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Second-line temozolomide in first recurrent MGMT-methylated glioblastoma after lomustine/temozolomide: Efficacy and safety

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Abstract

Background. The optimal salvage therapy for recurrent MGMT-methylated glioblastoma (GBM), IDH wildtype, remains undefined. While lomustine is often used in clinical trials and considered standard-of-care, cumulative toxicity precludes its use in patients previously treated with lomustine/temozolomide. The role of temozolomide rechallenge in this setting is unclear.

Methods. This monocentric retrospective study included 70 patients with MGMT-methylated GBM, IDH wildtype, who received lomustine/temozolomide as first-line therapy. Descriptive data on second-line therapies were collected, and therapy responses were assessed. Survival outcomes were evaluated using Kaplan-Meier analysis.

Results. Of 55 patients with documented tumor progression, 40 patients received second-line therapy. The most frequently used systemic therapy was temozolomide ($n = 33$, 79% of patients with second-line therapy), with a median number of 6 cycles and hematotoxicity grade 3 or 4 observed in <20% of patients. Among patients receiving temozolomide only, stable disease or partial response was achieved in 53.3%, with a progression-free survival rate at 6 months after first recurrence of 50% and a 1-year OS rate of 45%.

Conclusions. Temozolomide rechallenge is a common, safe, and effective second-line option for patients with MGMT-methylated, IDH wildtype GBM following first-line lomustine/temozolomide therapy. These findings support its consideration as a salvage therapy in appropriate clinical scenarios.

Key points

- Second-line temozolomide is a common and safe salvage therapy in MGMT-methylated GBM after initial therapy with lomustine/temozolomide.
- Second-line temozolomide is effective in recurrent MGMT-methylated GBM after initial therapy with lomustine/temozolomide.

Glioblastoma (GBM), isocitrate dehydrogenase (IDH) wildtype (CNS WHO grade 4), is characterized by diffuse brain infiltration and therapy resistance, leading to a fatal prognosis.[1] In case of progressive disease (PD), referring to tumor recurrence after initial therapy, the prognosis is particularly poor, with median survival times substantially lower than 12 months.[2]

The standard first-line treatment has remained largely unchanged in recent years. Following maximal safe resection, patients typically receive radiochemotherapy with the alkylating agent temozolomide (TMZ) that is applied first concomitant to radiotherapy (RT) followed by 6 adjuvant cycles.[3,4] Additional therapy with tumor-treating fields (TTF) is an additional option based on a positive randomized trial.[5] For the subgroup

Importance of the Study

The optimal salvage therapy for MGMT-methylated glioblastoma (GBM) after first-line treatment with lomustine/temozolomide remains undefined, leading to frequent concerns about limited therapeutic options at recurrence in this specific patient subgroup. This study demonstrates that temozolomide rechallenge at first recurrence is a feasible, safe, and effective treatment strategy. Additionally, it provides encouraging data on the feasibility of combining different therapeutic modalities at recurrence.

Overall, these findings help address concerns regarding salvage treatment options and might offer valuable guidance for clinical decision-making in this challenging clinical setting.

of O^6-methylguanine-DNA methyltransferase (MGMT)-methylated GBM, the addition of lomustine (CCNU) to the standard first-line treatment can be considered. Results from the randomized, open-label phase 3 CeTeG/NOA-09 trial suggest superior survival outcomes for patients receiving the combined CCNU/TMZ regimen compared to standard TMZ treatment, with a median overall survival (OS) of 48.1 months versus 31.4 months.[6] However, while these findings are promising, the superiority of CCNU/TMZ has yet to be definitively confirmed, as the efficacy signal in the NOA-09 trial was observed only in OS prolongation, not in progression-free survival (PFS), and the study's statistical power is considered limited. Encouragingly, a sufficiently powered replication study is currently recruiting (NCT05095376).

Optimal salvage therapy for recurrent GBM remains undefined and may include surgery, re-irradiation, and systemic therapy.[7] Among systemic treatment options, CCNU is broadly considered as the standard-of-care and often serves as control arm for clinical trials. However, its limited efficacy in second-line treatment is reflected by comprehensively reported PFS at 6 months (PFS-6) of less than 30%.[8] Unfortunately, none of the numerous studies conducted over the past years have identified a new recurrence treatment with significant efficacy signal for a broad population of GBM, although efficacy of dabrafenib/trametinib could be seen in the rare tumors harboring a *BRAF*^{V600E} mutation.[9] The vascular endothelial growth factor (VEGF) antagonist bevacizumab, which is considered a salvage therapy in the United States, has not received comprehensive approval in Europe. This is due to its demonstrated improvement in PFS without a corresponding improvement in OS.[10,11] In the prospective randomized EORTC 26101 trial, the median OS for patients receiving CCNU in combination with bevacizumab at recurrence was 9.1 months (8.1-10.1) vs 8.6 months without it (7.6-10.4).[12] For patients with MGMT-methylated GBM, survival time post progression is typically reported within 10-14 months.[12–14] For these patients, TMZ rechallenge may be offered following primary therapy with TMZ. The DIRECTOR[13] trial reported a PFS-6 rate of approximately 40%, along with a 1-year OS rate of around 54%. Notably, in the EORTC 26101 trial,[12] the CCNU treatment arm for MGMT-methylated GBM demonstrated a comparable PFS-6 rate of approximately 30% and a 1-year OS rate of about 50%. In contrast, the REGOMA trial reported a 1-year OS rate of less than 25% for patients with MGMT-methylated GBM treated with CCNU at first recurrence, although subgroup-specific PFS data were not provided.[15]

The lack of data on optimal salvage treatments for GBM is particularly evident in patients who received CCNU/TMZ as first-line therapy. In this context, repeat CCNU is often avoided due to the considerable risk of toxicity, such as cumulative myelotoxicity and pulmonary fibrosis, especially after exceeding 6 cycles.[16] This uncertainty might contribute to a perception of limited salvage treatment options, potentially hindering broader acceptance of CCNU/TMZ as a first-line regimen.

This study analyzed the recurrence treatment strategies for MGMT-methylated GBM patients who received CCNU/TMZ as first-line therapy, aiming to provide insights into outcomes and efficacy of approaches.

Methods

Patient Cohort and Outcomes

The medical records of the Department of Neurooncology at the University Hospital Bonn were screened, including data from January 2009 to July 2023. Patients were included if they met the following criteria: (1) Tissue-based diagnosis of GBM, IDH wildtype (WHO 2021 classification), harboring a methylated MGMT promoter; (2) initiation of primary treatment according to the CeTeG protocol (RT of the extended tumor region with 2 Gy ad 60 Gy or 2.67 ad 40.05 Gy, plus planned 6 cycles of combined lomustine [100 mg/m^2 body surface area] and TMZ [100-200 mg/m^2 body surface area]).[6]

Data on age, sex, extent of resection (EOR), and Karnofsky performance score [KPS]) post-surgery were retrieved. Outcome was assessed using PFS-2, defined as months from first tumor progression to second tumor progression or death, and OS after first progression, defined as months from first tumor progression to death.

Progression Assessment and Radiological Response

Progression assessment was performed according to the current RANO 2.0 criteria for high-grade gliomas in adults.[17] The first post-RT MRI scan was considered the baseline examination. Within the first 12 weeks after completion of RT, confirmation of PD within the high-dose radiation field required either follow-up MRI or histopathological evidence of recurrent tumor. In patients receiving bevacizumab as salvage treatment ($n = 4$), a confirmation

scan was required in cases of partial response (PR) or stable disease (SD) to rule out pseudoresponse. In cases of suspected progression but with indications of treatment-related MRI changes (eg, lack of increased regional cerebral blood volume [RCBV]), follow-up MRI scans 4-8 weeks later were required to confirm progression. If progression was confirmed, the progression date was backdated to the MRI date of suspected progression, in accordance with the RANO 2.0 criteria.

Second-Line Therapies

Data on second-line therapies were collected from the medical records, including the following:

- Therapy modalities: re-resection or re-irradiation [re-RT] and systemic therapy.
- Details of systemic therapy: substances used, their dosages (mg), number of completed therapy courses.
- Details of re-RT, including the mode (focal re-RT) and cumulative dosage (Gy).
- Timing of second-line therapy: the interval (in days) from the last TMZ intake as the end of first-line therapy (CeTeG protocol) to the initiation of second-line therapy.

In patients undergoing TMZ rechallenge, 8 cycles (up to 200 mg/m^2 body surface area) were planned and administered using the 5/28 schedule, as implemented in the NOA-04 trial,[18] aiming to ensure adequate treatment duration while minimizing the risk of cumulative toxicity associated with prolonged exposure to alkylating chemotherapy. The decision to pursue combination treatments (TMZ + RT and/or re-resection) was made by a multidisciplinary tumor board, considering specific patient and disease factors. Combination therapies were generally favored for patients with good clinical performance status (KPS of at least 70%) and a significant stable interval since first-line therapy (a minimum of 1 year since primary RT was required for local re-RT). Re-craniotomy was particularly considered when complete resection of the progressive tumor was deemed feasible.

Hematotoxicity occurring under TMZ rechallenge was assessed and graduated according to the Common Terminology Criteria for Adverse Events version 5 (CTCAEv5).[19] Patients that had bevacizumab treatment for recurrence were treated with 10 mg/kg bodyweight every 14 days.

Statistics/Data Analysis

Statistical analyses were conducted using SPSS (Version 29.0.0.0, IBM) and Prism (Version 10.4.0, GraphPad). Descriptive data analysis included the calculation of frequencies and median values for selected variables, accompanied by either the range or, where appropriate, the interquartile range (IQR). Kaplan-Meier survival analysis was employed to determine median survival times and 95% confidence intervals (CI), as well as to report the number of patients at risk, indicating how many remained under follow-up at specified time points. Logistic regression analysis was used to assess the association between time (defined as days from the end of first-line therapy to the start of second-line therapy, treated as a continuous variable) and the likelihood of achieving a therapy response (SD or PR, treated as a categorical variable). Cox regression analysis was performed to evaluate the relationship between PFS-2 and time from the end of first-line therapy to the start of second-line therapy, treated as a continuous variable. A P-value <.05 was considered statistically significant.

Ethics Statement

Ethical approval was not required for this retrospective monocentric study in accordance with local and national guidelines. Personal data have not been disclosed to third parties at any time.

Results

Demographics and Progression Assessment

A total of 70 patients were included in this analysis. The median age was 59 years (range: 31-74), with 91.4% of the patients being 70 years or younger. Females comprised 42.9% of the cohort. At first surgery, total resection had been achieved in approximately half of the patients (52.9%), while biopsy was performed in 20%. The median postoperative KPS was 90 (range: 40-100), with the majority of patients (94.3%) having a KPS of at least 70. Recurrence was documented in 55 of 70 patients (78.6%), while 9 patients showed no progression to date (median follow-up 32.5 months), and 6 were lost to follow-up. Among the 55 patients with confirmed progression, 40 (72.7%) initiated second-line therapy, 8 (14.5%) received best supportive care, and 7 (12.8%) did not undergo second-line therapy due to early death related to progression. Baseline characteristics are summarized in Table 1.

Second-Line Therapies

Among patients initiating second-line therapy (N = 40), 5 patients (12.5%) underwent re-resection with 3 patients achieving total resection. Fourteen of 40 patients (35%) received focal re-RT with a median dosage of 37 Gy (range: 18-60). Notably, a significant proportion of patients (12/40, 30%) underwent combined second-line therapy. This included re-RT combined with systemic therapy in 8 patients, re-resection combined with subsequent systemic therapy in 3 patients, and a combination of re-resection, re-RT, and systemic therapy in 1 patient (Figure 1).

Systemic second-line therapy was administered to 33 patients (82.5%). The most common regimen was a TMZ rechallenge (5/28 scheme), given to 24 patients as single systemic agent (72.7%), while 2 patients received TMZ in combination with other systemic therapies (meclofenamate[20] in 1 patient and CCNU in the other). The remaining patients received bevacizumab (10 mg/kg body weight) in 4 cases, CCNU plus bevacizumab in 1

Table 1. Data on age, sex, extent of resection (EOR), and post-surgery Karnofsky performance score (KPS)

	n = 70 patients
Age (years)	
Median (range)	59 (31-74)
≤70 (%)	64 (91.4)
Sex	
Female (%)	30 (42.9)
EOR	
Biopsy (%)	14 (20)
Subtotal resection (%)	19 (27.1)
Total resection (%)	37 (52.9)
KPS post-surgery	
Median (range)	90 (40-100)
≥70 (%)	66 (94.3)
Recurrence	
No recurrence (%)	9 (12.9)
Lost to follow-up (%)	6 (8.5)
Documented recurrence (%)	55 (78.6)
Recurrence therapy	*n* = 55 documented recurrence
Best supportive care (%)	8 (14.5)
No therapy due to death (%)	7 (12.8)
Initiation of recurrence therapy (%)	40 (72.7)

The table provides descriptive statistics on recurrence frequency and associated treatments. Median values are reported with their respective ranges, while categorical data are presented as absolute numbers with percentage frequencies.

case, regorafenib in 1 case, and larotrectinib in 1 case. In patients receiving TMZ rechallenge, the treatment settings were as follows: TMZ was applied as a monotherapy in 15 patients (57.7%), combined with re-RT in 8 patients (30.8%), applied after re-resection in 2 patients, and 1 patient received re-resection that was followed by re-RT and TMZ rechallenge (Figure 1). Supplementary Table 1 provides more detailed information (RT and TMZ dosages) on combination therapies including TMZ.

Tolerability of TMZ Rechallenge after First-Line CCNU/TMZ

The median dose of TMZ was 200 mg/m^2/d (5/28 scheme) of body surface area (range: 100-200 mg/m^2), with a median of 6 therapy cycles (range: 1-8). Eleven patients (42.3%) completed 8 therapy cycles, and 1 patient has completed 6 cycles of therapy, and treatment is still ongoing (indicated by the upper dark blue bar in the swimmer's plot of Figure 2A). The most common reason for discontinuing TMZ rechallenge before the eighth cycle was tumor progression, occurring in 11 patients (42.3%). Additional reasons included hematotoxicity in 1 patient, withdrawal by 1 patient, and symptomatic varicella zoster infection in another.

The majority of patients receiving TMZ rechallenge did not experience grade 3 or 4 hematotoxicity as per CTCAEv5 (20/26; 76.9%, Figure 2B). Grade 3 toxicity was observed in 3 patients, while grade 4 toxicity occurred in 2 patients (combined 19.2%). Specifically, 3 patients experienced grade 3 thrombocytopenia, 2 had grade 4 thrombocytopenia, and 1 developed grade 3 neutropenia. Notably, 1 patient required a platelet transfusion. Dose reductions of TMZ due to hematotoxicity were implemented in 5 patients. Hematotoxicity data were unavailable for 1 patient (Figure 2B).

Response to Recurrence Therapy and Outcome

Patients undergoing TMZ rechallenge alone ($n = 15$) experienced PR in 3 cases (20%) and SD in 5 cases (33.3%), while 5 patients had PD (33.3%, Figure 3A). Response evaluation was unavailable for 2 patients (13.3%). The median PFS-2 for patients treated with TMZ alone was 8 months (95% CI 0.2-15.9), and the median OS after first progression was 11.9 months (95% CI 5.1-18.7, Figure 3B,C). PFS-6 was 50%, and 1-year OS was 45%. In comparison, the median PFS-2 for patients who underwent TMZ combined with re-RT and/or re-craniotomy was 6.9 months (95% CI 2.7-11.1) (Supplementary Figure 2A, $P = .95$, log-rank test), with a median OS of 14.9 months (95% CI 0.2-29.6) (Supplementary Figure 2B, $P = .73$, log-rank test).

The median interval from completion of first-line CCNU/TMZ (ie, last intake of TMZ in first line) to progression was 12.5 months (IQR: 8-18.4, range: 4.1-82.9). However, the median interval to the initiation of recurrence therapy (first TMZ dose) in all patients ($n = 26$) was 14.5 months (IQR: 9-20, range: 4.4-83.8), and 12.7 months (IQR: 9-19.2, range: 4.4-31.4) in patients achieving SD or PR, compared to 15.6 months (IQR: 11.1-20.9, range: 4.8-83.8) in those who did not achieve SD or PR. Logistic regression analysis showed no significant association between the time interval (last TMZ intake during primary therapy and first TMZ intake during recurrence therapy) and therapeutic response (odds ratio 0.97, 95% CI: 0.91-1.03; $P = .34$). Similarly, Cox regression analysis found no significant association with PFS-2 (hazard ratio 0.99, 95% CI: 0.96-1.03; $P = .84$).

Among all patients receiving recurrence treatment, 50% achieved SD or PR as the best outcome. One patient had pseudoresponse upon bevacizumab therapy and was assessed as PD. The median time to second progression (PFS-2) was 5.4 months (95% CI: 2.9-7.8), with a PFS-6 rate of 47% (Supplementary Figure 1a). Median OS after first progression was 9 months (95% CI: 4.4-13.6) with a 1-year OS of 45% (Supplementary Figure 1b). Outcome data of patients receiving other systemic therapy than TMZ or receiving re-RT or re-craniotomy only are provided in Supplementary Table 2.

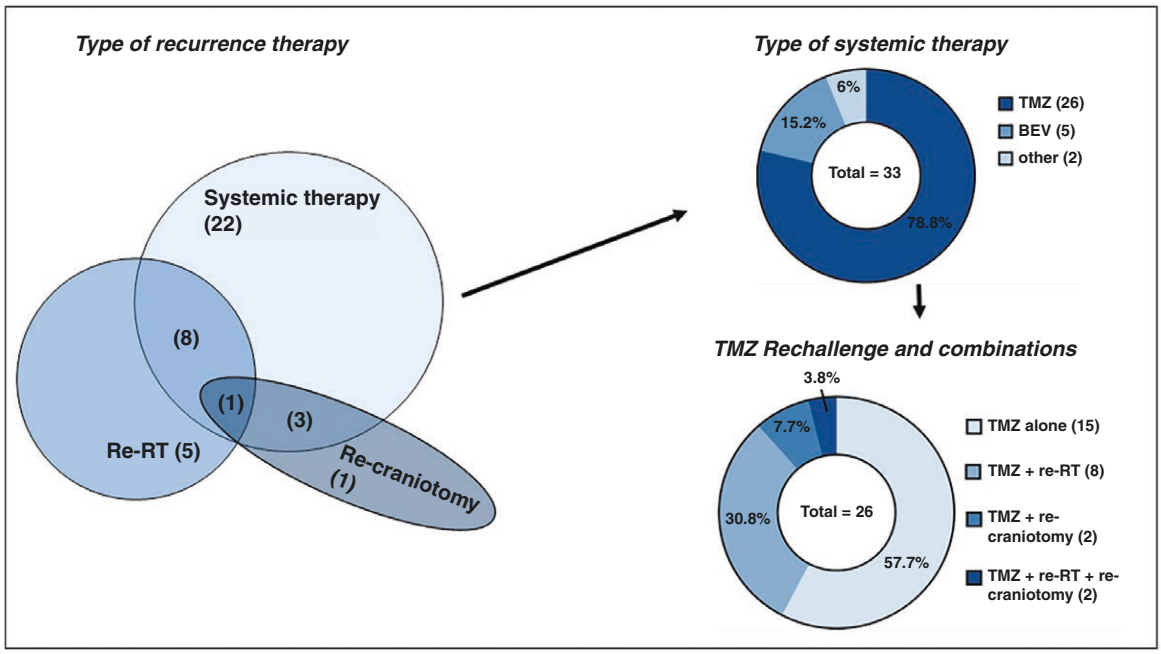

Figure 1. The treatment modalities employed for recurrence therapies. On the left, a Venn diagram depicts the distribution of different treatment approaches, including systemic therapy, re-irradiation (re-RT), and re-resection, with overlapping regions indicating combination therapies. In the upper right corner, a pie chart shows the distribution of systemic therapies, highlighting temozolomide (TMZ) as the most frequently used agent (78.8%). The bottom right corner presents the spectrum of TMZ rechallenge and its combination with other modalities, such as re-RT and/or re-resection.

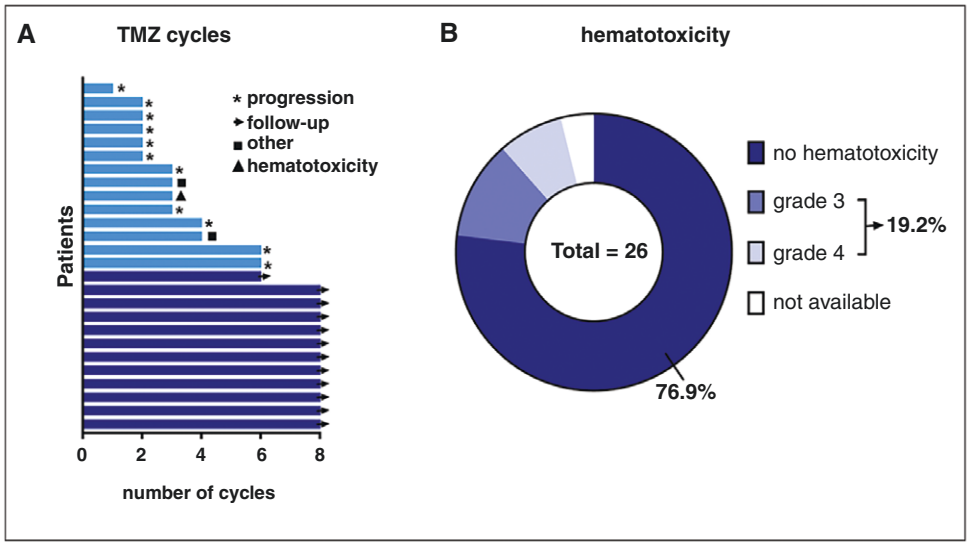

Figure 2. (A) A swimmer's plot displaying patients receiving TMZ rechallenge. Each bar represents 1 patient, with the *x*-axis indicating the number of completed cycles. An asterisk denotes tumor progression as the reason for discontinuation before the eighth cycle. A triangle marks discontinuation due to hematotoxicity, while a square represents other reasons for early discontinuation (withdrawal in 1 case and symptomatic varicella zoster infection in the other). (B) The frequency of hematotoxicity during TMZ rechallenge, assessed using CTCAE v5, is illustrated. For 1 patient, data on hematotoxicity were unavailable and are shown as a white proportion.

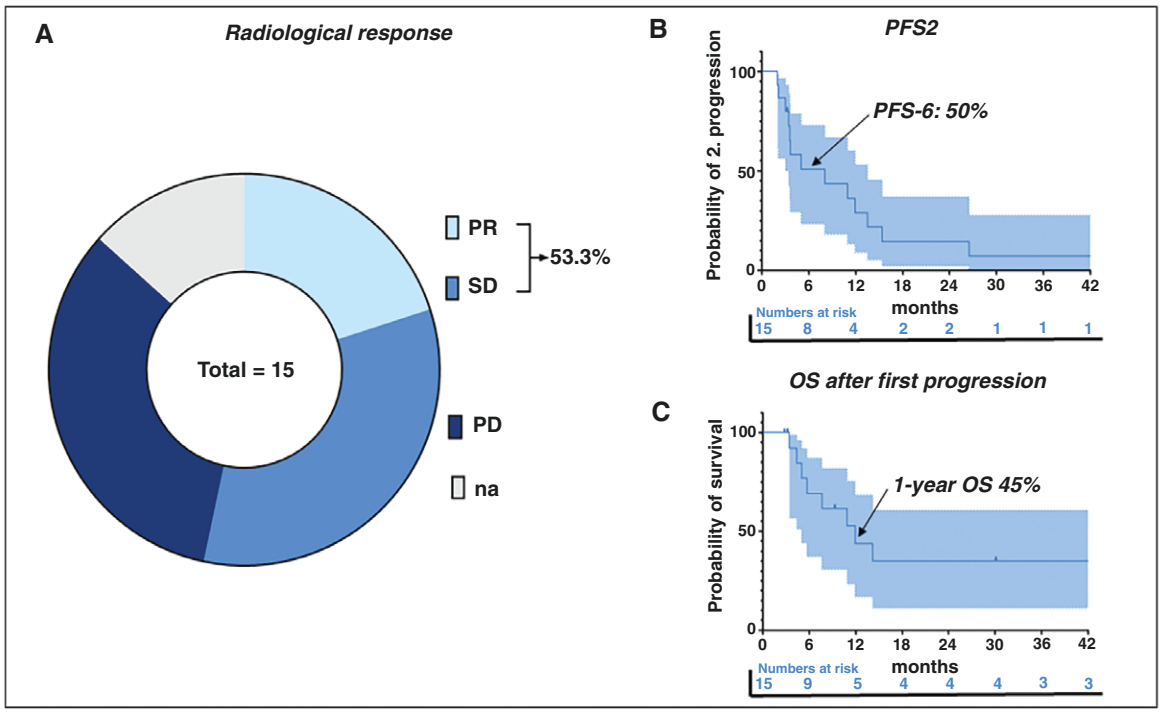

Figure 3. (A) A pie chart illustrating the frequency of achieved therapy responses in patients receiving TMZ rechallenge, with categories defined in detail in the Methods section. (B) and (C) present Kaplan-Meier curves for PFS-2 (progression-free survival from first to second progression, measured in months) and OS (overall survival from first progression to death), respectively. The dotted lines represent the 95% confidence intervals (CI). Numbers at risk are provided below the curves, indicating how many patients remained in follow-up at 6-month intervals. Within the Kaplan-Meier curves, PFS-6 (progression-free survival rate after 6 months) and 1-year-OS rate is highlighted.

Discussion

This single-center retrospective study for the first time provides insights into salvage treatment strategies for chemo-sensitive MGMT-methylated GBM patients following combined CCNU/TMZ radiochemotherapy. The key findings suggest that TMZ rechallenge is a commonly used and safe salvage therapy with encouraging efficacy. TMZ rechallenge alone resulted in SD or PR in >50% of patients, with a PFS-6 of 50% and a 1-year OS post-progression of 45%. These results support the use of TMZ rechallenge as a viable second-line option for this lomustine/TMZ-treated patient population. However, the median time to second progression and the median OS time remain limited to approximately 8 months and 1 year, respectively.

A significant proportion of patients (72.7%) with documented disease recurrence initiated second-line therapies, underscoring the feasibility of salvage treatment in this patient population. However, it is important to note that a substantial subset of patients either succumbed to their disease (with early death corresponding to PD) or received best supportive care, accounting for 12.7% and 14.4% of cases, respectively. These findings underscore the aggressive nature and often rapid progression of GBM, even within the prognostically favorable subgroup characterized by MGMT promoter hypermethylation.

The predominant second-line treatment used was TMZ rechallenge, which was frequently employed in combination with other modalities (in 11/26 patients or 42.3%). The results indicate that TMZ rechallenge is safe, which is reflected by a high median number of completed TMZ cycles (6) and a low frequency (<20%) of clinically relevant hematotoxicity. Of note, only one patient experienced severe hematotoxicity (grade 4 thrombocytopenia), which led to the necessity of a platelet transfusion. A considerable proportion of patients (42.3%) discontinued TMZ before the eighth cycle due to further disease progression, indicating limited efficacy in a substantial proportion of patients. Notably, the observed frequency of clinically relevant hematotoxicity (19%)—defined as grade 3 or 4 thrombocytopenia or neutropenia—was higher than reported in the DIRECTOR trial,[13] where 6 out of 104 (6%) patients experienced grade 3 or 4 thrombocytopenia or neutropenia, respectively. However, the comparison may be difficult to interpret, as patients in the DIRECTOR trial received a different treatment regimen (1 week on/1 week off, 7/14, with a starting dose of 120 mg/m^2 body surface area vs 3 weeks on/1 week off, 21/28, with a starting dose of 80 mg/m^2 body surface area). In the current analysis, half of the patients initiated the TMZ rechallenge with the maximum dose of 200 mg/m^2 body surface area (5/28 regimen). Nevertheless, 3 of the 5 patients who experienced clinically relevant hematotoxicity completed all 8 therapy cycles after dose modifications, indicating that hematotoxicity did

not jeopardize the feasibility of TMZ rechallenge. One patient discontinued TMZ due to grade 4 thrombocytopenia, and 1 patient discontinued after the fourth cycle due to PD. Apart from that, patients in this cohort had an inherently higher pre-exposure to chemotherapy as they were pretreated with combined lomustine/TMZ (median number of cycles in first-line: 6), which might explain a slightly higher rate of clinically relevant hematotoxicity.

Response rates were favorable (SD or PR in >50% of patients receiving TMZ rechallenge only) and comparable to the response rates reported in the DIRECTOR trial. Although objective response rates generally show an association with survival, the reporting of these categorical therapy responses may have inherent limitations, as they do not automatically convey information on the durability of a response.[21] In this study, a 6-month PFS rate of 50% was observed in patients receiving TMZ rechallenge only, which is comparable to the PFS-6 rate seen in the DIRECTOR trial for MGMT-methylated patients (around 40%) and may be superior to the PFS-6 rate observed in MGMT-methylated patients receiving lomustine in the EORTC 26101 trial (30%).[12] Additionally, 1-year OS rates were similar, with 45% observed in this cohort versus 54% observed in the DIRECTOR trial and 50% in the EORTC 26101 cohort. Of note, the reported 1-year OS rate in the REGOMA trial[15] for MGMT-methylated patients receiving lomustine is markedly lower, around 25%. Overall, these results indicate that a TMZ rechallenge after first-line therapy with lomustine/TMZ appears to be as effective as after first-line therapy with TMZ alone, suggesting that resistance to alkylating chemotherapy is not promoted by adding lomustine in the first-line setting.

The benefit of combination treatments at recurrence (ie, combining systemic therapies with other treatment modalities like re-RT or re-resection) is largely unknown and yet to be determined.[7] In this study, the efficacy of TMZ rechallenge alone versus TMZ rechallenge combined with re-RT or re-resection appears to be similar. The slightly higher median OS in patients undergoing combination treatments (median 14.9 months vs median 11.9 months) might be explained by selection bias, as combination treatments are generally initiated in patients with better clinical fitness. Although the results should be interpreted with caution due to the low sample size ($n = 15$ patients receiving TMZ alone and $n = 11$ patients undergoing combination treatments), they suggest that combining TMZ rechallenge with other treatment modalities is feasible but not necessary in all patients, as combination therapy is associated with similar efficacy while increasing the risk of toxicity.

Unlike in the DIRECTOR trial, no significant differences in therapy response or outcome were observed regarding the time interval between the last TMZ dose and the initiation of second-line therapy. This may be explained by reduced statistical power (low sample size and retrospective analysis), as well as the fact that alternative therapies (eg, bevacizumab) are typically preferred in clinical practice for patients experiencing early progression. The latter point is reflected by a long median time from the last TMZ dose in first-line therapy to the first TMZ dose in second-line therapy, which was 14.5 months (IQR: 9-20, range: 4.4-83.8). In contrast, this time was less than 2 months in almost 40% of patients in the DIRECTOR trial.

This study is subject to the limitations inherent to a retrospective analysis, including potential selection bias, and the relatively small sample size reduces the statistical power of the findings. Specifically, the cohort includes 55 patients with documented tumor progression, of whom 40 underwent salvage therapy. However, the narrow inclusion criteria provide a clear benefit in ensuring the study's relevance to this specific and well-defined patient subset—patients with GBM per WHO 2021 criteria, harboring MGMT promotor methylation, and receiving CCNU/TMZ as first-line treatment. While these criteria enhance the precision of the conclusions, they also limit the generalizability to a broader GBM population. Consequently, the subgroup of patients receiving TMZ rechallenge only is low ($n = 15$), restricting the interpretation of response and outcome findings and complicating comparisons with other studies. Ultimately, however, the findings convey that TMZ-based treatment strategies at recurrence—both as monotherapy and in combination with re-RT—are feasible and can lead to meaningful responses in this subgroup.

To summarize, this study provides the first detailed description of salvage treatments in MGMT-methylated GBM following first-line treatment with lomustine/TMZ. The findings might alleviate the concerns regarding a lack of therapeutic options at recurrence, offering reassurance about the feasibility and efficacy of TMZ rechallenge as second-line treatment in this subset of patients.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

Glioblastoma | MGMT | progression | salvage therapy | temozolomide

Conflict of Interest

The authors declare that there are no conflicts of interest directly related to this work. D.P. reports grants from BONFOR (UNTWIST), Deutsche Forschungsgemeinschaft (DFG) (project number: 445704496) and EKFS (EKES.33), consulting fees from Guerbet, and honoraria from Siemens Healthcare. E.G. reports speaker's honoraria from AstraZeneca, IntraOP and Novocure; travel support from AstraZeneca, IntraOP, and Novocure; and advisory board or DSMB member at AstraZeneca and Novocure. JPL reports stocks and travel expenses from TME Pharma AG, travel expenses and honoraria from Carl Zeiss Meditec AG, honoraria and clinical advisory board membership from OncoMAGNETx Inc., stocks and honoraria from Siemens Healthineers AG, and stocks from Bayer AG and BioNTech AG.

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Author Contributions

T.Z. designed the analysis. T.Z. and A.T. analyzed the data. T.Z. wrote the first draft of the manuscript. J.W. and U.H. supervised the work. All authors contributed to data acquisition, commented on previous versions, and read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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