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Efficacy and Safety of Targeted Therapies for Glioblastoma: A Systematic Review and Network Meta-Analysis

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Abstract

Purpose: Glioblastoma (GBM) is the most aggressive primary brain tumor with a poor prognosis. The current standard regimen of surgery combined with concurrent temozolomide chemoradiotherapy has limited efficacy. Multiple targeted therapies have been evaluated in randomized controlled trials (RCTs), but results are inconsistent and lack systematic comparisons. This review used network meta-analysis (NMA) to assess the relative efficacy and safety of different targeted drugs vs. standard treatment.

Methods: A systematic search was conducted in PubMed, Embase, Cochrane Library, and Web of Science up to March 7, 2025. RCTs comparing targeted drugs (monotherapy or combination therapy) with standard treatment (surgical resection ± radiotherapy ± temozolomide) or comparing different targeted drugs were included. Primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes included grade ≥3 adverse events (AEs). Bayesian NMA estimates hazard ratios (HR), risk ratios (RR), and their 95% credible intervals (CrI). Surface under cumulative ranking area (SUCRA) ranked interventions. Additionally, subgroup analyses were conducted based on the methylation status (methylated/unmethylated) of the O-6-methylguanine-DNA methyltransferase (MGMT) promoter.

Results: In total, 14 RCTs (10 targeted interventions) were included. Compared with standard therapy, bevacizumab (HR for PFS=0.57, 95% CrI 0.41–0.80) prolonged PFS but did not significantly improve OS. Compared with other targeted therapies, it still improved PFS. Some drugs (e.g., nivolumab) may even shorten survival. Regarding safety, marizomib, nivolumab, depatuxizumab mafodotin, cediranib, and nimotuzumab were associated with a high risk of AEs. In the subgroup analysis of MGMT methylation, no remarkable differences were noticed. In exploratory MGMT-stratified analysis, nivolumab was associated with less favorable OS and PFS estimates in the unmethylated subgroup.

Conclusion: Bevacizumab was associated with improved PFS, but not OS compared to standard therapy and other targeted therapies in newly diagnosed GBM patients. Exploratory subgroup findings suggested that nivolumab may be associated with less favorable OS and PFS estimates in MGMT-unmethylated patients. SUCRA rankings should be interpreted as exploratory because most interventions were supported by limited trial evidence. However, certain targeted drugs exhibit inadequate safety profiles, and careful risk–benefit assessment is required. Future research

should further explore safer and more effective multi-targeted combination strategies to overcome GBM's survival bottleneck.

Keywords: Glioblastoma, Network Meta-Analysis, Targeted therapies, Bevacizumab, Nivolumab

Background

Glioblastoma (GBM) is the most prevalent primary malignant brain tumor, constituting around 49% of all primary malignant brain tumors. Patients exhibit poor prognoses and short survival, with a median survival of 14 to 16 months and a 5-year survival rate of only 5% to 10% [1, 2]. Currently, the standard treatment for GBM involves surgical resection combined with radiotherapy, temozolomide, and maintenance chemotherapy. However, due to the heterogeneity in MGMT methylation status, invasive growth patterns, and resistance to conventional drugs, standard treatments yield limited efficacy, increasing the likelihood of tumor recurrence and imposing a comprehensive "physical-psychological-social" burden on patients' quality of life [3]. Therefore, optimizing treatment regimens and exploring and applying novel therapeutic approaches represent fundamental pathways to enhance patient survival rates and quality of life.

In recent years, targeted therapeutic drugs have been increasingly used in clinical trials due to their precision and ability to complement traditional treatments. These drugs include epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) antibodies, DNA damage repair inhibitors (PARP), and programmed death-1 (PD-1) immune checkpoint inhibitors [4]. Although some targeted therapies are shown to improve progression-free survival (PFS) in GBM, the results from clinical trials are heterogeneous, with no consistent improvement in overall survival (OS) or PFS for certain treatments [5-7]. Meanwhile, the methylation status of the MGMT promoter plays a key role in tumorigenesis, progression, and therapeutic response [8,

9]. Methylation status can significantly impact the efficacy of targeted therapies. Hence, it is crucial to assess its influence on treatment outcomes for the optimization of personalized treatments.

Although multiple randomized controlled trials (RCTs) have evaluated the application of various targeted therapies in newly diagnosed GBM patients, to date, no comprehensive study has systematically integrated all available RCT evidence while simultaneously comparing multiple targeted therapies against standard treatment and assessing their relative efficacy and safety. Furthermore, stratified efficacy analyses for O-6-methylguanine-DNA methyltransferase (MGMT)-methylated and unmethylated patients have not been adequately addressed in previous reviews. Based on this, the present study employed a systematic review and network meta-analysis (NMA) to integrate existing RCTs, comparing the relative efficacy and safety of multiple targeted therapies in newly diagnosed GBM patients. Additionally, subgroup analyses stratified by MGMT methylation status were performed to explore potential differential effects across subgroups and to provide theoretical references for subsequent methodological improvements and further research on therapeutic strategies.

Method

This study conducted a systematic review and NMA according to a predefined protocol that complied with the PRISMA-NMA extension statement [10]. The study was registered in advance on the PROSPERO website (registration number: CRD420251010579).

Data Sources

This study retrieved data from four databases (PubMed, Embase, Cochrane, and Web of Science) up to March 7, 2025. Searches employed a combination of subject headings and free-text terms, including “glioblastoma”, “targeted therapy”, and specific drug names, alongside keywords such as “randomized controlled trial”. The complete search strategy is detailed in Appendix Table

S1. Additionally, manual searches of references from included studies and relevant systematic reviews were conducted. Abstracts from major neuro-oncology and oncology conferences were screened for potentially eligible studies to minimize omissions.

Study Selection

Two researchers (Liu DH and Liu YW) independently reviewed full texts and screened articles based on the following criteria. Disagreements were addressed through discussion or consultation with a third expert. Inclusion criteria were developed according to the PICOS principles: P: Newly diagnosed adult GBM patients; I: Any targeted therapy (monotherapy, combination therapy, or combination with standard treatment) in patients with possible prior standard treatment, including surgical resection, radiotherapy and temozolomide; C: Other targeted therapies (monotherapy or combination therapy, or combination with standard treatment) or standard treatment; O: Trials reporting at least one of the following clinical outcome measures: OS, PFS, and ≥grade 3 AEs; S: RCTs.

The exclusion criteria were as follows: duplicates; non-clinical studies such as reviews or commentaries; animal studies; and studies lacking relevant outcome measures.

Risk of Bias Assessment

The Cochrane Risk of Bias 2 (ROB2) tool was adopted to appraise the included studies. The assessment process was independently conducted by Liu DH and Liu YW, evaluating five domains: randomisation process, deviations from the intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Assessment outcomes were categorized into three levels: low risk, some concerns, and high risk. The results were consolidated by Ci YZ.

Data Extraction

Two researchers (Liu DH and Liu YW) independently reviewed full texts and extracted data into a predefined Excel spreadsheet, including first author, publication year, country, group, patient number, MGMT promoter methylation status, age, sex ratio, and intervention. We also extracted the information on patients' baseline treatment (e.g., surgery, radiotherapy, temozolomide, and corticosteroids) prior to their enrollment in RCTs. Hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS were extracted from eligible studies, along with the number of patients experiencing grade ≥3 adverse events (AEs) and the total number of patients in each treatment arm. Weller et al. [11] divided subjects into 3 groups. To assess the overall efficacy and safety of targeted drugs, the HRs for OS and PFS were first extracted from the intention-to-treat population (all randomly assigned patients). Given that subgroup information for MGMT promoter methylation status was reported simultaneously for both the minimal residual disease and significant residual disease groups, the HRs for OS and PFS were further extracted separately within these two subgroups for methylation subgroup analysis.

Data Synthesis

The gemtc package in R software (version 4.4.3, RStudio) was used to conduct Bayesian network meta-analysis based on the MCMC framework. First, a network diagram was constructed based on the direct comparative relationships between interventions and controls in the included studies. Nodes represented different interventions; lines indicated intervention pairs with direct comparisons, with line thickness proportional to the number of studies. For survival outcomes, including OS and PFS, published HRs and 95% CIs were extracted from the included RCTs. HRs were transformed into log-HRs, and the corresponding standard errors (SEs) were calculated from the reported 95% CIs using the formula: SE = [ln(upper CI) − ln(lower CI)] / 3.92. These log-HRs and SEs were entered into the Bayesian NMA as relative-effect data using the data.re argument in

the gemtc package. Treatment effects were modeled on the log-HR scale, with standard treatment as the reference, and were back-transformed to HRs for interpretation. Results were reported as HRs with 95% credible intervals (CrIs). For binary outcomes (i.e., ≥ grade 3 AEs), binomial distribution likelihood was used, and a log link function was employed to estimate RR. We constructed both fixed-effects and random-effects models, and the final model was selected based on heterogeneity and model fit. The fixed-effects model was used when the $I^2 < 50\%$ and the difference in DIC between the fixed-effects and random-effects models was < 5. Otherwise, the random-effects model was used. MCMC was set to 4 chains, annealed (adapted) 10,000 times, followed by 40,000 iterations of sampling with a dilution interval of 1. Gelman–Rubin diagnostics (R-hat) were used. The default weak-information prior settings of gemtc are adopted: a normal prior with a mean of 0 was used for the relative treatment effect parameters, and its scale was given by the software's internal re.prior.sd (which was related to om.scale by default). In the random-effects model, the heterogeneity parameter τ was also set as the default prior settings of gemtc, dunif(0, om.scale), where om.scale was automatically determined by the data when not specified. For multi-arm randomized controlled trials, the data of each arm were imputed into the model. Accordingly, the correlation of multiple comparisons within the same study was considered within a unified model to avoid duplication of data and underestimation of uncertainty. When closed loops existed in the network diagram, the node-splitting approach was employed to compare direct and indirect evidence. Inconsistency tests yielding $P > 0.05$ indicated good consistency. The relative effectiveness and ranking probability of interventions were calculated via the surface under cumulative ranking area (SUCRA), where SUCRA values closer to 1 signified superior rankings. Additionally, pre-specified subgroup analyses based on MGMT promoter methylation status (methylated/unmethylated) were conducted to ascertain the impact of molecular subtyping on the

efficacy of targeted therapies. The complete analysis codes are provided in supplementary materials.

Results

General Features of the Studies and Risk of Bias Assessment

This review initially retrieved 2,859 articles. After screening titles and abstracts, 504 duplicates were identified. 2,269 articles were excluded due to being meta-analyses, animal studies, conference abstracts, or commentaries. Following preliminary screening, 86 articles met the inclusion criteria. After full-text review, 72 articles were excluded due to irrelevant methodological issues and outcome measures. Ultimately, 14 RCTs [5-7, 11-21] were included. Detailed data are presented in Figure 1.

5,208 patients aged 18 to 88 years from various countries and regions were randomly assigned to 14 experimental groups and 14 control groups. The experimental groups included 10 targeted therapies: marizomib, veliparib, nivolumab, depatuxizumab mafodotin, cediranib, bevacizumab, rindopepimut, temsirolimus, nimotuzumab, and cilengitide. Three involved nivolumab [13, 14, 17], two involved bevacizumab [5, 6], and two RCTs involved veliparib [7, 18]. Baseline features for all RCTs are summarized in Table 1. The specific interventions included in the articles (including pre-treatment background and the intervention measures) are shown in Table S2.

Using the ROB2, the 14 included RCTs were assessed. Among them, three RCTs [12, 20, 21] were open-label trials where both participants and researchers were aware of intervention assignments, posing a risk of deviation from the intended interventions. These were rated as some concerns. All other RCTs were rated as Low risk. Detailed quality assessment results are presented in Figure S1.

Results of OS and PFS

This review included 14 trials involving 5,208 patients, all of which reported OS. The network diagram showed that 10 interventions formed direct comparisons with standard therapy (RT+TMZ/RT/TMZ) (Figure 2A). The convergence of the model was good, as shown in Figure S2A. The forest plot of relative effects indicated that nivolumab markedly reduced OS compared with standard therapy (HR = 1.17, 95% CrI: 1.03-1.32), suggesting an enhanced risk of mortality. No statistical differences in OS were identified between other targeted therapies and standard therapy. SUCRA analysis indicated that among all interventions, bevacizumab ranked relatively high for OS (SUCRA = 80.37%) (Figure 2B). However, this ranking should be interpreted cautiously because most interventions were supported by limited trial evidence. League table analysis showed a HR of 0.86 (95% CrI: 0.76-0.97) for standard therapy versus nivolumab, suggesting a potential trend of increased mortality. In between-intervention comparisons, nivolumab had HRs of 1.44 (95% CrI: 1.00-2.06) versus bevacizumab and 1.31 (95% CrI: 1.06-1.63) versus rindopepimut, indicating a suggestive trend of relatively poorer survival (Figure S3).

All 14 trials reported PFS. The network diagram showed that 10 interventions formed direct comparisons with standard therapy (RT+TMZ/RT/TMZ) (Figure 3A). The convergence of the model was good, as shown in Figure S2B. The forest plot indicated that compared with standard therapy, bevacizumab (HR=0.57, 95% CrI: 0.41, 0.80) significantly delayed GBM progression, while nivolumab (HR=1.19, 95% CrI: 1.05, 1.35) indicated an enhanced risk of GBM progression. Exploratory SUCRA results suggested that bevacizumab had a relatively high probability of ranking favorably for PFS (SUCRA = 99.41%), although the ranking should not be interpreted as a clinically actionable hierarchy (Figure 3B). Analysis of the league table indicated that standard therapy tended to reduce the risk of GBM progression relative to nivolumab, while tending to increase the risk of GBM progression relative to bevacizumab. Bevacizumab showed a comparatively favorable

trend over any other interventions. Nivolumab appeared to carry a higher risk than depatuxizumab mafodotin, bevacizumab, rindopepimut, and cilengitide, with no statistically significant differences compared with other interventions. Depatuxizumab mafodotin seemed to carry a lower risk than cediranib (Figure S4).

Results of grade ≥3 AEs

9 RCTs reported AE≥3, involving direct comparisons between 7 interventions and standard therapy (RT+TMZ/RT/TMZ) (Figure 4A). The convergence of the model was good, as shown in Figure S2C. Forest plot results showed that compared with standard therapy, marizomib (RR = 1.42, 95% CrI: 1.25-1.60), nivolumab (RR = 1.36, 95% CrI: 1.17-1.58), depatuxizumab mafodotin (RR = 1.38, 95% CrI: 1.24-1.55), cediranib (RR = 1.25, 95% CrI: 1.03-1.60), and nimotuzumab (RR = 3.81, 95% CrI: 1.74-10.22) notably raised the risk of grade ≥3 AEs. SUCRA results suggested that veliparib had a relatively high ranking in safety (SUCRA = 94.90%), while nimotuzumab showed a comparatively low ranking (SUCRA = 0.28%) (Figure 4B). League table analysis suggested that compared with standard therapy, marizomib, nivolumab, depatuxizumab mafodotin, cediranib, and nimotuzumab tended to be associated with an increased risk of ≥ grade 3 AEs. In the between-interventions comparison, nimotuzumab appeared to exhibit a notably higher risk than all other agents; veliparib showed no statistical difference from cilengitide, but both seemed to carry lower risks than the other drugs. Furthermore, cilengitide also did not show statistical significance when combined with cediranib (Figure S5).

Subgroup Analysis

MGMT methylation subgroup data revealed that targeted therapy was not associated with improved OS or PFS compared to standard therapy, with no statistical differences in these outcomes across all interventions. Detailed information of the included studies can be found in Table S3, and

the convergence of the model was good, as shown in Figure S2D and E. In the exploratory analysis of the MGMT unmethylated subgroup, nivolumab markedly worsened both OS (HR=1.31, 95% CrI: 1.09, 1.58) and PFS (HR=1.38, 95% CrI: 1.15, 1.65) relative to standard therapy, suggesting a potential trend of increased GBM progression risk (Table 2). The convergence of the model was good, as shown in Figure S2F and G.

Discussion

This NMA of 14 RCTs suggested that bevacizumab was associated with prolonged PFS compared with standard therapy in patients with newly diagnosed GBM, whereas no clear OS benefit was observed. In exploratory indirect comparisons, bevacizumab also showed a relatively favorable profile for PFS compared with several other targeted therapies. However, these between-drug comparisons and SUCRA rankings should be interpreted cautiously given the sparse network evidence. Nivolumab showed less favorable OS and PFS estimates than standard therapy, particularly in the MGMT-unmethylated subgroup. Regarding safety, marizomib, nivolumab, depatuxizumab mafodotin, cediranib, and nimotuzumab were associated with a higher incidence of grade ≥3 AEs, while safety data were available for only 7 interventions from 9 RCTs. Therefore, the AE data reflect the safety profile of these specific interventions and may not fully represent the toxicity risks of all targeted therapies.

In our NMA, bevacizumab not only demonstrated significant benefits for PFS based on direct evidence but also exhibited a relatively unique advantage in delaying disease progression when compared with various targeted therapies. This advantage is strongly supported by its mechanism of action, which effectively inhibits tumor angiogenesis by binding to circulating VEGF-A [22, 23]. This normalization of tumor vasculature may help reduce vascular permeability, alleviate vasogenic edema, and improve hemodynamics such as perfusion, thereby alleviating mass effect-

related symptoms and reducing the clinical burden associated with intracranial hypertension to some extent. Clinically, this can manifest as perceptible benefits such as imaging enhancement/edema control, symptom improvement, and steroid-sparing [24, 25]. Meanwhile, long-term use of bevacizumab may lead to the activation of alternative pro-angiogenic pathways, resulting in a decline in efficacy. Therefore, it may be more beneficial during the disease control window, and thus it should be combined with other treatments in clinical practice [26, 27]. Unlike PFS, improvements in OS are often influenced by multiple factors, including treatment continuity, rotational use of drugs, and subsequent treatment plans, which may dilute or confound the true effect of the treatment strategy. In trials on GBM, the improvement in OS is also related to differences in the survival after disease progression and insufficient reporting of post-treatment information after disease progression [28, 29]. Therefore, although the benefits of PFS are relatively evident, improvements in OS still need to be validated in more high-quality clinical trials and longer-term follow-up data. Currently, bevacizumab is not approved for the treatment of newly diagnosed GBM, and related studies are still in the trial phase. It may be used in specific circumstances for recurrent or progressive GBM [30].

The methylation status of the MGMT promoter is a key predictor of GBM sensitivity to alkylating agents such as TMZ. Methylation suppresses MGMT expression, weakens DNA repair capacity, and enhances the efficacy of TMZ; conversely, an unmethylated status leads to high MGMT expression, mediating drug resistance [31].In this study, we conducted an exploratory analysis based on methylation status. Our results suggested that nivolumab was associated with a potentially less favorable outcome in the unmethylated MGMT subgroup, whereas in patients with methylated MGMT, its effects for OS and PFS appeared broadly comparable to those in the control group. These findings should be interpreted cautiously, given their exploratory nature. These

findings imply that MGMT status may influence treatment outcomes. It is an established predictor of the benefit of TMZ. However, its relationship with the outcomes of nivolumab remains to be clarified, particularly in unmethylated MGMT patients.

As a PD-1 inhibitor, nivolumab activates T-cell antitumor immunity by blocking the PD-1/PD-L1 pathway and has demonstrated efficacy in multiple solid tumors [32-34]. In our study, the overall pooled analysis indicated that nivolumab was associated with shorter OS and PFS. In contrast, in the subgroup analysis, nivolumab showed numerically less favorable outcomes in the unmethylated MGMT subgroup and no clear benefit in MGMT-methylated patients. This finding appears to be broadly consistent with results from an open-label non-comparative study. Among recurrent GBM patients receiving nivolumab monotherapy, the median OS in the MGMT promoter unmethylated subgroup was 9.0 months, significantly shorter than the 14.8 months observed in the MGMT promoter methylated subgroup. Due to the limited sample size, the difference in survival between the two groups did not reach statistical significance. However, the trend indicating the impact of methylation status on survival benefit from nivolumab monotherapy remains clearly observable at the numerical level, with patients in the methylation group associated with better survival potential [35]. Results from the Phase III clinical trial (CheckMate 143) also provide supportive evidence for this trend. In patients with recurrent GBM, while nivolumab demonstrated statistical significance compared to bevacizumab, the unmethylated subgroup exhibited a clear trend toward inferior survival (HR > 1, median OS 8.0 vs. 8.9 months). The HR exceeding 1 suggested that unmethylated status may be associated with reduced survival benefit under nivolumab treatment, although this should be interpreted cautiously[36]. In this study, nivolumab was associated with shorter OS and PFS. Furthermore, its effects were more pronounced in the MGMT-unmethylated subgroup, which may have contributed disproportionately to the overall findings.

However, given the exploratory nature of the subgroup analyses and possible confounding factors, this observation should be interpreted cautiously and needs to be validated in larger, prospectively stratified trials with longer follow-up. Nevertheless, these results suggest that treatment benefit in GBM may be highly context-dependent, and therapeutic strategies need to be individualized based on the molecular and immunological features of individual tumors.

In summary, this NMA helped clarify differences in the efficacy and safety profiles of various interventions relative to standard therapy, and exploratory subgroup analysis by methylation status of the MGMT promoter may offer preliminary insights into precision medicine. Future research should further focus on exploring rationally designed combination strategies with potential synergistic effects. Preclinical studies suggest that combining bevacizumab with PD-1 inhibitors may enhance the infiltration of $CD8^+$ T-cells and prolong survival [37]. Meanwhile, patient selection and stratification based on molecular features (e.g., MGMT promoter methylation status) may facilitate the theoretical development of individualized therapeutic strategies for GBM.

However, the findings should be interpreted cautiously due to several structural limitations. The network evidence was sparse and unevenly distributed across interventions. Bevacizumab was involved in two RCTs, nivolumab in three RCTs, and veliparib in two RCTs, whereas most other targeted agents were predominantly involved in a single trial. This sparse network likely indicates that the treatment therapies for GBM are updated rapidly, and the evidence for many novel regimens is at an early stage. For the reasons outlined above, the robustness and reliability of the SUCRA ranking results and the conclusions regarding indirect comparisons between drugs are limited in this study. Therefore, they should not be used directly as the basis for drug prioritization decisions in clinical practice, but should only serve as a reference for academic exploration and research. Moreover, across the included trials, patients in both targeted-therapy arms and control arms mostly

received foundational standard treatments (e.g., surgery and chemoradiotherapy) before randomization. However, there were differences in the extent of resection, completeness of radiotherapy or temozolomide delivery, and corticosteroid use. These differences may increase between-study heterogeneity and weaken the transitivity assumption, thereby affecting the interpretability of the incremental benefit attributed to targeted agents (particularly for OS). Therefore, related results should be interpreted with caution. Subgroup analyses also provide meaningful research insights but remain subject to uncertainty. In the subgroup analysis by the methylation status of MGMT, a significant adverse effect of nivolumab on OS and PFS was observed in unmethylated MGMT patients. Importantly, the observed effect should not be interpreted as definitive evidence, as it is derived based on subgroup-level data and limited sample sizes in certain methylation subgroups. Therefore, it should be considered hypothesis-generating and may inform future prospective studies.

We are fully aware of the above-mentioned limitations and have maximized the rigor and transparency of this analysis through the following measures: a robust core based on high-quality evidence, with all included studies assessed by the ROB 2 tool showing 11 studies with low bias risk and 3 studies with moderate bias risk due to open-label design, and overall low heterogeneity (I^2 < 50%). This provides a high basis for the internal validity of the effect estimates for the direct comparisons in our network. At the same time, we intuitively displayed the unevenness of the evidence through a network evidence diagram and fully reported broad confidence intervals in the forest plot, honestly presenting the uncertainty of the estimates.

In brief, this study explores the relative efficacy of targeted treatments for newly diagnosed GBM based on the highest level of evidence available. Results driven by sparse evidence or subgroup analyses, such as differences across methylation subgroups, should be interpreted

cautiously and mainly used to inform directions for future research. Findings supported by direct, multi-source evidence are more credible and deserve greater attention. Importantly, the results of this NMA are insufficient to support changing the current first-line standard of care for newly diagnosed GBM. In the future, it is necessary to conduct more head-to-head comparative RCTs and promote the sharing and integration of individual patient data, so as to validate these findings.

Conclusion

This NMA included 14 RCTs evaluating the impact of 10 targeted therapies versus standard treatment on OS, PFS, and safety in newly diagnosed GBM patients. It indicated that bevacizumab was associated with improved PFS and suggested an underlying mechanism. Among the 7 interventions evaluated, nimotuzumab was associated with the highest risk of AEs. Nivolumab efficacy may be associated with MGMT status, which tentatively suggests that patients with unmethylated MGMT may face a survival disadvantage. However, the quality of evidence supporting these conclusions ranged from moderate to high, baseline patient characteristics across included RCTs showed heterogeneity, and direct comparative evidence for some targeted agents was limited, potentially affecting the robustness and generalizability of findings. Therefore, future efforts should prioritize high-quality RCTs with long-term outcome assessments.

Declarations

Ethics approval

Not applicable. This research protocol has been registered with the PROSPERO International Prospective Systematic Reviews Registry (Registration Number: CRD420251010579).

Consent to publish

Not applicable

Availability of Data and Materials

All data generated or analysed during this study are included in this published article and its supplementary information files. Further inquiries can be directed to the corresponding author (Email to Wenyi Ma: mawenyi@cdmc.edu.cn).

Conflict of Interest Statement

The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contributions

Donghui Liu: Conceptualization, Methodology, Data curation.

Yingwen Liu: Writing- Original draft preparation, Software, Formal analysis.

Yunzhe Ci: Visualization, Investigation, Validation.

Chunyan Wang: Supervision.

Wenyi Ma: Project administration, Funding acquisition, Writing- Reviewing and Editing, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Human Ethics and Consent to Participate declarations

Not applicable

Clinic trial number

Not applicable

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Figure Legends

Figure 1 Flowchart of search results

Figure 2 Network diagram and relative effect forest plot of OS in GBM patients. A. Network diagram; B. Relative effect forest plot

Figure 3 Network diagram and relative effect forest plot of PFS in GBM patients. A. Network diagram; B. Relative effect forest plot

Figure 4 Network diagram and relative effect forest plot of ≥Grade 3 AEs in GBM patients. A. Network diagram; B. Relative effect forest plot

Tables

Table 1 Baseline characteristics of included RCTs

Table 2 Modulating effects of MGMT methylation status on survival benefits and comparisons with overall results

Supplementary documents

Figure S1 Risk of bias assessment for RCTs

Figure S2 Results of convergence diagnostics

Figure S3 League table of HRs for OS across 10 interventions. Red font indicates statistical significance.

Figure S4 League table of HRs for PFS across 10 interventions. Red font indicates statistical significance.

Figure S5 League table of RRs for ≥Grade 3 AEs across 7 interventions. Red font indicates statistical significance.

Table S1 Complete search strategy

Table S2 Baseline Treatment Regime

Table S3 MGMT Methylation Information Table

Figure 1.

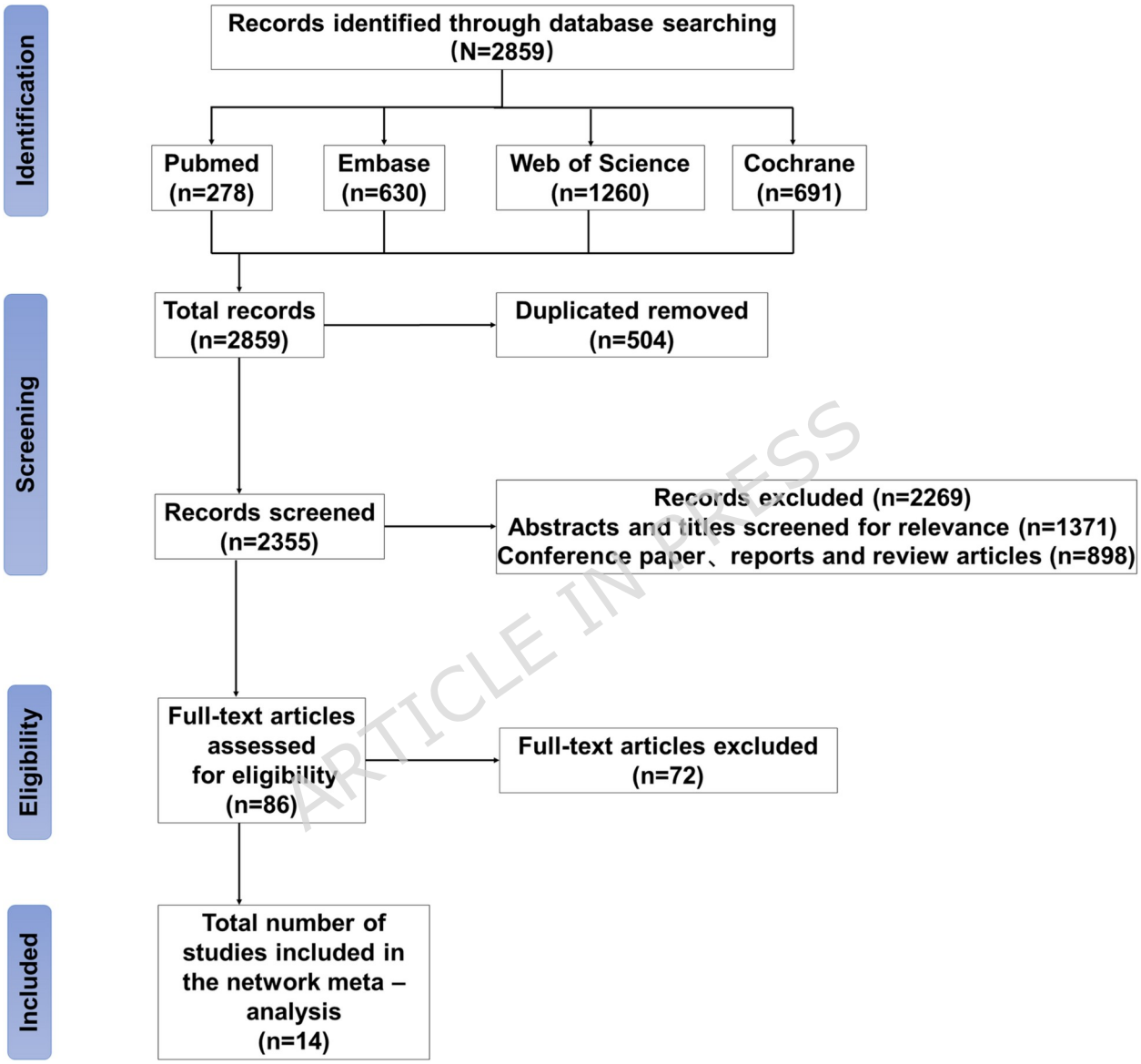

Fig. 2

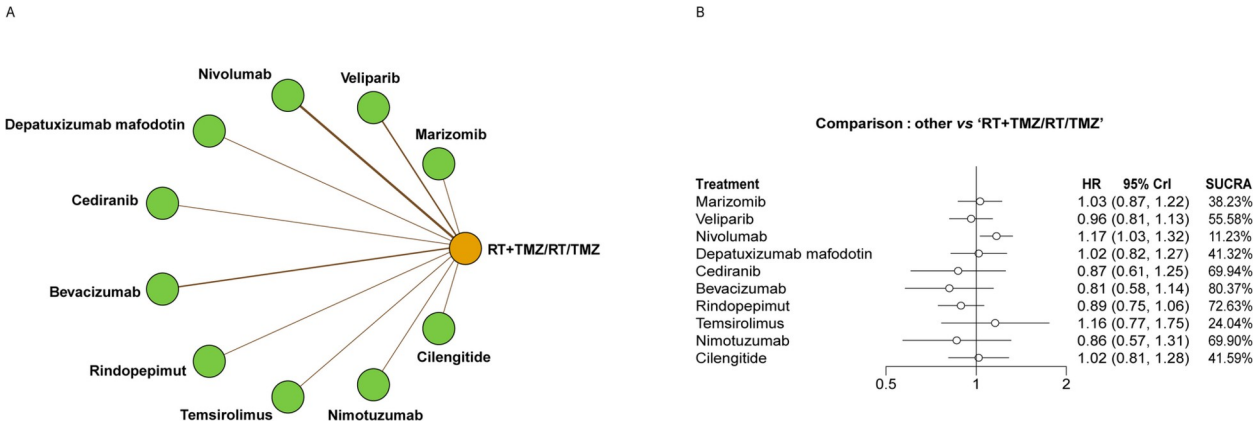

Fig. 3

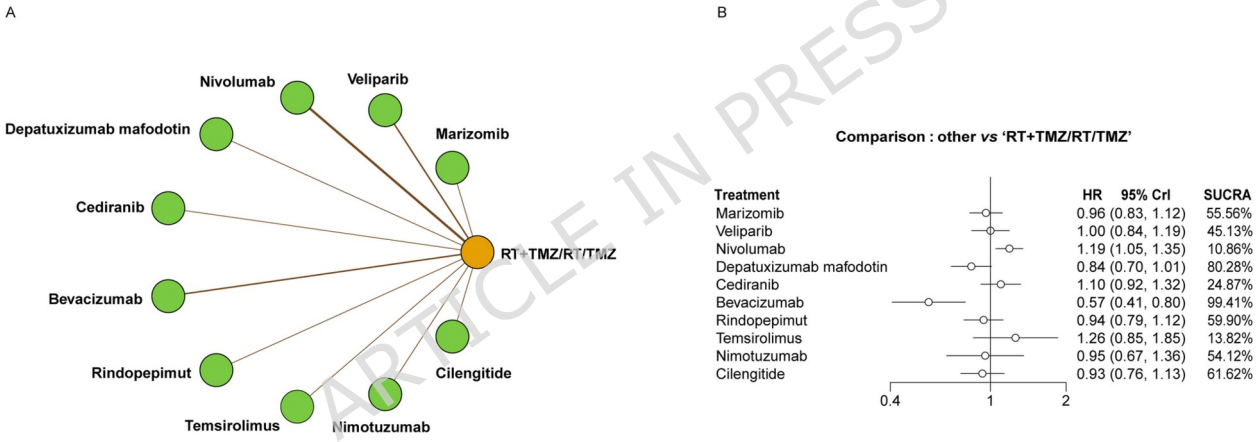

Fig. 4

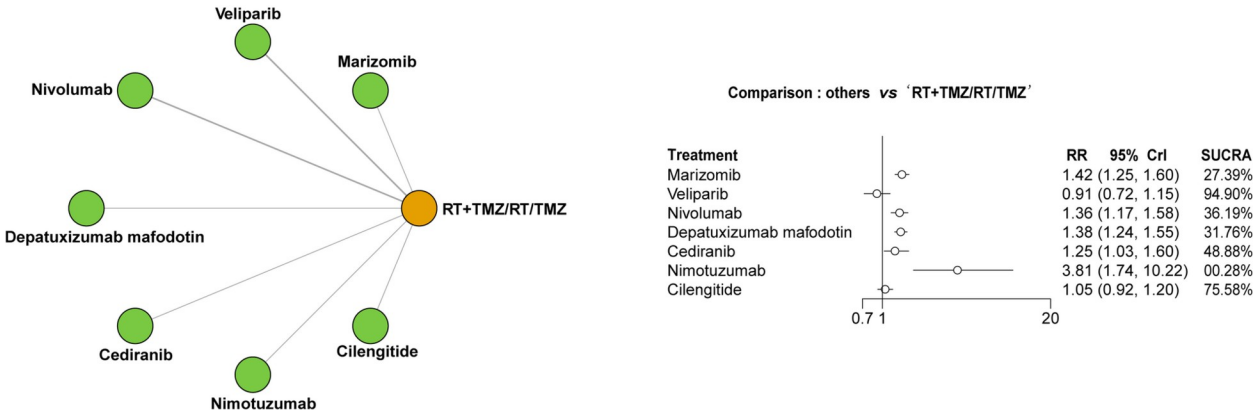

Table 1 Baseline characteristics of included RCTs

Author (year)	Country	Study design	Intervention	No.of patients	Unmethylated/ Methylated	Median age (range)	Gender (male/female)	Outcomes
Roth (2024)[12]	Switzerland	RCT	RT+TMZ	374	233/116	58.5(21.0-79.0)	255/119	OS、PFS、AE
			RT+TMZ+Marizomib	375	217/122	58.0(20.0-79.0)	233/142	
Sarkaria (2024)[7]	America	RCT	TMZ+ Placebo	224	0/224	60.0(20.0-85.0)	130/94	OS、PFS、AE
			TMZ+Veliparib	223	0/223	61.0(22.0-82.0)	127/96	
Sim (2023)[13]	America	RCT	RT+TMZ	34	21/13	73.0(66.0–84.0)	11/23	OS、PFS
			RT+TMZ+Nivolumab	69	38/31	73.0(65.0–88.0)	26/43	
Omuro (2023)[14]	Italy	RCT	RT+TMZ	280	280/0	56.0(23.0–81.0)	175/105	OS、PFS、AE
			RT+Nivolumab	280	280/0	59.5(18.0–83.0)	190/90	
Lassman (2023)[15]	America	RCT	RT+TMZ+Placebo	316	199/117	60.0(29.0–82.0)	188/128	OS、PFS、AE
			RT+TMZ+Depatux-M	323	205/118	59.0(22.0–84.0)	206/117	
Batchelor (2023)[16]	America	RCT	RT+TMZ+Placebo	55	31/18	59.0(37.0–82.0)	28/24	OS、PFS、AE
			RT+TMZ+Cediranib	103	57/36	61.0(27.0–83.0)	53/44	
Lim (2022)[17]	America	RCT	RT+TMZ+Placebo	358	0/349	60.0(18.0-81.0)	197/167	OS、PFS、AE
			RT+TMZ+Nivolumab	358	0/353	60.0(24.0-79.0)	205/153	
Sim (2021)[18]	America	RCT	RT+TMZ	41	41/0	62.0(24.0-73.0)	28/13	OS、PFS、AE
			RT+TMZ+Veliparib	84	84/0	60.0(22.0-78.0)	59/25	
Wirsching (2018)[5]	Switzerland	RCT	RT	25	18/6	70.0(65.0-79.0)	16/9	OS、PFS
			RT+Bevacizumab	50	37/10	70.0(65.0-87.0)	32/18	
Weller (2017)[11]	Switzerland	RCT	TMZ	374	218/130	58.0(52.0–64.0)	228/146	OS、PFS
			TMZ+Rindopepimut	371	224/124	59.0(51.0–64.0)	252/199	

Wick (2016)[19]	Germany	RCT	RT+TMZ	55	55/0	57.7(24.4–76.0)	36/19	OS、PFS
			RT+Temsirolimus	56	56/0	54.9(28.2–74.7)	35/21	
Balana (2016)[6]	Spain	RCT	RT+TMZ	45	18/12	62.0(36.0–75.0)	25/20	OS、PFS
			RT+TMZ+Bevacizumab	48	17/20	62.9(43.0–75.0)	31/17	
Westphal (2015)[20]	Germany	RCT	RT+TMZ	71	32/16	55.9(30.0–70.0)	45/26	OS、PFS、AE
			RT+TMZ+Nimotuzumab	71	33/15	52.9(25.0–71.0)	42/29	
Stupp (2014)[21]	Switzerland	RCT	RT+TMZ	273	0/272	58.0(50.0–64.0)	143/130	OS、PFS、AE
			RT+TMZ+Cilengitide	272	0/273	58.0(50.0–65.0)	148/124	

Note: RCT: Randomized Controlled Trial; TMZ: Temozolomide; RT: Radiation Therapy; OS: Overall Survival; PFS: Progression-Free Survival; AE: Adverse Event

Table 2 Modulating effects of MGMT methylation status on survival benefits and comparisons with overall results

Outcome	Subgroup	NO. of studies	Best-performing intervention	Worst-performing intervention	Significant pairwise comparisons
OS	Overall	14	—	Nivolumab (HR = 1.17,95% CrI:1.03-1.32)	Nivolumab vs standard(↑risk)
	Methylated	6	—	—	—
	Unmethylated	6	—	Nivolumab (HR＝1.31,95% CrI:1.09-1.58)	Nivolumab vs standard(↑risk)
PFS	Overall	14	Bevacizumab (HR=0.57,95% CrI:0.41-0.80)	Nivolumab (HR=1.19,95% CrI:1.05-1.35)	Bevacizumab vs standard(↓risk); Nivolumab vs standard(↑risk)
	Methylated	4	—	—	—
	Unmethylated	4	—	Nivolumab (HR＝1.38,95% CrI:1.15-1.65)	Nivolumab vs standard(↑risk)

'—': None (no significant difference)