurooncol 88:43–50. https://doi.org/10.1007/s11060-008-9530-8
27. Lou AM, Heery CR, Herndon JE et al (2009) Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. Cancer 115:3501–3511. https://doi.org/10.1002/cncr.24398
28. De Bonis P, Anile C, Pompucci A et al (2012) Safety and efficacy of gliadel wafers for newly diagnosed and recurrent glioblastoma. Acta Neurochir (Wien) 154:1371–1378. https://doi.org/10.1007/s00701-012-1413-2
29. Salmaggi A, Milanesi I, Silvani A et al (2013) Prospective study of carmustine wafers in combination with 6-month metronomic temozolomide and radiation therapy in newly diagnosed glioblastoma: preliminary results. J Neurosurg 118:821–829. https://doi.org/10.3171/2012.12.JNS111893
30. Chaichana KL, Zaidi H, Pendleton C et al (2011) The efficacy of carmustine wafers for older patients with glioblastoma multiforme: prolonging survival. Neurol Res 33:759–764. https://doi.org/10.1179/1743132811Y.0000000006
31. Noël G, Schott R, Froelich S et al (2012) Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior Gliadel implantation (Carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. Int J Radiat Oncol Biol Phys 82:749–755. https://doi.org/10.1016/j.ijrobp.2010.11.073
32. Akiyama Y, Kimura Y, Enatsu R et al (2018) Advantages and disadvantages of combined chemotherapy with carmustine wafer and bevacizumab in patients with newly diagnosed glioblastoma: a single-institutional experience. World Neurosurg 113:e508–e514. https://doi.org/10.1016/j.wneu.2018.02.070
33. Roux A, Peeters S, Zanello M et al (2017) Extent of resection and Carmustine wafer implantation safely improve survival in patients with a newly diagnosed glioblastoma: a single center experience of the current practice. J Neurooncol 135:83–92. https://doi.org/10.1007/s11060-017-2551-4
34. Westphal M, Hilt DC, Bortey E et al (2003) A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro Oncol 5:79–88. https://doi.org/10.1215/S1522-8517-02-00023-6
35. Valtonen S, Timonen U, Toivanen P, et al (1997) Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. Neurosurgery 41:44–8; discussion 48–9
36. Chinot OL, Wick W, Mason W et al (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370:709–722. https://doi.org/10.1056/NEJMoa1308345
37. Carlson JA, Reddy K, Gaspar LE et al (2015) Hypofractionated-intensity modulated radiotherapy (hypo-IMRT) and temozolomide (TMZ) with or without bevacizumab (BEV) for newly diagnosed glioblastoma multiforme (GBM): a comparison of two prospective phase II trials. J Neurooncol 123:251–257. https://doi.org/10.1007/s11060-015-1791-4
38. Lai A, Filka E, McGibbon B et al (2008) Phase II pilot study of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme: interim analysis of safety and tolerability. Int J Radiat Oncol Biol Phys 71:1372–1380. https://doi.org/10.1016/j.ijrobp.2007.11.068
39. Lai A, Tran A, Nghiemphu PL et al (2011) Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. J Clin Oncol 29:142–148. https://doi.org/10.1200/JCO.2010.30.2729
40. Van Linde ME, Verhoeff JJ, Richel DJ et al (2015) Bevacizumab in combination with radiotherapy and temozolomide for patients-with newly diagnosed glioblastomamultiforme. Oncologist 20:107–108. https://doi.org/10.1634/theoncologist.2014-0418
41. Narayana A, Gruber D, Kunnakkat S et al (2012) A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma. J Neurosurg 116:341–345. https://doi.org/10.3171/2011.9.JNS11656
42. Omuro A, Beal K, Gutin P et al (2014) Phase II study of bevacizumab, temozolomide, and hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma. Clin Cancer Res 20:5023–5031. https://doi.org/10.1158/1078-0432.CCR-14-0822
43. Vredenburgh JJ, Desjardins A, Reardon DA et al (2011) The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clin Cancer Res 17:4119–4124. https://doi.org/10.1158/1078-0432.CCR-11-0120

44. Reyes-Botero G, Cartalat-Carel S, Chinot OL et al (2018) Temozolomide plus bevacizumab in elderly patients with newly diagnosed glioblastoma and poor performance status: an ANOCEF phase II trial (ATAG). Oncologist 23:524–e44. https://doi.org/10.1634/theoncologist.2017-0689
45. Hata N, Yoshimoto K, Hatae R et al (2017) Add-on bevacizumab can prevent early clinical deterioration and prolong survival in newly diagnosed partially resected glioblastoma patients with a poor performance status. Onco Targets Ther 10:429–437. https://doi.org/10.2147/OTT.S125587
46. Hofland KF, Hansen S, Sorensen M et al (2014) Neoadjuvant bevacizumab and irinotecan versus bevacizumab and temozolomide followed by concomitant chemoradiotherapy in newly diagnosed glioblastoma multiforme: a randomized phase II study. Acta Oncol (Madr). https://doi.org/10.3109/0284186X.2013.879607
47. Jaeckle KA, Ballman KV, Giannini C et al (2010) Phase II NCCTG trial of RT + irinotecan and adjuvant BCNU plus irinotecan for newly diagnosed GBM. J Neurooncol 99:73–80. https://doi.org/10.1007/s11060-009-0103-2
48. Quinn JA, Jiang SX, Reardon DA et al (2009) Phase II trial of temozolomide (TMZ) plus irinotecan (CPT-11) in adults with newly diagnosed glioblastoma multiforme before radiotherapy. J Neurooncol 95:393–400. https://doi.org/10.1007/s11060-009-9937-x
49. Kim IH, Park CK, Heo DS et al (2011) Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial. J Neurooncol 103:595–602. https://doi.org/10.1007/s11060-010-0427-y
50. Shibui S, Narita Y, Mizusawa J et al (2013) Randomized trial of chemoradiotherapy and adjuvant chemotherapy with nimustine (ACNU) versus nimustine plus procarbazine for newly diagnosed anaplastic astrocytoma and glioblastoma (JCOG0305). Cancer Chemother Pharmacol 71:511–521. https://doi.org/10.1007/s00280-012-2041-5
51. Vinjamuri M, Adumala RR, Altaha R et al (2009) Comparative analysis of temozolomide (TMZ) versus 1,3-bis (2-chloroethyl)-1 nitrosourea (BCNU) in newly diagnosed glioblastoma multiforme (GBM) patients. J Neurooncol 91:221–225. https://doi.org/10.1007/s11060-008-9702-6
52. Wang Y, Chen X, Zhang Z et al (2014) Comparison of the clinical efficacy of temozolomide (TMZ) versus nimustine (ACNU)-based chemotherapy in newly diagnosed glioblastoma. Neurosurg Rev 37:73–78. https://doi.org/10.1007/s10143-013-0490-x
53. Metro G, Fabi A, Mirri MA et al (2010) Phase II study of fixed dose rate gemcitabine as radiosensitizer for newly diagnosed glioblastoma multiforme. Cancer Chemother Pharmacol 65:391–397. https://doi.org/10.1007/s00280-009-1155-x



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