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Standards of care for treatment of recurrent glioblastoma—are we there yet?

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Newly diagnosed glioblastoma is now commonly treated with surgery, if feasible, or biopsy, followed by radiation plus concomitant and adjuvant temozolomide. The treatment of recurrent glioblastoma continues to be a moving target as new therapeutic principles enrich the standards of care for newly diagnosed disease. We reviewed PubMed and American Society of Clinical Oncology abstracts from January 2006 to January 2012 to identify clinical trials investigating the treatment of recurrent or progressive glioblastoma with nitrosoureas, temozolomide, bevacizumab, and/or combinations of these agents. At recurrence, a minority of patients are eligible for second surgery or reirradiation, based on appropriate patient selection. In temozolomide-pretreated patients, progression-free survival rates at 6 months of 20%–30% may be achieved either with nitrosoureas, temozolomide in various dosing regimens, or bevacizumab. Combination regimens among these agents or with other drugs have not produced evidence for superior activity but commonly produce more toxicity. More research is needed to better define patient profiles that predict benefit from the limited therapeutic options available after the current standard of care has failed.

Keywords: bevacizumab, glioblastoma, MGMT, nitrosoureas, temozolomide.

Glioblastoma is the most aggressive malignant primary brain tumor in adults (median age, 64 y) with a preponderance in men (1.3–1.6:1), whites, and those of European descent (2:1 compared with African Americans).[1,2] The annual incidence ranges from 3 to 5 newly diagnosed cases per 100 000 population. Therapeutic advances over the last decade have led to improvements in both patients' life expectancy and quality of life. Based on data from the Surveillance, Epidemiology, and End Results program, median survival times of all patients with newly diagnosed glioblastoma improved from 8.1 months in 2000–2003 to 9.7 months in 2005–2008, likely owing to the introduction of temozolomide (TMZ).[3]

The current standard of care for patients with newly diagnosed glioblastoma was established in 2005, following the pivotal trial by the European Organisation for the Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group, in which concurrent TMZ (75 mg/m^2/d for $\leq$7 wk) and radiotherapy followed by 6 maintenance cycles of adjuvant chemotherapy (150–200 mg/m^2 on 5-d therapy every 28 d) improved progression-free survival (PFS) and overall survival (OS).[4] Improved survival in this trial was largely restricted to a subset of patients harboring promoter methylation of the DNA repair gene O^6-methylguanine-DNA methyltransferase (MGMT).[5] In a recent phase III trial of 833 eligible patients, no significant improvement in median OS (16.6 vs 14.9 mo; $P = .63$) or median PFS (5.5 vs 6.7 mo; $P = .06$) was found for patients who received dose-dense extended TMZ (75 mg/m^2 on 21-d therapy every 4 wk for 6–12 cycles) plus radiotherapy compared with patients who received standard-dose TMZ plus radiotherapy, respectively, regardless of methylation status.[6] However, *MGMT* promoter methylation was associated with improved median PFS (8.7 vs 5.7 mo; $P < .0001$) and OS (21.2 vs 14 mo; $P < .0001$).[6] Despite standard of care therapy,[7] recurrence rates remain high in patients with glioblastoma (~90%). Median OS is 15–18 months in clinical trial populations, and less than 10% of patients are alive at 5 years.[1]

The primary purpose of this paper is to discuss the role of second-line monotherapy and combination therapies for patients with recurrent or progressive

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glioblastoma. What is the current role of nitrosoureas, alone or in combination? Does efficacy outweigh their toxicity profile? We will also address the efficacy of the varied metronomic TMZ dosing regimens for rechallenge (ie, patients re-exposed to TMZ who had been previously treated, or patients switched to alternative dosing regimens of TMZ following signs of relapse or progression on standard TMZ therapeutic regimens) as well as for TMZ-naive patients. The availability of bevacizumab, alone or in combination, to treat recurrent disease is another relatively new option that requires perspective.

Numerous other issues must be considered when attempting to establish a standard of care for patients with recurrent glioblastoma. How is recurrence best determined? Which patients qualify for second surgery or repeat radiotherapy? Which patients should not be retreated at all? How should efficacy of treatment for recurrent glioblastoma be assessed in clinical trials? Is the 6-month PFS rate (PFS6) the optimal end point? Also, the prognostic value of the *MGMT* status in patients with recurrent glioblastoma is not well defined. Does *MGMT* status guide the selection of the appropriate agent at recurrence? Are other markers useful?

Diagnosis of Progression

Neuroimaging (serial MRI) remains the primary monitoring tool for glioblastoma, with assessments typically performed every 2 to 3 months during treatment and somewhat longer intervals during disease-progression-free periods. However, standard MRI contrast studies, even when adhering to the Macdonald criteria,[8] may be misleading and confound the diagnosis of recurrence. Within the first months following completion of radiotherapy and concomitant TMZ, it can be difficult to distinguish recurrence from pseudoprogression when using typical MRI modalities, such as T2, T1 with gadolinium, and fluid-attenuated inversion recovery (FLAIR).[9] Pseudoprogression is an apparent increase in tumor size that does not reflect tumor progression biologically and can be proven only post hoc if no further tumor-specific treatment is administered at the time point of pseudoprogression and if the lesion subsequently regresses. MRI patterns suggestive of pseudoprogression have been described in 20%–30% of patients receiving radiotherapy + TMZ followed by TMZ alone.[10,11] Furthermore, radionecrosis characterized by blood–brain barrier disruption, edema, and a mass effect mimicking progression appears earlier in these patients vs those receiving radiotherapy alone.[11] Both pseudoprogression and radionecrosis are likely related and consistent with the increased tumor cell killing caused by chemoradiotherapy or increased host normal tissue responses, including blood–brain barrier breakdown, ischemia, effects of steroid withdrawal, and inflammation.[9] Nonetheless, the recurrence of glioblastoma remains predominantly local.[12,13]

Currently, the roles of single photon emission-computed tomography, PET, MR spectroscopy, and functional MRI in determining progression are being evaluated. At present, we would advocate careful reimaging in case of suspected pseudoprogression. With no or minimal new symptoms, any rapid change of treatment is discouraged. Ultimately, some patients may need a biopsy if a definitive diagnosis needs to be established. In any case, before diagnosing pseudoprogression, it must be ascertained whether the scans selected for comparison are appropriate, eg, a postsurgical scan may not be useful to assess progression at the first scan after concomitant radiochemotherapy if that patient started radiotherapy only 4–6 weeks after surgery. Moreover, the first scan after radiochemotherapy should be considered as a new baseline for all further imaging assessments.

Radiographic Assessment of Treatment Response

Efficacy evaluation of treatment in recurrent glioblastoma commonly relies on neuroimaging, supported by clinical monitoring, but can be complicated. A complete resolution of blood–brain disturbance detected by contrast extravasation on MRI or CT will no longer qualify as a response if there is increased T2 or FLAIR abnormality. Such responses are now referred to as "pseudoresponses." The new Response Assessment in Neuro-Oncology (RANO) criteria, which integrate at least a qualitative measure for T2/FLAIR changes, appear to be an improvement over the Macdonald criteria and may facilitate the interpretation of therapeutic outcomes in patients with glioblastoma (Table 1).[14,15] In contrast to the Macdonald criteria, those of RANO define measurable and nonmeasurable lesions, with tumor size measured on T2/FLAIR-weighted images in addition to the contrast-enhancing tumor. The RANO criteria also apply to entry into clinical trials for recurrent high-grade glioma. For a first progression that allows screening for a recurrent therapy trial, time from initial chemoradiotherapy is pivotal. Patients will not be formally considered progressors within the first 3 months from the end of radiochemotherapy. Also, RANO criteria provide definitions of radiographic response that incorporate changes in nonenhancing lesions. For suspected cases of pseudoprogression not only in the context of TMZ-based radiochemotherapy but also in that of new therapies, notably local therapies, that influence the vascular biology of malignant gliomas, a close control MRI and clinical examination are recommended. The RANO criteria are likely to be valuable when assessing treatment response in clinical trials as well as for monitoring patients in daily practice but will require further validation.

Role of Repeat Surgery and Radiotherapy

About 1 in 4 patients with progressive or recurrent glioblastoma can be considered for repeat surgery. The documented benefits of reoperation have been derived primarily from retrospective studies. A more favorable

Table 1. Neuroimaging and glioblastoma: Macdonald vs RANO criteria

	Macdonald	RANO
CR	Requires all of the following: • Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 wk • No new lesions • No corticosteroids • Stable or improved clinically	Requires all of the following: • Disappearance of all enhancing measurable and nonmeasurable disease sustained for a minimum of 4 wk • Stable or improved FLAIR/T2 lesions • No new lesions • Stable or improved clinically • Patients cannot be receiving corticosteroids (physiologic replacement doses are acceptable)
PR	Requires all of the following: • ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 wk • No new lesions • Stable or reduced corticosteroid dose • Stable or improved clinically	Requires all of the following: • ≥50% decrease (compared with baseline) in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for a minimum of 4 wk • No progression of nonmeasurable disease • No new lesions • Stable or improved FLAIR/T2 lesions • Stable or improved clinically • Corticosteroid dosage at the time of the scan should be no greater than the dosage at the time of the baseline scan
SD	Requires all of the following: • Does not qualify for CR, PR, or PD • Stable clinically	Requires all of the following: • Patient does not qualify for CR, PR, or progression • Stable FLAIR/T2 lesions on a corticosteroid dose no greater than at baseline • Stable clinically
PD	Defined by any of the following: • ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions relative to best previous scan • Any new lesion • Clinical deterioration	Defined by any of the following: • ≥25% increase in sum of the products of perpendicular diameters of all measurable enhancing lesions compared with the smallest tumor measurement obtained either at baseline or best response following the initiation of therapy, while on a stable or increasing dose of corticosteroids • Significant increase in FLAIR/T2 lesions compared with baseline or best response following initiation of therapy, not caused by comorbid events (eg, radiation therapy, ischemic injury, seizures, postoperative changes, other treatment effects), while on a stable or increasing dose of corticosteroids • New lesions • Clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication side effects, complications of therapy, cerebrovascular events, or infection) or decreases in corticosteroid dose • Failure to return for evaluation owing to death or deteriorating condition • Clear progression of nonmeasurable disease

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease. (Adapted from Lutz et al.[14] and Wen et al.[15])

prognosis following surgery for recurrence or progression is associated with a younger age (70 years or younger), a smaller tumor volume (<50 cm^3), and a preoperative KPS greater than 80%.[16,17] Repeat surgery is not recommended for patients with involvement of prespecified eloquent/critical brain regions.[17] A controversial practice at the time of repeat surgery is the implantation of biodegradable chemotherapy wafers

containing carmustine, which may prolong survival but are rarely used today.[7,18]

Reirradiation remains a palliative option for a select group of patients with recurrent glioblastoma. Patients with a KPS greater than 60%, a tumor size of up to 40 mm, and progression more than 6 months from time of surgery appear to be the best candidates.[19] The most common approach involves the use of fractionated stereotactic radiotherapy with or without intensity modulation and a median total dose of 30–36 Gy.[20] In contrast, stereotactic radiosurgery (the administration of one single fraction), which has the theoretical advantage of sparing normal tissue, is rarely used in glioblastoma because of the poorly defined target volume. Interestingly, none of the reirradiation schedules has ever been looked at in a prospective or controlled fashion. In fact, the recent APG101 trial provided no sign of efficacy for reirradiation at 18 × 2 Gy in recurrent glioblastoma patients commonly deemed best candidates for that intervention.[21]

Monotherapy and Combination Chemotherapeutic Trials for Recurrent Disease

Over the last decade, an increased number of clinical trials have evaluated the benefits of single-agent and combination chemotherapy for patients with recurrent or progressive glioblastoma. Older studies usually evaluated a heterogeneous patient population, including those with a mix of WHO grades 3/4 gliomas. Older series often reported on therapeutic options in TMZ-naive patients, whereas more recent studies have included only those pretreated with TMZ. Almost all study designs were noncomparative or failed to include an adequate control arm. The majority considered PFS6 and median OS from the time of recurrence as the primary end points. Although PFS6 is advocated as a reliable measure of tumor control and a strong predictor of survival,[22] it is influenced by further salvage therapies. Radiographic responses were often incompletely reported, with most studies using the Macdonald criteria to assess response. Finally, interpretation of efficacy findings, specifically comparison of independent publications, may be confounded by other factors, including whether reirradiation or repeat surgery was performed, as well as a number of previous relapses, general health status, age, and other underlying factors.

This report is a systematic review that used PubMed and American Society of Clinical Oncology abstract reports from January 2006 to January 2012 as the primary sources of data. The objective of the analysis was to identify clinical efficacy trials following systemic treatment with nitrosoureas, TMZ, bevacizumab, and/or combinations of these agents in patients with recurrent or progressive glioblastoma. No specific limitations were placed on the selection of studies given the relative paucity of data.

Nitrosoureas—single and combination therapy— Nitrosoureas are DNA alkylating agents characterized by high lipophilicity that permit blood–brain barrier penetration, making them useful in the treatment of brain tumors. Prior to 1999, nitrosoureas (eg, carmustine, lomustine [CCNU], or nimustine) were commonly used in the first-line treatment of glioblastoma. Another alkylating agent, procarbazine, was used alone or in combination with CCNU. In 1999, 2 phase II trials changed the therapeutic landscape when TMZ was found to be efficacious for recurrent glioblastoma patients who had received no more than 1 course of nitrosourea-based chemotherapy.[23,24] These data, coupled with a favorable tolerability profile, led to approval of TMZ in 1999 for recurrent high-grade gliomas, and nitrosoureas were moved into second-line therapy. Subsequently, in 2005, TMZ became the treatment of choice for newly diagnosed glioblastoma. Despite the less than optimal safety profile of nitrosoureas—eg, induction bone marrow suppression, liver/renal toxicity, or interstitial lung disease—they remain a second-line treatment option in single and combination regimens for recurrent disease (Table 2).

Two phase II trials[25,26] and 1 retrospective series[27] evaluated a similar carmustine monotherapy regimen for recurrent/progressive disease in 104 patients, some of whom had received prior TMZ therapy. For 2 studies, PFS6 and median OS ranged 13.0%–17.5% and 5.1–7.5 months, respectively; no complete remissions were observed.[26,27] Efficacy end points for the one study were unevaluable (data not presented separately for carmustine).[25] The predominant side effects following carmustine monotherapy were hematologic and long-lasting hepatic and pulmonary toxicity (Table 2).

A recent prospective phase III trial in 92 lomustine-treated patients (70 at first relapse) reported a 19% PFS6 response rate, with a median OS of 7.1 months.[28] Grades 3 and 4 hematologic toxicities were very common (46 events), with thrombocytopenia and neutropenia reported most often. In a double-blind, randomized, multicenter phase III trial of 325 patients who received prior radiation and TMZ, the lomustine monotherapy arm ($n = 65$) provided PFS6 and median OS of 24.5% and 9.8 months.[29,30] Grades 3 and 4 thrombocytopenia, leukopenia, and lymphopenia were common.

In a small retrospective report, nimustine in TMZ-pretreated patients was given alone ($n = 14$) or in combination with teniposide ($n = 17$) or cytarabine ($n = 1$).[31] PFS6 for all 32 patients was 20%, and the median OS from the start of nimustine therapy was 6.7 months. Fifty percent of patients developed grade 3 or 4 hematologic toxicity. No patient developed pulmonary fibrosis.

Fotemustine is another nitrosourea compound, studied mostly in Europe, notably in Italy and France.[32] Four prospective phase II trials, using slightly different induction/maintenance dosage regimens, evaluated fotemustine in TMZ-pretreated patients with recurrent or progressive glioblastoma.[33–36] Two studies were exclusively in patients experiencing their first relapse.[33,35] Overall, PFS6 and median OS ranged 20.9%–61% and 6.0–11.1 months, respectively. The best findings were obtained with a protracted low-dose

Table 2. Nitrosourea trials in recurrent or progressive glioblastoma[a]

Reference	Study Design/Population	TMZ Pretreatment	Nitrosourea Regimen	*n*	Radiographic Response (%)	PFS6 (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Monotherapy									
van den Bent et al.[25]	Phase II, randomized. Median age: 54 y	Some (not clearly specified)	BCNU 60 mg/m^2 on days 1–3 q8wk for max 5 cycles *or* TMZ 200 mg/m^2 on days 1–5 q4wk in chemotherapy-naive pts *or* 150 mg/m^2 on days 1–5 q4wk after prior adjuvant chemotherapy, with dose escalation to 200 mg/m^2 in absence of significant toxicity (only combined data [cntrl] for BCNU and TMZ reported) *or* ERL 150 mg/d, with dose escalation to 200 mg/d if no toxicity	29 27 (52 evaluable in cntrl) 54	*CR:* 0 *PR:* Cntrl: 5 vs ERL: 2 *SD:* Cntrl:18 vs ERL: 9	Cntrl: 24.1 vs ERL: 11.4	Cntrl: 2.4 vs ERL:1.8	Cntrl: 7.3 vs ERL:7.7	*Hematologic:* BCNU: 13 TMZ: 4 ERL: 1 *Nonhematologic:* BCNU: 8 TMZ: 4 ERL: 11
Brandes et al.[26]	Phase II. Median age: 49.7 y; median KPS: 70	No	BCNU 80 mg/m^2 on days 1–3 q8wk for max 6 cycles	40	*CR:* 0 *PR:* 6 *SD:* 9 *PD:* NA	17.5	NA	7.53	*Hematologic:* NA *Nonhematologic:* 9
Reithmeier et al.[27]	Retrospective analysis. Median age: 53 y; median KPS: 70; 1st relapse: $n = 30$; 2nd relapse: $n = 4$; 4th relapse: $n = 1$	24 (69%)	BCNU 80 mg/m^2 i.v. on days 1–3 q8wk for max 6 cycles	35	*CR:* 0 *PR:* 2 *SD:* 19 *PD:* 11	13	2.6	5.1	*Hematologic:* 10 *Nonhematologic:* 4
Wick et al.[28]	Phase III open-label, randomized 2:1. 1st relapse: CCNU: $n = 70$; enzastaurin: $n = 129$ 2nd relapse: CCNU: $n = 21$; enzastaurin: $n = 45$	NA	CCNU 100–130 mg/m^2 on day 1 q6wk; Enzastaurin 500 mg p.o. daily (1125-mg loading dose on day 1)	92 174	*CR:* 0 *PR:* 4 *SD:* 33 *PD:* 38 *CR:* 0 *PR:* 5 *SD:* 67 *PD:* 72	19.0 11.1	1.6 1.5	7.1 6.1	*Hematologic:* 46 *Nonhematologic:* 3 *Hematologic:* 1 *Nonhematologic:* 13 ($P < .007$ for hematologic toxicities)
Ahluwalia et al.,[29] Batchelor et al.[30]	Phase III, multicenter, double-blind, randomized 1:2:2. Median age: 54 y	Yes	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	65 131 129	*CR:* 0 *PR:* 5 *SD:* 23 *PD:* 23 *CR:* 1 *PR:* 17 *SD:* 76 *PD:* 10 *CR:* 2 *PR:* 19 *SD:* 67 *PD:* 19	24.5 16 34.5	2.73 3.1 4.2	9.8 8.0 9.4	*Hematologic:* 30 *Nonhematologic:* 16 *Hematologic:* 7 *Nonhematologic:* 66 *Hematologic:* 116 *Nonhematologic:* 57

Happold et al.[31]	Retrospective analysis 2003–2008, after failed therapy with TMZ or recurrence	Yes	ACNU 72–90 mg/m^2/d i.v. in 6-wk cycles, alone or in combination	14 alone *or* 18 in combination	*CR:* 0[b] *PR:* 2[b] *SD:* 5[b] *PD:* NA[b]	20[b]	2.7[b]	6.7[b]	*Hematologic:* 16[b] *Nonhematologic:* 3[b]
Addeo et al.[33]	Phase II, multicenter, nonrandomized, single-arm. Median age: 52.8 y; median KPS: 90; 1st relapse: 100%	Yes	FOT i.v. 80 mg/m^2 on days 1, 15, 30, 45, and 60 (induction), then 80 mg/m^2 q4wk (maintenance)	40	*CR:* 1 *PR:* 9 *SD:* 16 *PD:* 14	61	6.7	11.1	*Hematologic:* Induction: 5; maintenance: 5 *Nonhematologic:* Induction: 0; maintenance: 3
Brandes et al.[34]	Phase II, nonrandomized, single-arm. Median age: 51 y; median KPS: 90	Yes	FOT 75–100 mg/m^2 for 3 weekly doses followed, after a 5-wk rest, by 100 mg/m^2 q3wk for $\leq$1 y	43	*CR:* 0 *PR:* 3 *SD:* 15	20.9	1.7	6.0	*Hematologic:* Induction (100 mg/m^2): 24; amended induction (75 mg/m^2): 19; maintenance: 8 *Nonhematologic:* NA
Scoccianti et al.[35]	Phase II, multicenter, single-arm. Median age: 56 y; median KPS: 80; 1st recurrence: 100%	Yes	FOT i.v. 100 mg/m^2 qwk for 3 consecutive wk (induction), then q3wk (maintenance)	27	*CR:* 0 *PR:* 8 *SD:* 5 *PD:* 14	48.2	5.7	9.1	*Hematologic:* 4 pts *Nonhematologic:* 0
Fabrini et al.[36]	Phase II, multicenter, prospective, open-label, noncomparative. Median age: 56.8 y; median KPS: 90	Yes	FOT 100 mg/m^2 i.v. on days 1, 8, and 15, followed by 4- to 6-wk rest period (induction). In nonprogressive pts, FOT 100 mg/m^2 i.v. q3wk (maintenance)	50	*CR:* 1 *PR:* 8 *SD:* 22 *PD:* 19	52	6.1	8.1	*Hematologic:* 7 pts *Nonhematologic:* 0
Combination Regimens									
Kappelle et al.[38]	Multicenter retrospective, 1994–1998. Median age: 46 y; median KPS: 80	Only 4 pts	Standard or intensified PRO, CCNU, and VIN	63	*CR:* 3 *PR:* 8 *SD:* 25	29	NA	7.7	*Hematologic:* NA *Nonhematologic:* NA
Schmidt et al.[37]	Retrospective chart review, 1994–2003. Median age: 49 y; 1st relapse: 100%	Only 12 pts	PRO 60 mg/m^2 p.o. days 8–21, CCNU 110 mg/m^2 p.o. day 1, VIN 1.4 mg/m^2 [max 2 mg] i.v. days 8 and 29; given in 8-wk cycles	86	*CR:* 0 *PR:* 3 *SD:* 45 *PD:* 18	38.4	4.0	7.8	*Hematologic:* 30 pts *Nonhematologic:* 0

Abbreviations: ACNU, nimustine; BCNU, carmustine; CCNU, lomustine; CED, cediranib; cntrl, control arm; CR, complete response; ERL, erlotinib; FOT, fotemustine; max, maximum; KPS, Karnofsky performance score; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PD, progressive disease; PFS6, 6-month PFS rate; PR, partial response; PRO, procarbazine; pts, patients; SD, stable disease; VIN, vincristine.

For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.

*Disease PFS and OS were calculated from beginning of retreatment.

[a]All data are presented for glioblastoma patients only.

[b]Data for ACNU alone were not available; the numbers listed represent responses for all patients (ACNU alone and in combination).

induction regimen and the administration of fotemustine at least 3 months after completing first-line TMZ therapy.[33] Grades 3 and 4 hematologic toxicities were commonly reported following fotemustine therapy; however, lower rates were observed,[33] perhaps owing to the implementation of a longer rest period (2 wk) between doses during the induction phase. The small sample sizes in each of these studies call for larger prospective trials to ascertain the efficacy and safety of fotemustine in a TMZ-pretreated population with recurrent glioblastoma.

Few data are published that assess nitrosourea combination therapies for recurrent disease. Two retrospective studies (1994–2003) encompassing nearly 150 patients, of whom 16 received front-line TMZ, evaluated the combination of procarbazine, lomustine, and vincristine.[37,38] Similar efficacy findings were reported in the 2 reports: 30%–38% PFS6 and 7.6–7.9 months OS. While grades 3/4 hematologic toxicity was common (26%), nonhematologic toxicity was mild, and pulmonary fibrosis was not reported.[37] Lomustine in combination with cediranib ($n = 129$) was not found to be more effective (PFS6, 34.5%; median OS, 9.4 mo) than lomustine given alone (see above).[29,30] However, grades 3 and 4 hematologic and nonhematologic toxicities were substantially greater with combination vs either of the monotherapy arms.

Significant hematologic-toxicity concerns and the availability of more effective agents have made the use of nitrosoureas overall less desirable. New schedules at lower doses may prove beneficial. The nitrosoureas seem comparable in terms of efficacy at clinically tolerated doses, whereas nonhematologic toxicity, notably lung fibrosis, may be more common with carmustine than with lomustine or nimustine.

***TMZ monotherapy trials*—**Numerous trials have evaluated the efficacy and safety of TMZ as a monotherapy for recurrent or progressive disease, albeit few of the trials were conducted as prospective randomized controlled designs (Table 3).

Nine trials evaluated TMZ monotherapy given in traditional (5-day cycle) and novel schedules in 372 TMZ-naive patients with recurrent disease.[24,39–46] Generally, patients were being treated for the first or second relapse. Approximately half of the patients had received previous chemotherapy, mostly nitrosourea-based; the remainder were managed with surgery and radiotherapy as first-line treatment. Five of these studies administered TMZ in traditional regimens of 5-day cycles, with doses ranging 150–200 mg/m^2.[24,39,40,42,44] Novel metronomic TMZ schedules (75–100 mg/m^2 once or twice/d for 21–42 d consecutively using 28- to 70-d cycles) were used in 3 studies.[41,43,45] A 1-week-on/1-week-off schedule of TMZ 150 mg/m^2 was investigated in one study, in which promising PFS6 approaching 50% was observed.[46,47] Across all 9 studies, PFS6 ranged 18%–48% and median OS was 5.4–9.9 months. Notably, survival appeared higher by about 2 months in the more recent studies,[43–45] which may be due to other changes in the standard of care of glioblastoma patients or to patient selection.

Six studies of TMZ-pretreated patients evaluated TMZ rechallenge.[48–53] A variety of metronomic schedules were employed, including 40–100 mg/m^2 daily doses given for 21–365 consecutive days, as well as alternating 1-week-on/1-week-off regimens. Overall, PFS6 and median OS ranged 23%–58.3% and 5.1–13 months, respectively. One retrospective analysis compiled data on 5 different TMZ dosing regimens among 47 patients (re)challenged while receiving adjuvant TMZ or after a TMZ-free interval (Table 3).[54] PFS6 was 26.3%–28.6% for patients progressing on TMZ vs after TMZ; corresponding median OS was 6.6 and 5.3 months, respectively.

Of particular note, the RESCUE study examined the benefits of TMZ rechallenge based on the "temozolomide-free interval," ie, the time between upfront treatment and rechallenge.[51] PFS6 and median OS were 27.3% and 3.6 months for patients receiving rechallenge early (progression while receiving adjuvant TMZ before completion of 6 cycles of adjuvant TMZ), 7.4% and 1.8 months for patients receiving rechallenge after an extended period (progression while receiving extended adjuvant TMZ beyond the standard 6 cycles but before completion of adjuvant treatment), and 35.7% and 3.7 months for patients receiving rechallenge after a prolonged interval (progression after completion of adjuvant treatment and a treatment-free interval longer than 2 months). Patients who experienced early progression derived the most benefit from TMZ rechallenge therapy. The authors considered the possibility that the results in this early rechallenge group could be in part attributable to pseudoprogression but noted that the study was intentionally designed to exclude patients who progressed within the first 12 weeks following completion of chemoradiation, in keeping with the RANO criteria. Furthermore, the median time from the end of radiotherapy in this early group was 5.2 months, thus minimizing the influence of pseudoprogression on these results.

Three randomized clinical trials were conducted using single-agent TMZ.[23,55,56] In one study, a standard TMZ regimen was more efficacious than procarbazine (PFS6 = 21% vs 8%), with a median survival time 1.5 months longer.[23] The latter study was conducted in TMZ-naive patients and led to the approval of TMZ in Europe for recurrent glioblastoma, although it is still not approved in the United States. The BR12 study did not provide separate data for glioblastoma patients but indicated that TMZ dose-intense regimens do not provide a survival or PFS benefit compared with standard doses in the treatment of TMZ-naive patients. The DIRECTOR trial evaluated 2 dose-intense regimens of TMZ (120 mg/m^2/d 1 wk on/1 wk off vs 80 mg/m^2/d 3 wk on/1 wk off) in patients experiencing a first relapse after at least 2 cycles of TMZ.[56] Specifically, patients were enrolled based on first progression of glioblastoma documented by MRI no earlier than 180 days after first surgery and no earlier than 90 days after completion of radiotherapy. Data are currently maturing.

Table 3. Temozolomide monotherapy trials in recurrent or progressive glioblastoma[a]

Reference	Study Design/Population	TMZ Pretreatment	TMZ Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Temozolomide-Naive Population									
Brada et al.[24]	Phase II, open-label, uncontrolled TMZ at 1st relapse. Median age: 54 y; median time to 1st relapse: 8.1 mo	No (40% of pts had prior nitrosourea-containing chemo-therapy)	Chemotherapy-naive pts: 200 mg/m^2/d p.o. for 1st 5 d of 28-d cycle. Pts with previous nitrosourea-containing adjuvant chemotherapy: 150 mg/m^2/d for 1st 5 d of 28-d cycle	126	*CR:* 2 *PR:* 8 *SD:* 57	18	2.1	5.4	*Hematologic:* 30 *Nonhematologic:* 30
Brandes et al.[39]	Phase II, 2nd relapse	No (previous PCV)	150 mg/m^2/d for 5 d q28d	22	*CR:* 2 *PR:* 3 *SD:* 4	31.8		7.6	*Hematologic:* 4 *Nonhematologic:* 2
Brandes et al.[40]	Phase II. Mean age: 48.4 y; median KPS: 80. 2nd relapse	No (previous PCV)	150 mg/m^2/d for 5 d q28d	42	*CR:* 2 *PR:* 6 *SD:* 9 *PD:* NA	24	NA	7.0	*Hematologic:* 1 *Nonhematologic:* 0
Khan et al.[41]	Phase II, prospective, extended, low-dose, single-center	No	75 mg/m^2/d for 42 d q70d	28	*CR:* 0 *PR:* 0 *SD:* 11 *PD:* 17	19	2.3	7.7	*Hematologic:* 8 *Nonhematologic:* 0
Wick et al.[46]	Phase II, nonrandomized, prospective	No	150 mg/m^2 on days 1–7 and days 15–21 of 28-d cycles for max 12 cycles	21	*CR:* 0 *PR:* 2 *SD:* 17 *PD:* 2	48	4.9	NA	*Hematologic:* 10 *Nonhematologic:* 7
Chan et al.[42]	Prospective, open-label, compassionate use in Chinese pts	No	200 mg/m^2/d for 5 d q28d for 4 cycles	13	NA	21.0	NA	NA	*Hematologic:* 0 *Nonhematologic:* 0
Brandes et al.[43]	Phase II. Median age: 57 y; Median KPS: 90	No	75 mg/m^2/d for 21 d q28d	33	*CR:* 1 *PR:* 2 *SD:* 17	30.3	3.8	9.3	*Hematologic:* 14 *Nonhematologic:* 4
Nagane et al.[44]	Prospective, open-label. Mean age: 48.2 y; Median KPS: 70	No (89.5% had previous nitrosourea-based therapy)	150–200 mg/m^2/d for 5 d q28d	19	*CR:* 1 *PR:* 3 *SD:* 6 *PD:* 7	22.2	2.2	9.9	*Hematologic:* 5 *Nonhematologic:* 9
Balmaceda et al.[45]	Phase II, single-arm, multicenter. Median age: 43 y; 1st relapse: $n = 48$; $\geq$2 relapses: $n = 20$	No (previous non-nitrosourea: $n = 7$; nitrosourea: $n = 33$; none: $n = 28$)	200 mg/m^2 initial dose, then 9 consecutive doses at 90 mg/m^2 q12h for 28 d; increased to 100 mg/m^2 q12h in absence of toxicity	68	*CR:* 3 *PR:* 18 *SD:* 22 *PD:* 19	35	4.0	9.0	NA
Temozolomide-Pretreated Population									
Franceschi et al.[48]	Retrospective analysis	Yes	150–200 mg/m^2/d for 5 d, q28d in 13 pts, 25 mg/m^2/d continuously in 1 pt	9	*CR:* 2 *PR:* 2 *SD:* 2 *PD:* 3	NA	7.0	12+	*Hematologic:* 1 *Nonhematologic:* 0

Continued

Table 3. *Continued*

Reference	Study Design/Population	TMZ Pretreatment	TMZ Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Kong et al.[49]	Pilot study, metronomic. Median age: 48.3 y	Yes	40 mg/m^2/d (3 mo)	12	*CR:* 0 *PR:* 2 *SD:* 5 *PD:* 5	58.3	6.0	11	*Hematologic:* 0 *Nonhematologic:* 0
Wick et al.[47]	Prospective, nonrandomized: alternating weekly regimen. Median age: 51 y	9/64 pts had received TMZ (+ CCNU)	150 mg/m^2 on days 1–7 and days 15–21 q28d (1-wk on, 1-wk off)	64	NA	43.8	5.5	NA	NA
Wick et al.[54b]	Retrospective analysis, 3 centers, 2000–2007. Median age: 52 y. *2 cohorts:* TMZ escalation with progression during TMZ vs TMZ rechallenge after SD and disease-free interval	Yes	75 mg/m^2/d (days 1–42 during radiotherapy), plus 150–200 mg/m^2/d for 5 d q28d *or* 150–200 mg/m^2/d for 5 d q28d *or* 150 mg/m^2/d for 1-wk on, 1-wk off *or* 75 mg/m^2/d for 21 d q28d *or* 40 mg/d continuous[c]	47	NA	27.7 (progressive cohort 26.3 vs stable cohort 28.6%)		5.8 (progressive cohort 6.6 vs stable cohort 5.3)	*Hematologic:* 22 *Nonhematologic:* 10
Berrocal et al.[50]	Phase II, multicenter	Yes	85 mg/m^2 for 21 d q28d	GB: 27 AA: 15 Misc: 5	*CR:* 0 *PR:* 2 *SD:* 15[a] *PD:* 30[a]	0	NA	5.1[a]	NA
Perry et al.[51]	Phase II, continuous, dose-intense (RESCUE study), multicenter. Pts prospectively divided into 3 groups (early, extended, and rechallenge) per timing of progression during adjuvant therapy	Yes	50 mg/m^2/d continuous for max 1 y or progression	91	NA	23.9 (early 27.3; extended 7.4; rechallenge 35.7)	NA (early 3.6; extended 1.8; rechallenge 3.7)	9.3	NA
Kong et al.[52]	Phase II, low-dose, continuous (metronomic). Median age: 51 y	Yes	40–50 mg/m^2/d	38	*CR:* 0 *PR:* 2 *SD:* 21	32.5	4.0	9.6	*Hematologic:* 4 *Nonhematologic:* 0

Hammond et al.[53] (prelim results only)	Phase II, dose-intense, single-arm, 1st recurrence. Median age: 57 y; median KPS: 90	Yes	75–100 mg/m^2/d for 21 d q28d	47	*CR:* 0 *PR:* 6 *SD:* 18	23	2.3	13	*Hematologic:* 7 *Nonhematologic:* NA
Randomized Studies									
Yung et al.[23]	Phase II, randomized, multicenter, open-label. Median age: 51–52 y; 1st relapse: 100%	No (65%–68% of pts received prior nitrosourea)	TMZ 150–200 mg/m^2/d for 5 d q28d *or* procarbazine 150 mg/m^2/d (or 125 mg/m^2/d if prior chemotherapy) p.o. for 28 d, repeated q56d	112 113	*CR:* 0 *PR:* 6 *SD:* 45 *CR:* 0 *PR:* 6 *SD:* 31	21 8	2.9 1.9	NA	*Hematologic:* 14 *Nonhematologic:* 12 *Hematologic:* 9 *Nonhematologic:* 17
Brada et al.[55]	Prospective, randomized 1st progression: 100%	No (chemotherapy-naive)	TMZ 200 mg/m^2 for 5 d *or* TMZ 100 mg/m^2 for 21 d *or* PCV	GB: 72 AA: 15 GB: 66 AA: 15 GB: 139 AA: 23	NA	NA	5.0[a] 4.2[a] 3.6[a]	8.5[a] 6.6[a] 6.7[a]	*Hematologic:* 38[a] *Nonhematologic:* 37[a] *Hematologic:* 28[a] *Nonhematologic:* 38[a] *Hematologic:* 57[a] *Nonhematologic:* 64[a]

Abbreviations: AA, anaplastic astrocytoma; CCNU, lomustine; CR, complete response; GB, glioblastoma; KPS, Karnofsky performance score; mOS, median overall survival; mPFS, median progression-free survival; PCV, procarbazine, CCNU, and vincristine; PD, progressive disease; PFS6, 6-month PFS rate; PR, partial response; pts, patients; SD, stable disease.
For the most part, only GB data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.
*Disease PFS and OS were calculated from beginning of retreatment with TMZ.
[a]Data are presented for GB patients only except for the Berrocal study,[50] where 27 patients had GB, 15 had AA, and 5 had miscellaneous brain tumors, and the Brada study,[55] where 277 patients had GB, 53 had AA, and 20 had miscellaneous brain tumors.
[b]Retrospective study.
[c]11 patients also received 13-cis-retinoic acid or pegylated liposomal doxorubicin.

Toxicity following single-agent TMZ therapy after rechallenge is outlined in Table 3. Grades 3 and 4 hematologic adverse events were reported in most studies, although there was no evidence of cumulative toxicity. Considering the small numbers of patients in most studies and the wide range of TMZ regimens tested, there was no evidence that one metronomic schedule was advantageous over another in terms of safety.

Bevacizumab monotherapy trials—Bevacizumab is a human recombinant monoclonal antibody to vascular endothelial growth factor (VEGF), a critical mediator of tumor angiogenesis.[57,58] Bevacizumab was approved in 2009 by the FDA in the United States for the treatment of recurrent glioblastoma based on response rate, with durable responses relative to historical controls from noncomparative phase II trials[59,60]; it is also available for use in various other countries throughout the world, but not in the European Union. The rejection in Europe was based on the absence of a randomized trial with a bevacizumab-free control arm.

Three prospective phase II trials and 1 retrospective analysis have evaluated bevacizumab monotherapy in 233 TMZ-pretreated patients with recurrent or progressive disease (Table 4).[59–62] Three studies used an identical dosage regimen of 10 mg/kg i.v. every 2 weeks,[59,60,62] whereas 1 study administered 15 mg/kg every 3 weeks.[61] PFS6 ranged 25%–42.6% with a median OS of 6.5–9.2 months (Table 4). Radiographic responses were encouraging, with complete and partial responses reported in 62/183 patients (33.9%).[59,60,62] Grades 3 and 4 toxicity across the 4 studies was primarily nonhematologic and included hypertension, thromboembolic events, and fatigue. Prospective phase III studies are needed to determine more clearly the role of bevacizumab in the management of patients with recurrent or progressive glioblastoma. Meanwhile, data from 2 large randomized trials, AVAglio and Radiation Therapy Oncology Group (RTOG) 0825, adding bevacizumab to TMZ chemoirradiation, are likely to shape the future standards of care both at diagnosis and at recurrence.

Other anti-angiogenic agents—Various novel agents targeting potential regulators critical to glioblastoma cell growth, invasion, and angiogenesis have been evaluated in phase II trials in patients with recurrent disease. The VEGF receptor (VEGFR) inhibitor cediranib was explored in patients with recurrent glioblastoma in a very sophisticated fashion using advanced neuroimaging and biomarker studies.[63,64] PFS6 of 31 patients with recurrent glioblastoma treated with cediranib monotherapy at a starting dose of 45 mg/d was 25.8%. Response rates were 56.7% for 3-dimensional measurements and 27% for 2-dimensional measurements. Toxicities were moderate. Changes in plasma placental growth factor, basic fibroblast growth factor, matrix metalloproteinase (MMP) 2, soluble VEGFR1, stromal cell–derived factor 1, soluble Tie2, and urinary MMP-9/neutrophil gelatinase-associated lipocalin activity in response to cediranib were associated with radiographic response or survival.[64]

Aflibercept (VEGF trap), a recombinant fusion protein that inhibits both VEGF and placental growth factor, was administered to 42 patients with recurrent glioblastoma at first relapse.[65] Efficacy of VEGF trap as a single agent for recurrent disease was minimal, with PFS6 of 7.7%, although 2 patients had durable response (alive at >150 wk). Furthermore, grade 3 nonhematologic toxicity was common and included fatigue and hypertension. XL184, an inhibitor of MET, VEGFR2, and RET, was given p.o. (125 mg/d or 175 mg/d) to 124 patients with recurrent glioblastoma.[66] Modest activity was observed in patients with and without prior anti-angiogenic exposure. Overall, interim PFS6 for the 125-mg and 175-mg cohorts were >25% and 21%, respectively.[67] The most common grades 3 and 4 toxicities were fatigue (23%), hypophosphatemia (10%), serum lipase elevation (10%), and alanine aminotransferase elevation, headache, lymphopenia, and convulsion (9% each).

Cilengitide, an inhibitor of αvβ3 and αvβ5 integrin receptors, showed modest single-agent activity, ie, PFS6 of 15% and median OS of 9.9 months, following a 2000-mg twice-daily continuous regimen among 40 patients with recurrent glioblastoma (Table 4).[68] Significant hematologic or nonhematologic toxicities following single-agent cilengitide therapy were uncommon. A phase II trial among 26 evaluable patients with recurrent glioblastoma also found that cilengitide was only modestly effective (PFS6 = 12%).[69]

TMZ-containing combination trials—Over the last decade, more than a dozen phase I and II studies have investigated the efficacy and safety of TMZ in combination with bevacizumab,[70,71] nitrosoureas,[72,73] and interferon,[74] as well as a plethora of conventional/miscellaneous chemotherapeutic agents, such as irinotecan, pegylated doxorubicin, cisplatin, capecitabine, and sorafenib, for recurrent or progressive glioblastoma (Table 5).[75–85] In general, the efficacy findings following TMZ combination therapy failed to indicate a significant advantage over TMZ or bevacizumab monotherapy regimens. However, evaluation of these studies is hampered by small sample sizes, heterogeneous study populations (TMZ-naive vs TMZ-pretreated; varied number of recurrences; number and type of prior therapies; time from last treatment to progression), and various TMZ dosing regimens. Several recently conducted combination studies in TMZ-pretreated patients deserve mention.

Desjardins and colleagues[71] evaluated the combination of protracted TMZ (50 mg/m^2/d) and bevacizumab (10 mg/kg i.v. every 2 wk) in 32 TMZ-pretreated patients who predominantly were experiencing a first or second recurrence (94%). A radiographic response (all partial) was observed in 9/32 (28%) patients. PFS6 was 18.8% with a median OS of 8.7 months. Not surprisingly, patients not receiving dexamethasone had a significantly higher PFS6 than did those receiving steroids (31.3% vs 6.3%; $P = .03$). No difference in

Table 4. Bevacizumab monotherapy and miscellaneous anti-angiogenic trials in recurrent or progressive glioblastoma[a]

Reference	Study Design/ Population	TMZ Pretreatment	Anti-angiogenic Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Bevacizumab Monotherapy									
Friedman et al.[59]	Phase II, multicenter, open-label. 1st relapse: $n = 69$; 2nd relapse: $n = 16$	Yes	10 mg/kg i.v. q2wk (28-d cycle)	85	*CR:* 1 *PR:* 23	42.6 (1st relapse 46.4 vs 2nd relapse 27.8)	4.2 (1st relapse 4.4 vs 2nd relapse 3.1)	9.2 (1st relapse 9.1 vs 2nd relapse 9.2)	*Hematologic:* 3 *Nonhematologic:* 36
Kreisl et al.[60]	Phase II. 1st recurrence; median age: 53 y; median KPS: 90	Yes	Initial monotherapy with 10 mg/kg i.v. q2wk (28-d cycle)	48	*CR:* 1 *PR:* 16	29	3.7	7.2	*Hematologic:* 1 *Nonhematologic:* 12
Raizer et al.[61]	Phase II	Yes	15 mg/kg q3wk	GB: 50	NA	25	NA	6.5	NA
Chamberlain et al.[62]	Retrospective review, 2005–2008. Pts aged 36–70 y. Salvage regimen: PCV: $n = 21$; CYC: $n = 13$; $n = 13$ underwent repeat surgery	Yes	10 mg/kg i.v. q2wk (14-d cycle) (median 2 cycles received)	50	*CR:* 0 *PR:* 21 *SD:* 0 *PD:* 29	42	10	8.5	*Hematologic:* 1 *Nonhematologic:* 11
Miscellaneous Anti-angiogenic Therapies									
Ahluwalia et al., [29] Batchelor et al.[30]	Phase III, multicenter, double-blind, randomized 1:2:2. Median age: 54 y	Yes	CCNU 110 mg/m^2 q6wk + placebo *or* CED 30 mg/d *or* CED 20 mg/d + CCNU 110 mg/m^2 q6wk	65 131 129	*CR:* 0 *PR:* 5 *SD:* 23 *PD:* 23 *CR:* 1 *PR:* 17 *SD:* 76 *PD:* 10 *CR:* 2 *PR:* 19 *SD:* 67 *PD:* 19	24.5 16 34.5	2.73 3.1 4.2	9.8 8.0 9.4	*Hematologic:* 30 *Nonhematologic:* 16 *Hematologic:* 7 *Nonhematologic:* 66 *Hematologic:* 116 *Nonhematologic:* 57
de Groot et al.[65]	Phase II, single-arm, 2007–2008. 1st relapse; Median age: 55 y; Median KPS: 90	Yes	Aflibercept (VEGF trap) 4 mg/kg i.v. on day 1 of q2wk cycle	42	*CR:* 0 *PR:* 7 *SD:* NA *PD:* NA	7.7	2.8	9.1	NA
Wen et al.[67,115]	Phase II randomized. Median age: 55 y; 34% received prior anti-angiogenic therapy; 2nd relapse: 34%	NA	XL184 125 mg p.o. *or* 175 mg q.d	78 46	NA	>25 21	NA	NA	NA

Continued

Table 4. *Continued*

Reference	Study Design/ Population	TMZ Pretreatment	Anti-angiogenic Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Reardon et al.[68]	Phase II randomized, 2004–2005 ≤1 prior chemotherapy regimen. Median age: 52 y; 1st recurrence: 100%	Yes (99%)	CIL 500 mg *or* 2000 mg, 2×/wk on a continuous basis	41[a] 40[a]	*CR:* 0[a] *PR:* 2[a] *SD:* NA *PD:* NA *CR:* 0[a] *PR:* 5[a] *SD:* NA *PD:* NA	10[a] 15[a]	NA	6.5[a] 9.9[a]	*Hematologic:* 5[a] *Nonhematologic:* 2[a] *Hematologic:* 3[a] *Nonhematologic:* 2[a]
Gilbert et al.[69]	Phase II, single-agent, randomized. Progressive disease following radiotherapy. Median age: 54 y	NA	CIL i.v. 500 or 2000 mg × 3 doses (on days −8, −4, and −1), followed by resection, then 2000 mg 2×/wk	26	NA	12	1.9	NA	*Hematologic:* 8 *Nonhematologic:* 1

Abbreviations: CCNU, lomustine; CED, cediranib; CIL, cilengitide; CR, complete response; CYC, cyclophosphamide; GB, glioblastoma; KFS, Karnofsky performance score; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PCV, procarbazine, CCNU, and vincristine; PD, progressive disease; PFS6, 6-month PFS rate; PR, partial response; pts, patients; SD, stable disease.

For the most part, only GB data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.

*Disease PFS and OS were calculated from beginning of retreatment.

[a]Data presented are for GB patients only, except for Reardon,[68] where 6 patients had either anaplastic astrocytoma or low-grade glioma.

survival was observed between patients who had experienced disease progression on 5-day TMZ before enrollment vs those who did not progress on 5-day TMZ. *MGMT* status, determined in 21 patients, did not appear to be related to outcome. The regimen was well tolerated and characterized primarily by nonhematologic toxicities; 2 patients discontinued therapy secondary to toxicity (prolonged thrombocytopenia and grade 4 pancreatitis).

Gaviani et al.[73] evaluated the combination of TMZ and fotemustine in 10 patients with recurrent disease following chemoradiation.[73] The study was terminated early (planned enrollment of 105) because of severe hematologic toxicities (predominantly grades 3 and 4 thrombocytopenia and granulocytopenia). The authors concluded that this combination does not merit further study.

A protracted daily TMZ (50 mg/m^2/d) + sorafenib regimen had very limited activity, despite a good safety profile, in 32 patients with recurrent disease.[75] Only 1 patient achieved a partial response. PFS6 was very low (9.4%). Importantly, approximately 50% of enrolled patients had 2 or more prior progressions and had progressed while receiving 5-day TMZ, and more than one-third of patients had failed either prior bevacizumab or VEGFR inhibitor therapy. Despite potentially complementary direct and indirect mechanisms of antitumor activity, the TMZ + sorafenib combination was not effective in this phase II trial. The poor results may be attributed to heavy pretreatment, higher failure rate to previous bevacizumab therapy, lack of selection of patients with sorafenib target expression, and the relatively high use of CYP3A-inducing antiepileptic drugs that may have compromised sorafenib activity.

The combination of TMZ and afatinib (40 mg/d), an irreversible blocker of epidermal growth factor receptor, was investigated in a phase II study.[82] PFS6 by independent review was 10% for the combination compared with 3% for afatinib alone ($P = .008$) and 23% for TMZ alone ($P = .59$). Serious adverse events (grade ≥ 3) for the combination were primarily nonhematologic (eg, diarrhea or skin reactions).

A retrospective study of 28 patients (of whom 24 received TMZ pretreatment) found that the combination of continuous low-dose TMZ (10 mg/m^2 b.i.d.) and celecoxib (200 mg/d) had some activity in treating recurrent glioblastoma without significant toxicity.[84] The majority of patients (86%) were being treated for their first recurrence. Notably, 19 (68%) patients underwent resection before retreatment. PFS6 was 43%. *MGMT* promoter methylation did not predict a favorable outcome. The only severe toxicity was grade 3 lymphopenia in 1 patient.

The combination of TMZ and O^6-benzylguanine, an MGMT-depleting agent, was tested in 34 patients with recurrent disease.[83] One patient responded to this regimen. PFS6 was low (9%) with median OS of 4.5 months. This 1-day TMZ combination regimen failed to restore TMZ sensitivity in patients with recurrent glioblastoma.

Table 5. Temozolomide-containing combination trials for recurrent or progressive glioblastoma[a]

Reference	Study Design/Population	TMZ Pretreatment	Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Temozolomide + Bevacizumab Combinations									
Desjardins et al.[85]	Phase II. Median age: 56 y; 1st progression: $n = 15$; 2nd progression: $n = 15$; 3rd progression: $n = 2$	Yes (prior BEV 4 pts)	TMZ 50 mg/m^2/d + BEV 10 mg/kg i.v. q2wk	32	*CR:* 0 *PR:* 9 *SD:* 16 *PD:* 7	18.8	3.7	8.7	*Hematologic:* 0 *Nonhematologic:* 11 (including 1 grade 5 infection)
Verhoeff et al.[70]	Phase Median age: 55 y	Yes	TMZ 50 mg/m^2/d q3wk + BEV 10 mg/kg i.v. q3wk	15	NA	6.7	2.4	3.7	NA
Temozolomide + Nitrosourea Combinations									
Gaviani et al.[73]	Noncomparative, single-arm	Yes	TMZ 150 mg/m^2 on days 1–7 and 15–21 of 28-d cycles + FOT single i.v. infusion 110 mg/m^2 monthly on day 15	20 (only 10 evaluable)	NA	40	4.3	NA	*Hematologic:* Severe *Nonhematologic:* NA
Temozolomide + Interferon Combinations									
Groves et al.[74]	Two phase II noncomparative studies. Short-acting IFN: median age: 55 y; median KPS: 80. PEG-IFN: Median age: 56 y; median KPS: 90	No	TMZ 150–200 mg/m^2/d for 5 days every month + short-acting IFN-α2b: 4 MU/m^2 s.c. 3 ×/wk *and* TMZ 150–200 mg/m^2/d × 5 days every month + long-acting PEG-IFN-α2b s.c. 0.5 μg/kg/wk	29 26	*CR:* 0 *PR:* 4 *SD:* 18 *CR:* 0 *PR:* 1 *SD:* 17	31 38	3.6 4.4	7.2 10.0	*Hematologic:* 18 *Nonhematologic:* 10 *Hematologic:* 17 *Nonhematologic:* 23
Temozolomide + Miscellaneous Chemotherapy Combinations									
Reardon et al.[75]	Phase II. single-arm; Median age: 53.6 y;	Yes	TMZ continuous daily 50 mg/m^2/d + sorafenib 400 mg 2 ×/d	32	*CR:* 0 *PR:* 1 *SD:* 15 *PD:* 16	9.4	1.5	9.7	*Hematologic:* 1 *Nonhematologic:* 27
Eisenstat et al.[82]	Phase II. median age: 58 y; 1st recurrence: 100%	Yes (prior chemoradiotherapy)	TMZ 75 mg/m^2 for 21 d per 28-d cycle + afatinib 40 mg/d *or* afatinib 40 mg/d *or* TMZ 75 mg/m^2 for 21 d per 28-d cycle	39 41 39	*CR:* 1 *PR:* 2 *SD:* 14 *PD:* 17 *CR:* 0 *PR:* 1 *SD:* 14 *PD:* 23 *CR:* 0 *PR:* 4 *SD:* 21 *PD:* 13	10 3 23	1.5 1.0 1.9	NA	*Hematologic:* 0 *Nonhematologic:* 11 *Hematologic:* 5 *Nonhematologic:* 10 *Hematologic:* 3 *Nonhematologic:* 17
Quinn et al.[83]	Phase II, open-label	Yes	TMZ 472 mg/m^2 p.o. on day 1 of 28-d cycle + O^6-BG 1-h infusion of 120 mg/m^2, followed immediately by a 48-h infusion of 30 mg/m^2 on day 1 of 28-d cycle	34	*CR:* 0 or 1 *PR:* 0 or 1 *SD:* NA *PD:* NA	9	1.8	4.5	NA[b]
Stockhammer et al.[84]	Retrospective analysis. 1st recurrence: $n = 24$; 2nd recurrence: $n = 4$	Yes (except 4 pts)	TMZ 10 mg/m^2 b.i.d. + CEL 200 mg/d	28	*CR:* 0 *PR:* 3 *SD:* 15 *PD:* 10	43	4.2	16.8	*Hematologic:* 1 *Nonhematologic:* NA

Continued

Table 5. *Continued*

Reference	Study Design/Population	TMZ Pretreatment	Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Boiardi et al.[76]	Nonrandomized, retrospective	No	TMZ 200 mg/m^2 days 1–5 every 28 days + resection + mitoxantrone, delivered through Rickam reservoir (4 mg/d on days 1–5 q28d) *or* TMZ + resection *or* TMZ 200 mg/m^2 days 1–5 q28d alone	65 50 161	NA	70.7 64 39.3	NA	11 8 5	NA
Reardon et al.[77]	Phase I	No	TMZ 200 mg/m^2/d days 1–5 + CPT-11 40 mg/m^2 to 375 mg/m^2 i.v. on weeks 1, 2, 4, and 5 of each 6-wk cycle	91	NA[b]	27.3	12.8	NA[b]	NA[b]
Chua et al.[78]	Phase II, open-label. Median age: 55 y; 1st relapse	No (prior chemotherapy: 9%)	TMZ 200 mg/m^2 p.o. on days 1–5 q4wk + liposomal DOX 40 mg/m^2 i.v. on day 1 q4wk	22	*CR:* 1 *PR:* 3 *SD:* 11 *PD:* 7	32	3.6	8.2	*Hematologic:* 8 *Nonhematologic:* 9
Silvani et al.[79]	Phase II, single-center. Median time from 1st diagnosis: 8 mo	No	TMZ 200 mg/m^2 on days 2–6 q4wk + CIS 40 mg/m^2, on days 1 and 2 q4wk	20	*CR:* 0 *PR:* 2 *SD:* NA *PD:* NA	35	NA	NA[b]	NA[b]
Brandes et al.[80]	Phase II, multicenter. median age: 53.4 y; Median KPS: 80	No (chemotherapy-naive)	TMZ 130 mg/m^2 bolus followed by 9 doses of 70 mg/m^2 q12h (total of 5 d) from day 2 q4wk (if no hematologic toxicity dose, increased to 100 mg/m^2) + CIS 75 mg/m^2 on day 1 q4wk	50	*CR:* 1 *PR:* 9 *SD:* NA *PD:* NA	34	4.3	11.2	*Hematologic:* 13 *Nonhematologic:* 4

Abbreviations: BEV, bevacizumab; CEL, celecoxib; CIS, cisplatin; CPT-11, irinotecan; CR, complete response; DOX, doxorubicin; FOT, fotemustine; IFN, interferon; KPS, Karnofsky performance score; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; O^6-BG, O^6-benzylguanine; PD, progressive disease; PEG-IFN, PEGylated interferon; PFS6, 6-month PFS rate; PR, partial response; SD, stable disease.

For the most part, only glioblastoma data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.

*Disease PFS and OS were calculated from beginning of retreatment with TMZ.

[a]Data are presented for glioblastoma patients only.

[b]Data are not available because not presented separately for glioblastoma and other glioma patients.

Overall, the TMZ combination studies available to date do not suggest that one particular chemotherapy combination regimen is more effective than administration of TMZ alone.

***Bevacizumab-containing combination trials*—**In addition to the studies that evaluated bevacizumab in combination with TMZ (see prior section above), another series of studies have been conducted that evaluated bevacizumab and miscellaneous other agents, including irinotecan, carboplatin, etoposide, erlotinib, and cetuximab, in patients with recurrent glioblastoma (Table 6).[59,86–97] Unfortunately, the bevacizumab combination studies performed on a background of standard surgery, radiotherapy, and concurrent/adjuvant TMZ therapy did not provide clear insight into new options for recurrent disease. Six studies in 357 evaluable patients, including 1 retrospective analysis, evaluated bevacizumab in combination with irinotecan.[59,88,89,92,94,96] In theory, the combination of irinotecan and bevacizumab might improve efficacy owing to a synergy of anti-angiogenic and cytostatic properties. Most trials employed a bevacizumab dosage of 10 mg/kg (range, 5–15 mg/kg) every 2 weeks. Irinotecan was administered every 2 weeks in doses of 125 mg/m^2 without or 340 mg/m^2 with coadministration of enzyme-inducing antiepileptic drugs. Overall, PFS6 was 30.0%–50.3% with median OS of 6.1–9.7 months. One phase II trial provided PFS6 stratified by patients experiencing first and second recurrences: 49% and 57.1%, respectively.[59] Overall, no additional benefit of irinotecan over bevacizumab alone became apparent.

A small phase II study (32 evaluable patients) tested the triple combination of bevacizumab, irinotecan, and cetuximab in patients experiencing a first relapse within 6 months of standard TMZ therapy.[87] Complete and partial responses were achieved in 2/32 (6.3%) and 9/32 (28.1%) patients, respectively. PFS6 was 33% with median OS of 7.0 months. A total of 4 and 20 grades 3/4 hematologic and nonhematologic events, respectively, were reported. The addition of cetuximab was relatively well tolerated, except for skin toxicity; however, overall efficacy did not appear to be enhanced with the addition of cetuximab to the bevacizumab + irinotecan combination regimen.

A retrospective analysis of triple combination therapy with bevacizumab, carboplatin, and etoposide included 6 patients treated at first ($n = 2$), second ($n = 2$), third ($n = 1$), or fourth ($n = 1$) recurrence.[86] All patients had received focal radiation therapy and concurrent and adjuvant TMZ following initial diagnosis and surgical intervention. Following 2 to 3 cycles of the triple drug regimen, a partial response was achieved in 5/6 patients. The combination was generally well tolerated. However, only marginally improved survival end points were reported: 22% PFS6 and median OS of 6.9 months. Recurrent tumors were was found in 4/5 patients with an initial response.

Reardon et al[91] evaluated the efficacy of bevacizumab and etoposide among 27 patients with primarily first recurrences ($n = 14$). Complete and partial response was observed in 1 and 6 patients, respectively. PFS6 of 44.4% and median OS of 10.2 months were reported. Notably, high VEGF expression (>30% of cells; $P = .006$) detected by immunohistochemistry of archival, paraffin-embedded tumor sections was associated with a better PFS.

Sathornsumetee et al[90] evaluated bevacizumab in combination with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in a phase II study of 24 evaluable TMZ-pretreated patients with recurrent glioblastoma. PFS6 and median OS were 29.2% and 10.3 months, respectively. Survival end points of patients treated more than 3 months postradiotherapy were similar to those of the overall population. In summary, this combination did not appear to provide improved survival benefits compared with historical bevacizumab-containing regimens.

Bevacizumab was also studied in combination with hypofractionated stereotactic radiotherapy in a small pilot study.[98] The investigators hypothesized that bevacizumab might increase tumor sensitivity to radiotherapy via depletion of VEGF and reduction of its signaling. Among 20 evaluable patients with recurrent glioblastoma (median number of recurrences = 1), PFS6 was 65% with median OS of 12.5 months. Most patients had reirradiation in the same local region as originally treated. The combination was well tolerated with no unusual adverse events in this heavily pretreated population. Notably, this bevacizumab/radiotherapy combination was superior to that applied in another study, where patients received reirradiation alone for recurrent disease.[99] This approach deserves further consideration for the minority of eligible patients.

Significance of MGMT *Promoter Methylation Status in Recurrent Disease*

MGMT, a cellular DNA repair protein, rapidly reverses methylation via its suicide inactivation, thereby minimizing mutations and replication errors and restoring normal cellular homeostasis.[100–102] Patients whose tumors have a methylated *MGMT* promoter, which probably results in lower MGMT protein levels, are more likely to respond to alkylating agents because the tumor cells are unable to repair chemotherapy-induced DNA damage.[103,104]

A direct, real-time methylation-specific PCR assay (MSP) is the current preferred method for determining *MGMT* status.[105] The MSP assay detects cytosine–phosphatidyl–guanine island methylation with high sensitivity and specificity in clinical samples and has been shown to be highly reproducible compared with the clinically validated, nested, gel-based assay.[5] At present, methylation assays remain the most reliable technique for assessing the prognostic impact of MGMT status.

Two important issues are evident regarding *MGMT* status and recurrent glioblastoma: (i) whether changes in status occur between primary and recurrent glioblastoma and (ii) whether positive status correlates with better outcome following recurrent disease.

Table 6. Bevacizumab-containing combination trials (other than TMZ) in recurrent or progressive glioblastoma[a]

Reference	Study Design/Population	TMZ Pretreatment	Bevacizumab Regimen	*n*	Radiographic Response (%)	PFS6* (%)	mPFS* (mo)	mOS* (mo)	WHO Grades 3/4 Toxicities (*n*)
Bevacizumab + Temozolomide Combinations									
Bevacizumab + Miscellaneous Chemotherapy Combinations									
Francesconi et al.[86]	Retrospective, single-center review	Yes	BEV 10 mg/kg i.v. on day 2 + CP i.v. on day 1 + ETO phosphate 113.6 mg/m^2 (equivalent to ETO 100 mg/m^2) i.v., days 1–3. Treatment repeated q3wk	6	*CR:* NA *PR:* 5 *SD:* NA *PD:* NA	22	4.4	7.0	*Hematologic:* 2 *Nonhematologic:* NA
Hasselbalch et al.[87]	Phase II. Recurrent primary (within 6 mo of standard TMZ concomitant and adjuvant therapy)	Yes	BEV 5 mg/kg first 10 pts, then 10 mg/kg i.v. q2wk + CPT-11 340 mg/m^2 i.v. if receiving EIAED or if not, 125 mg/m^2 q2wk + CET 400 mg/m^2 i.v. as loading dose, followed by 250 mg/m^2/wk	43 (32 evaluable)	*CR:* 2 *PR:* 9 *SD:* 17 *PD:* 4	33	3.7	7.0	*Hematologic:* 4 *Nonhematologic:* 20
Sathornsumetee et al.[90]	Phase II, open-label. Median age: 52.4 y; 1st relapse: 52%; 2nd relapse: 36%; 3rd relapse: 12%	Yes	BEV 10 mg/kg i.v. q2wk + ERL 500 mg/kg/d i.v. if receiving EIAED or, if not, 200 mg/kg/d (42-d cycle)	25 (24 evaluable)	*CR:* 1 *PR:* 11 *SD:* 10 *PD:* 2	29.2	4.2	10.3	*Hematologic:* 4 *Nonhematologic:* 64
Gilbert et al.[96]	Phase II: RTOG 0625. Median age: 57 y; median KPS: 80	Yes	BEV 10 mg/kg + CPT-11 200 mg/m^2 q2wk	57	*CR:* NA *PR:* NA *SD:* NA *PD:* NA	37	NA	NA	*Hematologic:* 14 *Nonhematologic:* NA
Nghiemphu et al.[89]	Retrospective chart review, Jul 2005–Jul 2006, single-center. BEV cohort: median age: 55 y; median KPS: 90; 1st relapse: 50%; 2nd relapse: 32%; 3rd relapse: 18%	Yes	BEV 5 mg/kg q2wk + chemotherapy: CPT-11: 31; CP: 8; CCNU: 3; ETO: 2 (dosages not provided)	Chemotherapy w/ BEV: 44 vs chemotherapy w/o BEV: 79	NA	41 vs 18	4.25 vs 1.82	9.0 vs 6.1	NA
Friedman et al.[59]	Phase II, multicenter, open-label. Median age: 57 y; 1st relapse: 80%; 2nd relapse: 20%	Yes	BEV 10 mg/kg q2wk + CPT-11 340 mg/m^2 i.v. if receiving EIAED or if not, 125 mg/m^2 q2wk	82	*CR:* 2 *PR:* 29 *SD:* NA *PD:* NA	50.3 (1st relapse: 49; 2nd relapse: 57.1)	5.6	8.7	*Hematologic:* 20 *Nonhematologic:* 62
Narayana et al.[88]	Prospective, consecutive analysis, 2005–2007	Yes (except 1 pt)	BEV 10 mg/kg i.v. q2wk for 4 doses in 8-wk cycle + CPT-11 125 mg/m^2/d q2w or CP (dose to achieve AUC = 6 q4wk)	GB: 37 AA: 24	*CR:* 7[a] *PR:* 32[a] *SD:* 11[a] *PD:* 3[a]	44.3[a]	5.0[a]	9.0[a]	NA

Vredenburgh et al.[94]	Phase II	Yes	BEV 10 mg/kg i.v. q2wk + CPT-11 340 mg/m^2 i.v. if receiving EIAED or if not, 125 mg/m^2, q2wk	23	*CR:* 1 *PR:* 13 *SD:* 8 *PD:* 1	30	4.7	9.3	NA
Vredenburgh et al.[92]	Phase II. *Both cohorts:* median age 48 y; median number of progressions: 2	Yes	*Cohort 1*: BEV 10 mg/kg i.v. q2wk + CPT-11 340 mg/m^2 i.v. if receiving EIAED or if not, 125 mg/m^2, q2wk (6-wk cycle) *Cohort 2*: BEV 15 mg/kg i.v. q21d + CPT-11 340 mg/m^2 i.v. if receiving EIAED or if not, 125 mg/m^2 on days 1, 8, 22, and 29 (6-wk cycle)	23 (35 total) 12	NA	46[c]	5.6[c]	9.8[c]	NA
Reardon et al.[91]	Phase II, open-label. Median age: 54.3 y; 1st relapse: 52%; 2nd relapse: 30%; 3rd relapse: 19%	NA	BEV 10 mg/kg i.v. q2w + ETO 50 mg/m^2 daily for 21 consecutive days each month	27	*CR:* 1 *PR:* 5 *SD:* 19 *PD:* 2	44.4	4.2	10.8	*Hematologic:*15 *Nonhematologic:* 17 (including 1 grade 5 thrombosis; includes only those AEs that occurred in $\geq$10% of pts)
Stark-Vance[97]	NA	NA	BEV 5 mg/kg every other wk for 2 doses + CPT-11 125 mg/m^2 qwk for 4 doses, followed by 2-wk rest period	GB: 11; 10 other gliomas	*CR:* 1[a] *PR:* 8[a] *SD:* 11[a] *PD:* 1[a]	NA	NA	NA	NA
Pope et al.[93]	Retrospective database review	NA	BEV + CP, CPT-11, or ETO (dosages NA)	10	*CR:* 0 *PR:* 4 *SD:* 3 *PD:* 3	NA	NA	NA	NA
Norden et al.[95]	Retrospective analysis Jun 2005–Mar 2007. Median age: 50 y; median KPS: 80	Yes	BEV 10 m/kg (1 pt received 5 mg/kg) q2wk + chemotherapy: CPT-11: $n = 47$; CP: $n = 6$; BCNU: $n = 1$; TMZ: $n = 1$	33	NA[b]	42	NA[b]	NA[b]	NA[b]
Gutin et al.[98]	Cohort study. Median age: 56 y; median KPS: 90	NA	BEV 10 mg/kg i.v. q2wk (28-d cycle) (median, 7 cycles) + 30 Gy HFSRT in 5 fractions after first BEV cycle	20	NA[b]	65	7.3	12.5	NA[b]

Abbreviations: AA, anaplastic astrocytoma; AE, adverse event; AUC, area under the curve; BCNU, carmustine; BEV, bevacizumab; CET, cetuximab; CP, carboplatin; CPT-11, irinotecan; CR, complete response; EIAED, enzyme-inducing antiepileptic drug; ERL, erlotinib; ETO, etoposide; GB, glioblastoma; HFSRT, hypofractionated stereotactic reirradiation; inst, institution; mOS, median overall survival; mPFS, median progression-free survival; NA, not available; PD, progressive disease; PFS6, 6-month PFS rate; PR, partial response; pts, patients; SD, stable disease.
For the most part, only GB data are presented in the table. We have reported enrollment numbers for different patient populations only when all data in a paper are presented for combined patient populations.
*Disease PFS and OS were calculated from beginning of retreatment.
[a]Data presented for GB patients only, except for the Narayana study,[88] where 37 patients had GB and 24 patients had AA, and Stark-Vance,[97] where 11 patients had GB and 10 had other high-grade gliomas.
[b]Data are not available because not presented separately for GB, AA, and other glioma patients.
[c]Data are presented for both cohorts combined.

Among 80 patients with recurrent glioblastoma, including 64 patients treated with radiotherapy and TMZ after the first operation, changes in *MGMT* promoter methylation status using the MSP technique were rarely found.[106] Overall, 88.8% of patients showed unchanged methylation status upon comparison of individual pairs of primary and recurrent glioblastomas. Seven patients (8.8%) showed loss or reduction of *MGMT* promoter methylation at recurrence. These findings suggest that *MGMT* retesting is unnecessary in patients with recurrence. Notably, the prognostic significance of *MGMT* status was upheld for patients experiencing a recurrence. Significantly longer PFS and OS were found in patients with *MGMT* promoter-methylated tumors and correlated with favorable outcome under salvage alkylating chemotherapy.

A preliminary report found that patients with a methylated *MGMT* status had a higher median PFS of 7.4 months than did those with an unmethylated status (2 mo; $P = .08$).[53] Median OS was also significantly higher in patients with *MGMT*-methylated tumors (16 mo vs 11.5 mo; $P = .05$). Additionally, the probability of achieving a radiographic response (partial response/stable disease) was higher in patients with *MGMT* promoter methylation ($P = .03$).

Among 24 patients with *MGMT* status determined by MSP, the disease control rate was greater in patients with tumors with a methylated (3/7; 42%) as opposed to an unmethylated (6/17; 35%) *MGMT* promoter.[33] A trend toward a prolonged PFS6 was also observed; however, neither end point achieved statistical significance.

In a prospective report[107] conducted from 2005 to 2007 that included 22 patients who had recurrent glioblastoma and underwent surgery with carmustine wafer implantation, methylated *MGMT* status determined by MSP was correlated with better outcome. Median PFS and OS rates in methylated patients were 8.9 and 14.2 months, respectively, vs 2.7 and 9.2 months in unmethylated patients ($P \leq .031$ for both end points). Notably, this small study also found that *MGMT* status did not appear to change between primary and recurrent tumors.

In contrast, several other studies describe the absence of significant PFS and OS differences with regard to the methylation status of the *MGMT* promoter in patients with recurrent disease.[43,47,52,84,108] In most of these studies, *MGMT* promoter methylation status was analyzed using MSP. The absence of a correlation between *MGMT* promoter status and positive outcome in these studies may be attributed to the overall poor prognosis at glioblastoma recurrence, a small sample size, or the lack of a true association between *MGMT* status and outcome at time of recurrence. In the RESCUE study, 50/120 patients had tissue available for *MGMT* analysis, and 42% were methylated. The use of a continuous daily TMZ regimen at first recurrence in the glioblastoma groups was associated with similar PFS6, time to progression, and OS in both methylated and unmethylated patients.[51] It is unclear whether the absence of correlation in this trial relates to the clinical factors listed previously or may in part be an effect of MGMT depletion with the protracted treatment schedule. Further validation studies in larger patient populations are needed to confirm that *MGMT* status is useful in predicting response to therapy and prognosis in patients with recurrent/progressive disease. The DIRECTOR trial[57] will provide prospective data that may clarify this issue. Yet, the impact of *MGMT* status, if any, is likely to be small and in the range of a few months as can be estimated from the studies that reported any effect at all.

Standard of Care Recommendations for Recurrent/Progressive Glioblastoma

Appropriate management outside of clinical trials requires individualization based on patient age, performance status, histology, extent of initial resection, type of and response to initial therapy, time since diagnosis, and whether the recurrence is local or diffuse.[109] Repeat surgery, reirradiation, and second-line mono- or combination therapy are all directed primarily at reducing tumor burden and extension. All therapies aim to improve neurologic symptoms, such as headaches or seizures; reduce the need for certain medications or lower total daily doses, eg, corticosteroids or antiepileptic drugs; and prevent thromboembolic complications.

Predicting response to subsequent therapy in patients with recurrent disease remains difficult because of the biological complexity of glioblastoma[110] as well as numerous other patient-specific factors. The role of *MGMT* as a prognostic or predictive marker following relapse remains ambiguous. Most contemporary clinical trials include a translational research program, but no biomarkers of practical use have yet been established.[111]

PFS6 and median OS remain the most useful and accessible end points for monitoring outcomes following chemotherapy. OS is commonly considered the gold standard end point because it can be measured objectively and has clinical significance.[112] However, interpretation of OS can be affected by subsequent salvage therapy. PFS relies on a standardized method that defines tumor progression, but its determination can be challenging.[15] Currently, median OS and PFS6 remain the best end points available for assessing therapeutic outcome in patients with recurrent disease. However, earlier PFS assessments also have been shown to similarly predict survival time and may become new end points in future clinical trials.[22]

Despite advanced imaging techniques, detecting tumor progression remains a clinical challenge in patients with glioblastoma because of the complexities of pseudoprogression and radionecrosis.[113] An international expert panel has recently recommended that PFS should be correlated with OS end points and ideally validated with the RANO criteria.[112]

Which patients are most likely to benefit from dose-dense (metronomic) TMZ therapy?—The theoretical benefit of the metronomic approach is that it may deplete MGMT, leading to restoration of TMZ sensitivity in *MGMT*-methylated tumors and/or may limit endothelial cell recovery and upregulate thrombospondin 1, leading to a sustained anti-angiogenic effect.[109,114] Two randomized trials, RTOG 0525 for newly diagnosed patients[6] and BR12 for recurrent malignant glioma patients,[55] failed to demonstrate superiority of dose-intensified TMZ over conventional TMZ. Yet, neither of these trials can answer the question of whether dose-intensified TMZ is a suitable option for patients who did not respond to standard TMZ because this setting was not examined in either trial. Many dose-dense rechallenge schedules have been evaluated as we have already discussed—eg, 7/14 days, 21/28 days, 6/8 weeks, or continuously daily. The RESCUE study provides a glimpse of possible subpopulations that might benefit the most from metronomic TMZ therapy. Patients who progressed after concomitant TMZ/radiotherapy during the 6-month course of adjuvant TMZ as well as patients who progressed later than 2 months after completing adjuvant TMZ therapy appeared to benefit more from continuous TMZ therapy (50 mg/m^2/d for 1 y) compared with those who progressed while undergoing an extended adjuvant treatment of more than 6 months.[51] Larger trials with prospective stratification of patients by extent of prior TMZ therapy are needed to fully answer the question of which patients are best treated by TMZ rechallenge.

Which TMZ schedule provides the best outcome?—Despite the increased number of prospective clinical trials conducted over the past 5 years, available data suggest that 6-month PFS and OS outcomes are similar among the various extended TMZ dose-dense regimens used in patients with recurrent disease. However, most studies were small phase II trials and often included heterogeneous populations—eg, varying types of prior chemotherapy, number of previous relapses—making it difficult to truly compare dose-dense regimens within or between trials. It may all come down to physician/patient preference and convenience, unless the DIRECTOR trial[57] generates a clear signal for 1 of the 2 evaluated regimens.

Which TMZ regimen has the least toxicity and is the best tolerated?—In general, dose-dense TMZ is associated with manageable toxicity in patients with recurrent glioblastoma previously treated with TMZ. Wick et al[54] reported that among the various dose-dense schedules tested in phase II trials, each had a similar distribution of grades 1–4 toxicities. However, compared with a standard 5-of-28-day regimen, dose-dense regimens are associated with an increased incidence and severity of lymphocytopenia.[114] Available data from phase II trials suggest that lymphopenia occurs at a greater rate on the 3-weeks-on/1-week-off regimen compared with the standard regimen. In general, at recurrence, starting at a moderate rechallenge dose may be advisable to identify the individual tolerance of the patients.

Which combination chemotherapies make the most sense?—Currently, no single combination regimen has clearly emerged as a favorite for the treatment of recurrent or progressive glioblastoma. TMZ in combination with cisplatin, fotemustine, interferon, sorafenib, celecoxib, irinotecan, or procarbazine/lomustine/vincristine has not been demonstrated to be more effective than TMZ alone (Table 5). Similarly, various bevacizumab-based combinations were not superior to historical data obtained with bevacizumab alone (Table 6).

Several small studies have investigated the combination of protracted daily TMZ (50 mg/m^2/d for 2–3 wk) and biweekly bevacizumab for recurrent disease.[70,71] This combination provided similar efficacy compared with either agent alone, although heterogeneous patient populations (eg, inclusion of patients who responded and did not respond to upfront therapy) may have confounded the findings.

Conclusions

A plethora of monotherapy and combination chemotherapy strategies have been evaluated in patients with recurrent or progressive glioblastoma. Despite some minor improvements in PFS, no obvious increase in survival has been associated with any particular regimen. Future clinical trials that adopt the revised Macdonald criteria (RANO) may provide new clues as to which agent or combination is most beneficial. Despite definitive data, standard of care guidance for managing patients with recurrent or progressive glioblastoma is evolving. Forthcoming is further insight regarding which patients should undergo a second resection or radiotherapy procedure, how to best use TMZ and bevacizumab therapy, and the value of *MGMT* status assessment in the recurrent setting.

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