Cancer Treatment and Research Communications 47 (2026) 101231

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Original Article

Prolonged sequential temozolomide in glioblastoma: A systematic review with exploratory quantitative synthesis

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ARTICLE INFO

Keywords:
Glioblastoma
Post-operative treatment
Temozolomide
Adjuvant treatment

ABSTRACT

Background: In patients with glioblastoma (GBM), the optimal number of adjuvant temozolomide (TMZ) cycles following combined radio-chemotherapy remains uncertain. This study aimed to synthesize the available randomized evidence addressing treatment duration.

Methods: Following PRISMA 2020 recommendations, we conducted a systematic review with exploratory quantitative synthesis of prospective randomized trials in newly diagnosed GBM. Studies were critically appraised with particular attention to survivorship bias, post-randomization selection, molecular heterogeneity, and trial design. Quantitative synthesis was based on reported median overall survival (OS) values according to planned TMZ duration (6 vs 12 cycles).

Results: Nine studies met the inclusion criteria, comprising 7 studies with planned 6-cycle TMZ (965 patients) and 5 studies with planned 12-cycle TMZ (504 patients). Across studies, prolonged TMZ was not associated with a clear survival advantage. Pooled median OS was 17.10 months for six cycles and 17.64 months for twelve cycles, however, with no statistically significant difference. Studies reporting apparent benefit were consistently affected by post–six-cycle selection and survivorship bias.

Conclusions: Current evidence does not allow a definitive determination of the optimal duration of adjuvant TMZ in newly diagnosed GBM. Although extended treatment has been associated with numerically longer survival in some studies, these findings are difficult to interpret due to methodological limitations and heterogeneity. Therefore, it remains uncertain whether prolonging TMZ beyond six cycles provides a meaningful clinical benefit, and treatment decisions should be individualized.

1. Introduction

Glioblastoma (GBM) is the most aggressive and prevalent primary malignant brain tumour in adults [1,2]. Despite advances in diagnostic imaging, surgical techniques, and multimodal treatments, the prognosis of this malignancy remains extremely poor, with a median life

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https://doi.org/10.1016/j.ctarc.2026.101231

Available online 27 April 2026

expectancy of approximately 14 to 16 months and a five-year survival rate below 10% [3]. The global incidence of glioblastoma is estimated at 3–5 cases per 100,000 people per year, and its associated mortality closely overlaps the incidence, underscoring the lethality of the disease and the urgent need for therapeutic advancement [2].

Since the phase 3 study by Stupp et al. in 2005, the current standard of care for operated glioblastoma relies on concomitant radiotherapy and chemotherapy with temozolomide (TMZ), followed by sequential TMZ [4]. This combined radio-chemotherapy approach has remained the milestone of treatment for almost two decades, improving survival compared to radiotherapy alone [5]. However, following upfront therapy, tumour relapse is expected in most cases, often occurring within the initial months after completion of postoperative therapy. This poor outcome highlights the biological resilience of GBM and the limited efficacy of current therapeutic strategies in eradicating residual disease.

Despite the large body of literature on post operative standard of care, the optimal length of sequential TMZ remains a matter of ongoing debate [6]. In the original trial of Stupp in 2005, six cycles of TMZ were administered after concomitant radio-chemotherapy, and this regimen was widely adopted as the standard [4]. Subsequent clinical practice has explored the potential benefits of extended administration—up to 12 cycles or more—to delay recurrence and prolong survival [7–9]. Yet, the evidence has been conflicting: while some retrospective and non-randomised studies showed improved outcomes with prolonged therapy, others found no additional benefit and reported just increased potential toxicity, treatment fatigue, and higher cumulative costs [6,10,11]. Additionally, variability in study design, patient selection, and molecular characteristics, including MGMT promoter methylation status, has made more difficult the result interpretation and impeded the formulation of a standardised recommendation [8,7–10].

Given these inconsistencies, a clear understanding of the most appropriate number of sequential TMZ cycles is essential for evidence-based clinical decision-making, balancing the potential benefits that could arise from continuing sequential therapy beyond 6 cycles with toxicity that could undermine quality of life.

The present systematic review aims to assess the optimal duration of sequential TMZ therapy (6 versus 12) in terms of overall survival (OS) and progression free survival (PFS) by prospective randomised studies in newly diagnosed operated glioblastoma with at least one arm of the study consisting of radio-chemotherapy treatment with concomitant and sequential TMZ.

2. Methods

2.1. Study design and review question

The aim of this systematic review with exploratory quantitative synthesis was to describe the current state of adjuvant TMZ beyond standard 6 cycles according to Stupp' protocol in patients with GBM. The methods used were prespecified and are presented in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. Enrolment criteria included all GBMs, with no selection for O6-methylguanine-DNA methyltransferase (MGMT) or other biomolecular characteristics. We included prospective randomized trials in newly diagnosed glioblastoma in which adjuvant temozolomide was administered for six or twelve cycles as part of the protocol-defined standard treatment backbone or control arm, regardless of whether treatment duration represented the primary randomized comparison. Because treatment duration was not the primary randomized variable in several included trials, quantitative synthesis was intentionally framed as exploratory and descriptive rather than confirmatory.

The review questions, according to PRISMA statement, were formulated following the PICO scheme (P: patients; I: intervention; C: comparison; O: outcomes), as follows: In newly diagnosed adult patients with GBMs (P), have 12 adjuvant TMZ cycles versus 6 cycles (I) been shown to be more effective when compared to 6 adjuvant TMZ cycles beyond standard 6 cycles (C), in terms of overall survival (OS) and PFS (O)? The present study has been registered on PROSPERO registry (Registration ID CRD420251024415).

2.2. Search strategy

An extensive literature search using MEDLINE (via PubMed) and EMBASE databases was conducted through a comprehensive query to identify original reports describing adjuvant TMZ beyond standard 6 cycles according to Stupp protocol in patients with GBM [4]. In addition, reference lists of relevant studies were manually screened to identify further eligible articles. The search has been carried out including the creation of search queries based on MeSH terms and Emtree categories. Data regarding the queries were created for MEDLINE and EMBASE and are listed in Table 1. The content areas were combined using the Boolean operator "and". Reference lists of studies were also reviewed to identify additional relevant studies. Any discordance in the screening process was solved by consensus, in each screening step the agreement amongst authors was evaluated by using the interobserver correlation coefficient (Cohen's k coefficient) [13].

For the most comprehensive detection of papers the search query was built as follows using a combination of medical subject headings (MeSH): ("clinical trials, phase ii"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "phase"[All Fields] AND "2″[All Fields]) OR "phase II clinical trials"[All Fields] OR ("clinical"[All Fields] AND "trial"[All Fields] AND "phase"[All Fields] AND "II"[All Fields] OR "2″[All Fields]) OR "clinical trial phase ii"[All Fields]) AND ("glioblastoma"[MeSH Terms] OR "glioblastoma"[All Fields] OR "glioblastomas"[All Fields] OR "glioblastoma multiforme"[All Fields]) AND ("temozolomide"[All Fields] OR "temozolomide"[MeSH Terms] OR "temozolomide s"[All Fields] OR "Temodal"[All Fields] OR "Temodar"[All Fields] OR "Methazolastone"[All Fields]).

We included studies published from 2005 to May 2025, comparing OS. The 95%CI of OS must have been reported. Case reports, review articles, meta-analyses, abstracts, reports of aggregated data and clinical trial phase that reports different radio-chemotherapy protocols with other chemotherapy drugs were excluded. In addition, exclusion criteria encompassed language other than English, non-comparative studies, and nonreported quantitative data.

Table 1
Composition of the search query according to respectively Medline and Embase synta.

MEDLINE search accessed on May 2025	EMBASE search accessed on May 2025
QUERY ("clinical trials, phase ii"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "phase"[All Fields] AND "2″[All Fields]) OR "phase II clinical trials"[All Fields] OR ("clinical"[All Fields] AND "trial"[All Fields] AND "phase"[All Fields] AND "II"[All Fields] OR "2″[All Fields]) OR "clinical trial phase ii"[All Fields]) AND ("glioblastoma"[MeSH Terms] OR "glioblastoma"[All Fields] OR "glioblastomas"[All Fields] OR "glioblastoma multiforme"[All Fields]) AND ("temozolomide"[All Fields] OR "temozolomide"[MeSH Terms] OR "temozolomide s"[All Fields] OR "Temodal"[All Fields] OR "Temodar"[All Fields] OR "Methazolastone"[All Fields]) 456 results	QUERY (" clinical trials, phase ii":ab,ti or "phase II clinical trials":ab.ti) AND ("glioblastoma":ab,ti or "glioblastomas":ab.ti) AND ("temozolomide":ab,ti OR "temodal": ab,ti OR "temodar":ab.ti OR "methazolastone":ab.ti) 396 results

2.3. Inclusion and exclusion criteria

To be eligible for inclusion in this systematic review, the manuscripts had to: report primary data; include adult patients (>18 years) with GBMs and be published in English language. If there was uncertainty about whether a manuscript was relevant or not, or if the manuscript did not contain exclusively standards protocol with t TMZ, it was decided to include it for full-text review. Studies were excluded if they met any of the following criteria: single patient case reports, case series with <10 patients; dissertation abstracts; conference abstracts; book chapters/ books; studies mainly focused on children, without a predominantly adult population. Following the initial search, bibliography data in *.nbib* format were imported into Endnote (Clarivate Analytics, London, UK) for duplicate removal. After this step, all articles were screened independently by two investigators by evaluating titles and abstracts. In case of lack of consensus, disagreements were resolved by a third independent investigator. Following abstract selection, all full-text papers were retrieved, and carefully analysed. No formal adjustment for patient- or treatment-level confounding factors (e.g., extent of resection, radiotherapy technique/dose, or molecular characteristics) was performed, as these variables were inconsistently reported across studies and the analysis was conducted at the aggregate study level. Where available, data on treatment completion (i.e., number of patients receiving the planned number of adjuvant TMZ cycles) were extracted.

Studies were required to report survival outcomes (e.g., median overall survival and/or hazard ratios) to ensure adequate reporting quality. However, hazard ratios were not required to compare different durations of temozolomide and were not used as the primary metric for quantitative synthesis.

All data collected were saved in an electronic spreadsheet

2.4. Statistical analysis

To calculate overall median time related to OS nine studies were analysed by meta-analysis and the DerSimonian and Laird random-effects model was applied. Subgroup analysis was also performed using the cycles number (six or twelve) as moderator. Difference between subgroups was assessed through the 95% CI. Statistical heterogeneity across studies was assessed using the I^2 statistic and between-study variance (τ^2). Given the exploratory nature of the analysis and the heterogeneity in study design and reporting, these measures were interpreted descriptively.

Because hazard ratios directly comparing 6 versus 12 cycles were not consistently available across studies, and treatment duration was not the primary randomized variable in several trials, a formal time-to-event meta-analysis was not performed. Instead, an exploratory descriptive synthesis of reported median overall survival values was conducted.

All analyses were carried out with SPSS v.30 technology.

3. Results

3.1. Study selection process

Using a combination of keywords, MeSH and Emtree hierarchical terms, we found 852 potentially relevant articles, that were saved in a unique Pubmed (nbib) file, which was then imported into Endnote to identify possible duplicates. After the removal of duplicates, the remaining 456 studies were screened by title, and subsequently by abstract, leading to the exclusion of 415 more studies. Forty-one studies were suitable for full-text reading, including 20 papers for the final analysis. Among these, only 9 papers held the information required to perform the meta-analysis [4,7–9,14–18]. The selection process followed PRISMA guidelines. The findings of this systematic review are summarized in Table 2 and Fig. 1.

Table 2
Selected studies.

Authors	Year	Patients (N)	Cycles	Median OS (months)
Stupp et al.	2005	287	6	14.6
Chauffert et al.	2014	60	6	11.1
Refae et al.	2015	29	6	14.1
Balana et al.	2020	79	6	23.3
Laprie et al.	2023	90	6	22.6
Anvari et al.	2024	46	6	35
Roth et al.	2024	374	6	17
Gilbert et al.	2014	309	12	16.1
Refae et al.	2015	30	12	18.8
Lee et al.	2016	36	12	15.9
Balana et al.	2020	80	12	18.2
Anvari et al.	2024	49	12	23

3.2. Meta-analysis

We identified a total of 7 studies in which 6 cycles of TMZ were prescribed, involving a total of 965 patients, and 5 studies in which 12 cycles of TMZ were prescribed, involving a total of 504 patients. In the meta-analysis, OS was evaluated for patients undergoing either six or twelve cycles of treatment (Fig. 2). The six-cycle group had a median OS of 17.10 months (95% CI: 14.17–20.03), and the twelve-cycle group showed a median OS of 17.64 months (95% CI: 15.28–20.01), with no statistical difference between them ($p = 0.841$). Combined, the groups had a median OS of 17.40 months (95% CI: 15.35–19.45). Baseline characteristics and treatment-related variables are summarized in Table 3. Due to inconsistent reporting of variance measures (e.g., confidence intervals) across studies, formal quantification of heterogeneity using I^2 was not feasible for all included data. Therefore, heterogeneity was assessed qualitatively based on study design, patient characteristics, and treatment variability. The evaluation of the statistical difference of (PFS) between the two groups was not calculated because of the different methods used to assess disease progression. In the group of studies that prescribed 6 cycles of TMZ, 3 studies used the RANO criteria, 3 used the McDonald criteria, and in one study, the type of criteria was not specified. In the other group, 1 study used the RANO criteria, 3 used the McDonald criteria, and in another study, the criteria were not specified.

4. Discussion

The optimal duration of adjuvant temozolomide following standard concomitant radio-chemotherapy for glioblastoma remains one of the most debated and unresolved issues in neuro-oncology [19]. Despite the widespread adoption of extended adjuvant temozolomide beyond six cycles in routine clinical practice, the present critical systematic review and exploratory meta-analysis demonstrates that currently available randomized evidence does not provide clear evidence of a clinically meaningful survival benefit.

To investigate the optimal duration of sequential chemotherapy, in this critical systematic review, incorporating an exploratory and descriptive meta-analysis, we adopted a novel approach by analyzing the control arms of randomized trials in which standard concomitant radiotherapy with temozolomide followed by adjuvant temozolomide was used as the reference or experimental treatment.

We selected only those studies in which the number of planned cycles were clearly indicated in the paper and the results included HR with a 95% confidence interval. The data we obtained did not show a clear advantage of one approach over the other. The meta-analysis carried out in this paper demonstrates only marginal numerical differences in OS (just 0.54 months) between the six- and twelve-cycle groups, with no statistically significant advantage for extended treatment. We encountered significant challenges in evaluating the difference in progression-free survival between the two groups due to the inconsistency in

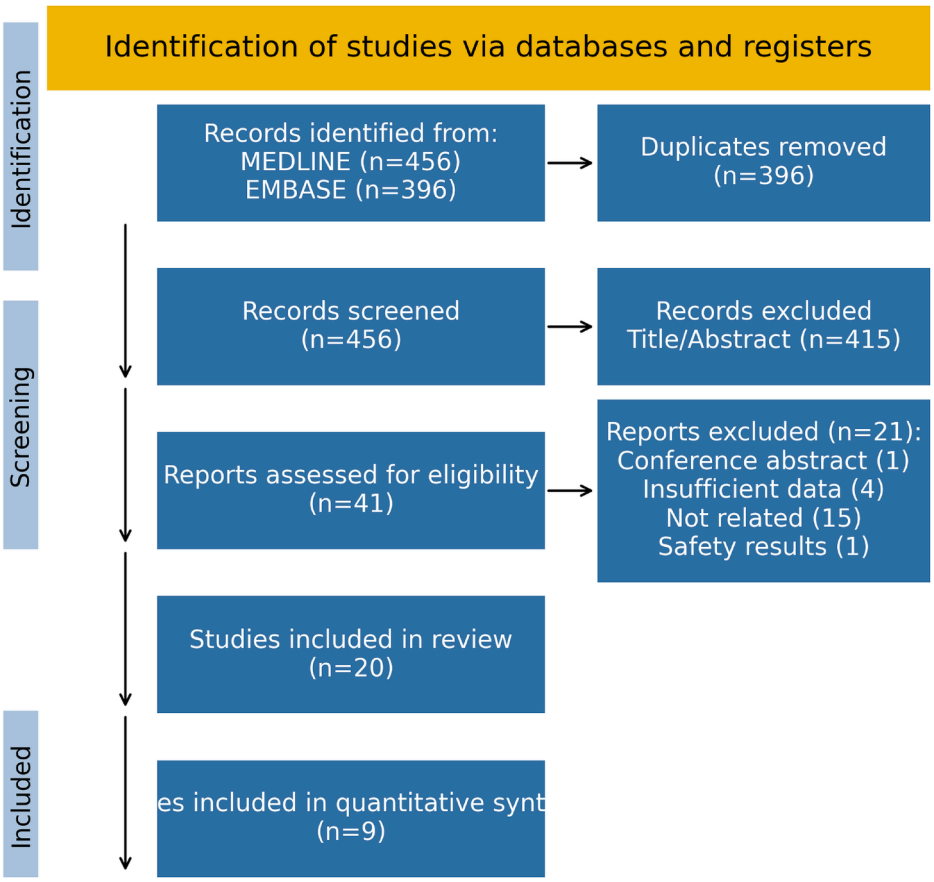

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

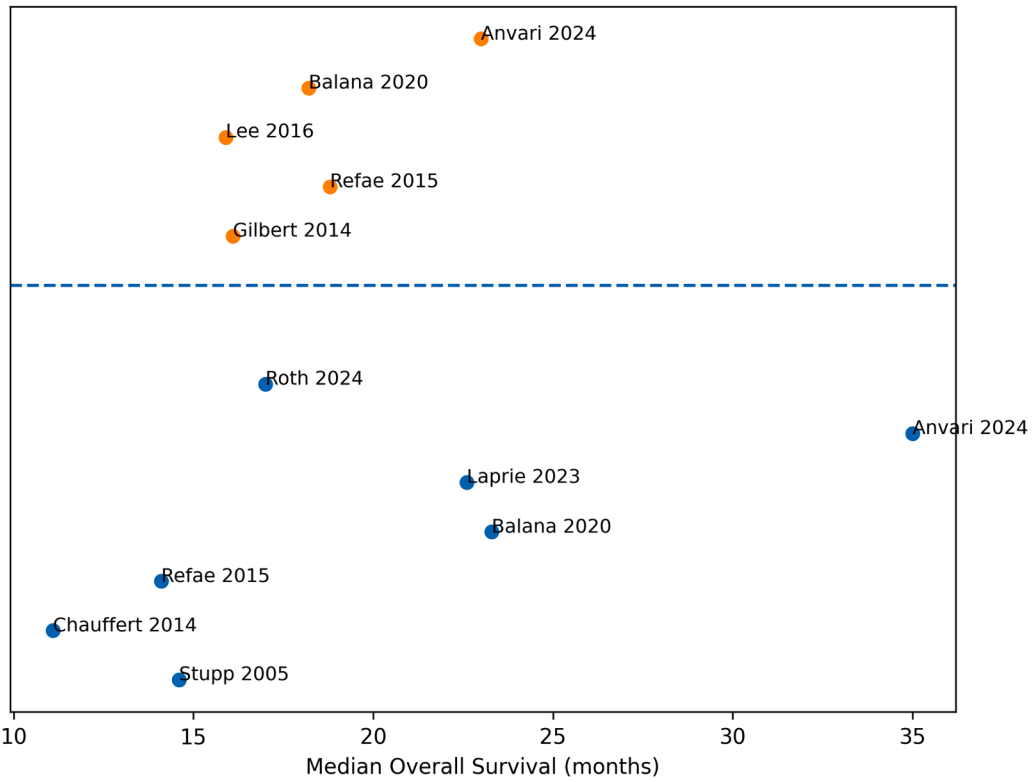

Fig. 2. Distribution of median overall survival (OS) across included studies according to planned temozolomide duration (6 vs 12 cycles). Results are presented as an exploratory descriptive synthesis.

Table 3
Study characteristics and baseline variables.

Study (Author, Year)	N patients	TMZ cycles (planned)	Median age	Extent of resection	MGMT status	IDH status	Completion TMZ	Notes
Stupp 2005	287	6	56	GTR/STR mixed	NR	NR	105 (47%)	Landmark trial
Chauffert 2014	60	6	60,9	NR	NR	NR	17 (47,2%)	Phase II
Refae 2015	29/30	6/12	NR	GTR/STR mixed	NR	NR	16 (76,2%) / 19 (86,4%)	Small sample
Balana 2020	79/80	6/12	60,4/60,7	GTR/STR mixed	60/40	IDH 1mut in 7 (8.9%) / 2 (2.5%)	79 (100%) / 77 (96.3%)	GEINO trial
Laprie 2024	90	6	NR	NR	50/50	3 (5%)	NR	SPECTRO GLIO
Anvari 2024	46/49	6/12	NR	Low GTR	NR	NR	42 (91.3%) / 27 (55.1%)*	Limited molecular data
Roth 2024	374	6	58,5	GTR/STR mixed	30/60	Wild type	104 (33%)	Phase III
Gilbert 2014	309	12	NR	GTR/STR mixed	30/70	NR	59 (19.1%)*	RTOG 0825
Lee 2015	36	12	55	GTR/STR mixed	NR	NR	7 (24.1%)	Non-comparative

Completion Temozolomide (TMZ): Percentages were calculated considering only patients who initiated sequential treatment. Percentages marked with an asterisk (*) were calculated based on the total number of patients in the control group.

methods used to assess disease progression.

A key finding of this review is that apparent numerical advantages observed with extended temozolomide administration may be influenced by methodological factors rather than representing a clear therapeutic effect. Among these, survivorship bias emerges as a pervasive and structurally unavoidable limitation across trials evaluating prolonged adjuvant therapy [20]. Our findings suggest that prolonging TMZ therapy beyond six cycles does not confer meaningful clinical benefit. However, the wide confidence intervals highlight potential heterogeneity among included studies. Determining the optimal duration for adjuvant TMZ therapy beyond six cycles through a meta-analysis is difficult due to inherent biases and heterogeneity among studies. Extended treatments introduce a selection bias, especially when randomisation occurs after six cycles, which leads to a "survivor bias." This issue is relevant in trials like GEINO 14–01, which only included patients who completed six cycles without progression, skewing the population towards those with a favourable prognosis [8]. Similarly, the study by Refae and co-workers emphasises patients who completed their treatment, which can inflate the perceived benefits of prolonged TMZ use [7]. For a rigorous meta-analysis, it's crucial to account for these biases and analyse studies with post-six-cycle randomisation separately to avoid overestimating benefits for newly diagnosed GBM patients. Additional biases arise from open-label and non-comparative trial designs, such as those seen in the marizomib and vandetanib trials, which lack the robustness of double-blind, placebo-controlled designs like the bevacizumab trial [14,18,15]. Furthermore, patient heterogeneity complicates comparisons due to variations in characteristics such as MGMT methylation and IDH mutation status, which significantly affect prognosis. Differences in this distribution introduce considerable heterogeneity. For example, while the marizomib trial reported a 60% unmethylated and 30% methylated tumor distribution, the SPECTRO GLIO trial found a near 50/50 distribution, affecting expected OS [14,16]. Additionally, trials conducted by Anvari and colleagues lacked MGMT data, limiting adjustment for this prognostic factor [9]. Variability in IDH mutation status, as seen in GEINO 14–01, further complicates comparisons. Additionally, disparities in treatment adherence and completion rates, along with variations in radiographic criteria like PFS measurements, complicate the assessment of TMZ efficacy across various studies [8]. Table 4 reported for each selected study of potential biases.

After the investigation of the available data in scientific literature, was not possible to determine the optimal number of cycles to administer after combination therapy, because retrospective studies designed to determine the optimal number of sequential TMZ cycles are inherently limited and cannot provide robust evidence [6,21,22]. Furthermore, currently, no studies prospective have been designed with the aim of evaluating, with an adequate sample size, the impact of sequential chemotherapy duration based on the presence or absence of residual tumours, MGMT promoter methylation, and age stratification. Differences in molecular distribution across trials (e.g., MGMT status) further contribute to heterogeneity [11,23]. An additional source of heterogeneity that deserves consideration is the temporal evolution of the included studies. Notably, trials conducted after 2020 tend to report longer median overall survival compared to earlier studies. This difference is unlikely to reflect a true effect of treatment duration alone, but rather a combination of factors, including improvements in neurosurgical techniques and extent of resection, advances in radiotherapy planning and delivery, better supportive care, and more accurate imaging-based assessment of disease.

Moreover, more recent trials increasingly incorporate molecular stratification and may include more favourable patient populations due to stricter eligibility criteria, leading to improved baseline prognosis. These temporal trends further complicate cross-study comparisons and reinforce the need to interpret pooled survival estimates with caution.

Because the present study is based on aggregated study-level data and these variables were inconsistently reported across trials, it was not possible to perform adjusted or stratified analyses. As a result, differences in survival across studies may reflect, at least in part, underlying differences in patient populations and treatment approaches rather than the duration of adjuvant temozolomide itself. This limitation further reinforces the need to interpret the results of this exploratory synthesis with caution. Moreover, the presence of moderate-to-high statistical heterogeneity further reflects the substantial clinical and methodological variability across studies, supporting the decision to interpret pooled estimates as exploratory rather than confirmatory.

Importantly, the present analysis does not represent a direct comparison between treatment strategies within randomized trials, but rather a cross-study descriptive synthesis of outcomes according to planned treatment duration. As such, findings should not be interpreted as evidence of comparative efficacy, but as a reflection of the current structure and limitations of the available evidence. A key finding of this review is that apparent numerical advantages observed with extended temozolomide administration should be interpreted cautiously, as they may be influenced by methodological factors—such as selection and survivorship bias—rather than representing a clear and generalizable therapeutic effect.

Taken together, these findings highlight a persistent gap between clinical practice and evidence-based medicine in the management of glioblastoma. The continued use of extended adjuvant temozolomide appears to be driven more by therapeutic inertia, clinician optimism,

Table 4
Risk of bias of the attached studies formatted according to **ROBVIS** principles (Risk of Bias assessment).

Study Title/ID	Domain 1: Bias arising from the Randomization Process	Domain 2: Bias due to Deviations from Intended Interventions (Blinding/ Protocol)	Domain 3: Bias due to Missing Outcome Data (Attrition/Futility)	Domain 4: Bias in Measurement of the Outcome	Domain 5: Bias in Selection of the Reported Result
Lee et al. (Vandetanib) (15)	High risk of bias: **Noncomparative design** meant groups were not statistically compared for efficacy against each other. Seven patients in the control arm **withdrew consent** upon learning their assignment, introducing selection bias post-randomization.	High risk: **Open-label** design. The comparison was primarily intended against historical controls, undermining the parallel control arm.	High risk: The study was **terminated early for futility** based on interim analysis. Survival data was *not collected* for patients who withdrew before treatment start.	Low risk (Assessment): Used established, albeit *modified*, Macdonald Criteria (pre-RANO era).	High risk: **Early termination** implies the trial failed to demonstrate the intended benefit.
Gilbert et al. (RTOG 0825 - Bevacizumab) (19)	Low risk: Randomized, double-blind, placebo-controlled trial.	Some concerns: Crossover design allowed placebo patients to receive Bevacizumab at progression, potentially masking OS differences between initial strategies.	Low risk (Attrition): Analysis included most randomized patients.	Some concerns (Threshold): Although PFS was statistically prolonged (P=0.007), it **did not meet the prespecified stringent threshold** (P<0.004) for the coprimary endpoint.	Low risk: Results clearly reported, even though OS benefit was absent. Inclusion criteria required tissue specimen, potentially **excluding biopsy-only patients**.
Chauffert et al. (TEMAVIR) (17)	High risk of bias: **Non-comparative Phase II design**, intended only to measure if the experimental arm hit a target PFS-6 rate (66%), not to compare statistically to the control arm.	High risk: **Differential completion rate:** Only 58.3% of the experimental arm completed radiotherapy (RT) compared to 81.7% in the control arm. **Salvage therapy**: BEV salvage allowed in 25% of the control arm, potentially confounding OS findings.	Low risk (Attrition): Generally low withdrawal rate.	Low risk: Used Macdonald criteria for response.	High risk: **Primary objective not achieved** (PFS-6 was 50.0% vs target 66%).
Balana et al. (GEINO 14-01 - Extended TMZ) (18)	Low risk (Selection): Stratified randomization ensured balance in key prognostic factors (MGMT status, measurable disease). Included only **highly selected patients** (non-progressors after 6 TMZ cycles).	High risk: **Open-label design** (not blinded) because TMZ capsules could not be blinded due to trademark/dosage markings.	High risk: The study was **not powered** to detect differences in median PFS or OS.	Low risk: Used RANO criteria for progression definition.	Some concerns (IDH Imbalance): Slight, non-significant **imbalance in IDH-mutated tumours** between arms.
Anvari et al. (Extended TMZ) (21)	Low risk: Randomized, single-blind trial.	High risk (Uncertainty): **Lack of prognostic molecular data** (e.g., MGMT methylation and IDH status), which is critical for TMZ efficacy and GBM prognosis, potentially leading to erroneous interpretation.	High risk: **Small sample size** (N=100 enrolled) limits statistical power, despite pre-calculation.	Low risk: OS and PFS definitions are standard.	Some concerns (Generalizability): Proportion of patients undergoing Gross Total Resection (GTR) was **substantially lower** than in other trials (17.9% GTR in total group).
Roth et al. (MIRAGE - Marizomib) (20)	Low risk: Phase 3 trial, centrally randomized.	High risk: **Open-label** design. **High rate of major protocol violations** in the Marizomib arm (52% excluded from per-protocol analysis due primarily to missed required ECG evaluation).	High risk: **Early recruitment closure** based on interim futility analysis and concerning adverse events (AEs).	Low risk: Used RANO criteria.	High risk: **No efficacy benefit** demonstrated (HR=1.04 for OS). Early closure confirms failure to meet superiority hypothesis.
Laprie et al. (SPECTRO GLIO) (16)	Low risk: Phase III randomized trial, stratified.	Low risk: High dose RT was generally well tolerated.	High risk: Trial **prematurely closed** due to slow accrual.	High risk: Reliance on **MMSE** for late cognitive assessment, which is considered suboptimal for this purpose.	High risk: Failure to meet the primary endpoint of increased OS. **Missing IDH status** for 37.2% of patients. Exclusion of tumors >5 cm potentially limits generalizability.
Stupp et al. (EORTC-NCIC) (Stupp 2005)	Low risk: Multicenter phase III randomized trial with protocol-defined treatment allocation. However, treatment duration was not the randomized variable for the purposes of the present analysis.	Some concerns: Open-label treatment administration was inherent to the trial design. The adjuvant TMZ schedule was protocol-defined, but delivered treatment could differ from planned treatment because of toxicity, progression, or clinical deterioration.	Low risk: Mature survival data were reported, and OS was the primary clinically relevant endpoint. Attrition was acceptable for the main survival analysis.	Low risk: Overall survival is an objective endpoint. Radiographic progression assessment reflected standards available at the time of the trial.	Low risk: Main survival results were clearly reported. For the present study, limitations relate mainly to use of the TMZ arm as study-level evidence rather than to selective reporting.

(*continued on next page*)

Table 4 (*continued*)

Study Title/ID	Domain 1: Bias arising from the Randomization Process	Domain 2: Bias due to Deviations from Intended Interventions (Blinding/ Protocol)	Domain 3: Bias due to Missing Outcome Data (Attrition/Futility)	Domain 4: Bias in Measurement of the Outcome	Domain 5: Bias in Selection of the Reported Result
Refae et al. (Protracted TMZ) (Refae 2015)	Some concerns: Small randomized study with limited reporting of randomization procedures and baseline prognostic balance.	High risk: Open-label comparison of conventional versus protracted adjuvant TMZ. Interpretation is limited by treatment adherence and by the distinction between planned and actually completed cycles.	Some concerns: Small sample size and incomplete reporting of treatment completion and prognostic covariates limit the robustness of outcome interpretation.	Some concerns: OS and PFS were reported, but radiographic assessment methods and timing were not fully harmonized with contemporary criteria.	High risk: Limited sample size, incomplete molecular characterization, and limited protocol/reporting detail increase the risk that reported outcomes may be affected by selection and reporting bias.

and the absence of clearly superior alternatives than by robust randomized evidence. Future studies addressing treatment duration must incorporate upfront randomization, molecular stratification, adequate statistical power, and trial designs that explicitly account for survivorship bias in order to provide clinically actionable guidance.

5. Conclusion

Current evidence does not allow a definitive determination of the optimal duration of adjuvant temozolomide in newly diagnosed glioblastoma. Although extended treatment has been associated with numerically longer survival in some studies, these findings are difficult to interpret due to methodological limitations and heterogeneity. Therefore, it remains uncertain whether prolonging treatment beyond six cycles provides a meaningful clinical benefit, and treatment decisions should be individualized.

Funding

This research was funded by Italian Ministry of Health - Ricerca Corrente.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests that could have influenced the work reported in this paper. No financial support, honoraria, consultancies, stock ownership, or other financial relationships relevant to this study were received.

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