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Review Article

Identifying the best treatment choice for relapsing/refractory glioblastoma: a systematic review with multiple Bayesian network meta-analyses

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Abstract

Background: Glioblastoma is a highly aggressive primary central nervous system tumor characterized by poor outcomes. In case of relapse or progression to adjuvant chemotherapy, there is no univocal preferred regimen for relapsing glioblastoma.

Methods: We conducted a systematic review and Bayesian trial-level network meta-analyses (NMA) to identify the regimens associated with the best outcomes. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and overall response rates (ORR). We estimated separate treatment rankings based on the surface under the cumulative ranking curve values. Only phase II/III prospective comparative trials were included.

Results: Twenty-four studies (3733 patients and 27 different therapies) were ultimately included. Twenty-three different regimens were compared for OS, 21 for PFS, and 26 for ORR. When taking lomustine as a common comparator, only regorafenib was likely to be significantly superior in terms of OS (hazard ratio: 0.50, 95% credible interval: 0.33-0.75). Regorafenib was significantly superior to other 16 (69.6%) regimens, including NovoTTF-100A, bevacizumab monotherapy, and several bevacizumab-based combinations. Regarding PFS and ORR, no treatment was clearly superior to the others.

Conclusions: This NMA supports regorafenib as one of the best available options for relapsing/refractory glioblastoma. Lomustine, NovoTTF-100A, and bevacizumab emerge as other viable alternative regimens. However, evidence on regorafenib is controversial at best. Moreover, most studies were underpowered, with varying inclusion criteria and primary endpoints, and no longer adapted to the most recent glioblastoma classification. A paradigmatic change in clinical trials' design for relapsing/refractory glioblastoma and more effective treatments are urgently required.

Key words: glioblastoma; regorafenib; bevacizumab; network meta-analysis; Bayesian.

Implications for Practice

This is the most updated network meta-analysis on prospective phase II/III trials in the setting of relapsing/refractory glioblastoma, and the first to include randomized trials with immunotherapy or re-irradiation. An attempt to provide clinicians with treatment rankings based on overall survival, progression-free survival, and overall response rates was carried out. Study results support regorafenib as the best therapeutic option in this context, with lomustine and bevacizumab-based regimens being viable alternatives. However, where our study mostly succeeds, is in pointing out the intrinsic limitations of published literature in refractory/relapsing glioblastoma, supporting recruitment in clinical trials as the preferential approach, and advocating for a paradigmatic change in how we design studies to tackle this prognostically unfavorable disease.

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Introduction

Glioblastoma is a highly aggressive primary central nervous system (CNS) tumor.[1] Despite increasing knowledge of its biology, the median overall survival (OS) of patients affected by glioblastoma is roughly 15 months for newly diagnosed lesions, depending on MGMT mutational status.[2] The standard-of-care is usually represented by surgical resection of the tumor lesion when feasible, followed by adjuvant radiotherapy with concurrent and subsequent chemotherapy with temozolomide for 6 cycles, with or without alternating electric field therapy.[3-5] However, tumor recurrence occurs almost always, with an average OS usually not exceeding 5-7 months after relapse.[2] Numerous efforts are ongoing to improve the survival outcome of patients affected by primary and recurrent glioblastoma. Although in the adjuvant setting a clear therapeutic standard exists,[3-5] there is no univocal standard-of-care for relapsing glioblastoma. In this case, either surgery, radiotherapy, monochemotherapy, or polichemotherapy with alkylating agents and/or target therapies with antiangiogenetic agents (bevacizumab or regorafenib, where approved) are a feasible option.[6] Yet, survival remains poor, with a 2-year and 5-year survival rate of 30% and 10%, respectively.[2,7]

Given the uncertainty regarding the best treatment strategy and the lack of direct comparisons in randomized clinical trials (RCTs) among the most commonly adopted regimens, we decided to conduct a network meta-analysis (NMA) to evaluate the activity and efficacy of all available therapeutic strategies tested for recurrent/refractory glioblastoma in prospective comparative studies and generate a ranking of treatments based on the surface under the cumulative ranking (SUCRA) curve method.[8,9]

Materials and methods

Literature search and inclusion criteria

A systematic literature review was performed on August 13, 2024 on PUBMED and Cochrane CENTRAL in order to identify prospective phase II or III comparative studies evaluating the anti-tumoral activity and clinical efficacy of local and systemic oncologic treatments for refractory/relapsing glioblastoma in adult patients. No language, nor time restrictions were adopted. We followed the recommendations of the Cochrane Collaboration, in order to identify all relevant published and unpublished trials. The search strategy was based on the use of a combination of disease, treatment, and study design terms. The full query is reported in Supplementary Methods. Also, European Society for Medical Oncology (ESMO) Congress and American Society of Clinical Oncology (ASCO) annual meeting online proceedings were consulted, along with references to the latest ESMO, ASCO, and US National Comprehensive Cancer Network (NCCN) guidelines.[3-5] Two reviewers (V.B., F.S.) independently evaluated each identified single study against the established predetermined criteria, and a third reviewer (DG) was consulted in case of controversy.

Study inclusion criteria were:

1. Prospective comparative phase II or III trials;
2. Availability or computability from published data of hazard ratios (HR) for OS and/or progression-free survival (PFS) and/or objective response data to calculate odds ratios (OR) for overall response rate (ORR).

Study endpoints and data extraction

The primary endpoint was OS. Secondary endpoints were PFS and ORR. Objective responses in included trials were defined according to the MacDonald Criteria[10] or RANO Criteria (for studies published after their introduction in 2010),[11] depending on the year of study design and conduction.

From each included publication, details were extracted on study design, study population characteristics and interventions, previous treatments, and *MGMT* mutational status. The HR for PFS and OS and associated 95% CIs were extracted or computed by extrapolating data from digitalized Kaplan-Meier curves.[12] OR and associated 95%CI for ORR were calculated based on the published objective response data.

When phase I/II was reported in the same publication, only phase II data from comparative studies was used.

Statistical analyses

A Bayesian trial-level NMA framework was adopted for each endpoint, for a total of 3 networks (OS, PFS, and ORR).[13-15] Treatment rankings for each endpoint were obtained with the SUCRA method. The SUCRA values range from 0% to 100%. A higher SUCRA value indicates a greater likelihood that a therapy ranks at the top, while a SUCRA value closer to 0 suggests a higher likelihood that the therapy ranks at the bottom.[9] The HR for PFS and OS and the OR for ORR with their respective Bayesian 95% credible intervals (CrI) were estimated using a Markov Chain Monte Carlo method as implemented in the WinBUGS software package.[13] For all the analyses, the WinBUGS sampler, using 3 chains, was run for 1 000 000 iterations that were discarded as "burn-in," and the model was run for a further 2 000 000 iterations on which inferences were based. A thinning rate of 100 iterations was used to reduce autocorrelation of the sampled values, thus leaving 20 000 iterations per chain to use for estimation and inference. Convergence of the chains was confirmed by the Gelman-Rubin statistic and by inspection of the trace plots. For each NMA, the model providing the best fit to the data between random- and fixed-effect was chosen based on the deviance information criterion (DIC). The DIC provides a measure of model fit that penalizes model complexity. The model with the lowest DIC was considered to provide the best fit to the data. When DIC values were similar (difference of <5), a fixed-effect model was preferred.[13,16,17] For the NMA of the HR, we assumed that the logHR was normally distributed with the logHR mean equaling the true logHR observed in each study, and the variance equaling the observed variability in each study. We used a vague flat (ie, uniform) prior distribution for between-study SD τ. Moreover, as for the correlations between the random effects for each trial, we adopted the standard approach to set this correlation equal to 0.5.[8] We used a common between-study variance parameter τ^2 for all studies.

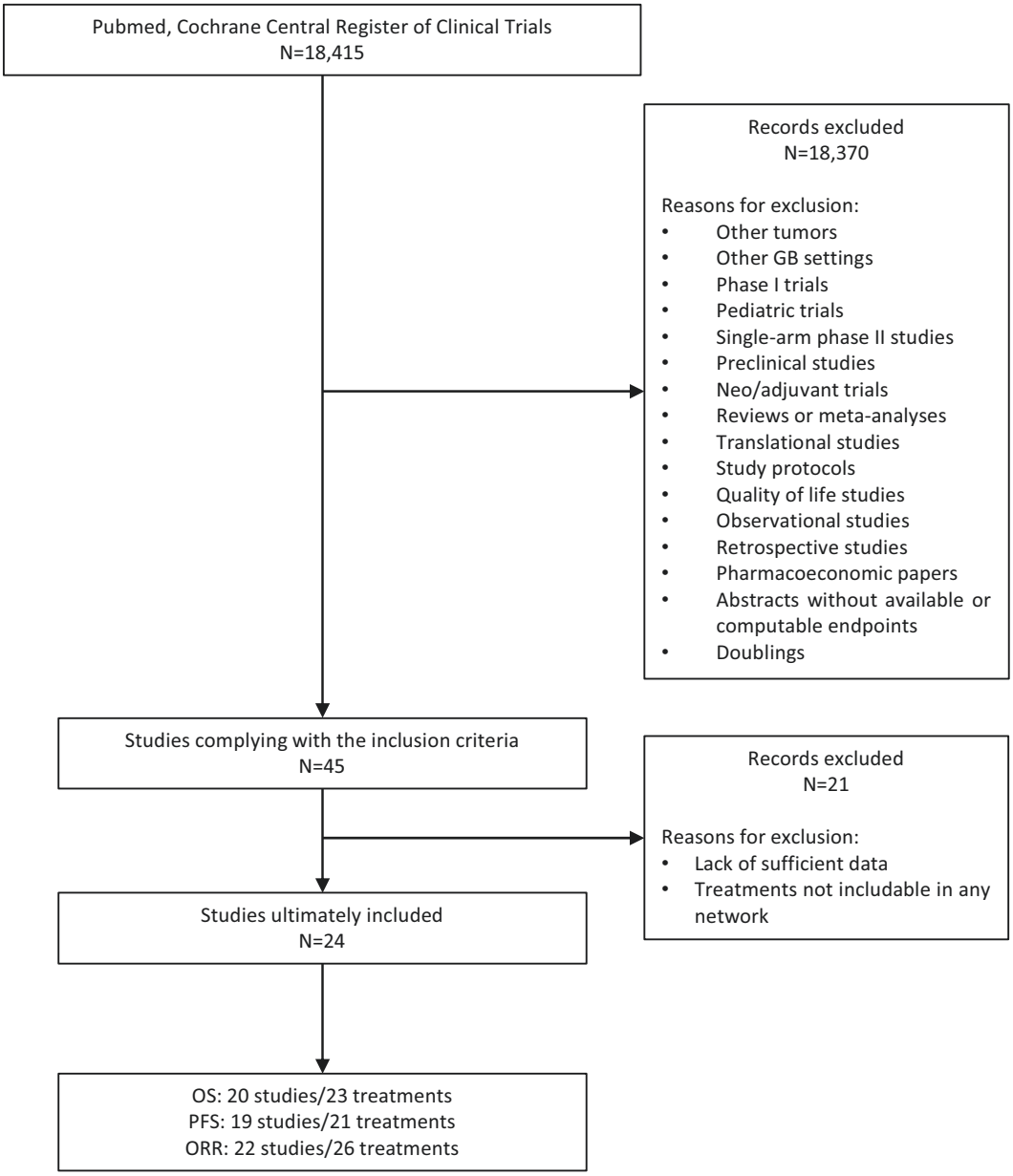
The PRISMA guidelines for NMA were followed.[18] Inconsistency of the results was explored, as recommended.[18-20] For all treatment line networks according to each endpoint, an inconsistency model was obtained by omitting the consistency equations. Then, for each endpoint, the consistency and inconsistency models were compared in terms of goodness of fit by using their relative DIC.[19,20] A difference of less than 5 points was considered to be not significant.

All the analyses were performed with WinBUGS version 1.4.3 and the results were processed using R version 4.2.0.[13,21] All the equations adopted had been published elsewhere and adapted for our analyses.[8] The risk of bias for each trial was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[22] Internal validity of eligible studies was assessed according to the Cochrane Collaboration's "Risk of Bias" tool in Review Manager[23] (RevMan 5, http://tech.cochrane.org/revman).

A formal review protocol was not prepared. This study was registered in the Open Science Framework online public database, registration DOI: 10.17605/OSF.IO/UMF8C.

Results

Overall, 18 415 references were screened. Among them, only 45 were prospective interventional comparative phase II and III studies concerning refractory/relapsing GB.[24-68] However, based on the available published data and treatment type, 24 studies could be ultimately included in our analyses (Figure 1),[24,28,30,31,33-35,39,42-44,46,47,49,51-55,60-64] for a total of 3733 patients and 27 different therapies. The median age of patients in the included studies was 56.3 years (interquartile range [IQR]: 55.0-63.1). Eighteen (75.0%) trials were phase II and 6 (25.0%) were phase III, with 1 phase II trial being non-randomized (5.6%).[54] A total of 4 (16.7%) studies included patients in 2nd or further lines,[42,46,51,60] while the



Legend. OS: overall survival; PFS: progression-free survival; ORR: overall response rate; GB: glioblastoma.

Figure 1. PRISMA flow-chart. Abbreviations: GB, glioblastoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Table 1. Main characteristics of the included studies.

First author	Line	Phase	Randomized	N. Arms	Treatments	Centers	N. patients	Age (median years)	Primary endpoint(s)	Bevacizumab-pretreated	MGMT-methylated (%)	IDH1/2-mutant (%)	EGFRvIII (%)
Batchelor 2013 J Clin Oncol	2nd	III	Yes	3	Cediranib vs Cediranib + Lomustine vs Lomustine	Multicenter	325	54, 54, 54	PFS	No	—	—	—
Brandes 2016 Neuro-Oncology	2nd	II	Yes	3	Galunisertib + Lomustine vs Galunisertib vs Lomustine	Multicenter	158	58, 58, 58	OS	No	—	3.8, 10.3, 2.5	—
Brown 2016 PLOS One	2nd	II	Yes	2	Cediranib + Gefitinib vs Cediranib	Multicenter	38	55, 61	PFS	No	—	—	—
Cloughesy 2017 J Clin Oncol	2nd	II	Yes	2	Bevacizumab + Onartuzumab vs Bevacizumab	Not reported	129	57, 55	PFS	No	37.5, 48.1	6.9, 8.8	—
Field 2015 Neuro-Oncology	2nd	II	Yes	2	Bevacizumab + Carboplatin vs Bevacizumab	Multicenter	122	55, 55	PFS	No	—	—	—
Friedman 2019 J Clin Oncol	2nd	II	Yes	2	Bevacizumab vs Bevacizumab + Irinotecan	Multicenter	167	54, 57	6-month PFS and ORR	No	—	—	—
Gilbert 2016 J Neurooncol	2nd	II	Yes	2	Bevacizumab + Irinotecan vs Bevacizumab + Temozolomide	Not reported	117	55, 58	6-month PFS	Allowed	—	—	—
Reardon 2011 J Neurooncol	2nd	II	Yes	2	Bevacizumab + Temozolomide vs Bevacizumab + Etoposide	Single center	23	50.8, 52.4	6-month PFS	Allowed	—	—	—
Tsien CI 2022 J Clin Oncol	≥2nd	II	Yes	2	Bevacizumab + Radiotherapy vs Bevacizumab	Multicenter	170	60, 57	OS	Unclear, but mostly no	20.9, 14.3	—	—
Stupp 2012 Europ J Can	2nd	III	Yes	2	NovoTTF-100A vs Bevacizumab/Lomustine/Other	Multicenter	237	54, 54	OS	Yes (19% and 18%)	—	—	—
Taal 2014 Lancet Oncol	2nd	II	Yes	4	Bevacizumab vs Lomustine vs Bevacizumab + Lomustine 90mg/m2 vs Bevacizumab + Lomustine	Multicenter	153	58, 56, 53, 58	9-month OS	No	43.0, 53.0, 46.0, 33.0	3.0, 7.0, 10.0, 0.0	—
Weathers 2016 J Neurooncol	2nd	II	Yes	2	Bevacizumab vs LD Bevacizumab + Lomustine	Single center	71	—	PFS	No	—	—	—
Wick 2010 J Clin Oncol	2nd	III	Yes	2	Enzastaurin vs Lomustine	Multicenter	266	—	PFS	No	—	—	—
Wick 2017 New Eng J Med	2nd	III	Yes	2	Bevacizumab + Lomustine vs Lomustine	Multicenter	437	—	OS	No	23.3, 24.8	—	—
Brandes 2019 The Oncologist	≥2nd	II	Yes	2	Bevacizumab + Lomustine vs Lomustine	Multicenter	123	56, 58.5	OS	No	19.4, 18.0	—	—
Lombardi 2019 Lancet Oncol	2nd	II	Yes	2	Regorafenib vs Lomustine	Multicenter	119	54.8, 58.9	OS	Allowed	49.0, 46.0	5.0, 0.0	—
Reardon 2017 Cancer	2nd	II	No	2	Trebananib vs Bevacizumab + Trebananib	Multicenter	48	61.9, 63.1	6-month PFS	No	18.1, 8.1	18.1, 5.4	—

Table 1. Continued

First author	Line	Phase	Randomized	N. Arms	Treatments	Centers	N. patients	Age (median years)	Primary endpoint(s)	Bevacizumab-pretreated	MGMT-methylated (%)	IDH1/2-mutant (%)	EGFRvIII (%)
Reardon 2020 JAMA Oncol	2nd	III	Yes	2	Nivolumab vs Bevacizumab	Multicenter	369	55.5, 55	OS	No	23.4, 22.7	—	—
Bota 2018 Future Medicine	2nd	II	Yes	2	Bevacizumab + ERC1671 (Gliovac) vs Bevacizumab	Not reported	9	—	OS	No	—	0.0, 0.0	—
Cloughesy 2020 Neuro-Oncology	≥2nd	III	Yes	2	Bevacizumab + VB-111 vs Bevacizumab	Multicenter	256	—	OS	No	15.6, 20.3	10.2, 9.4	20.3, 18.8
Galanis 2019 Cancer	2nd	II	Yes	2	Bevacizumab + Dasatinib vs Bevacizumab	Multicenter	121	58, 56.5	6-month PFS	No	—	—	—
Lee 2020 Cancer	2nd	II	Yes	2	Bevacizumab + Trebananib vs Bevacizumab	Multicenter	115	57, 58	6-month PFS	No	—	—	—
Puduvalli 2020 Neuro-Oncology	2nd	II	Yes	2	Bevacizumab + Vorinostat vs Bevacizumab	Multicenter	87	—	PFS	No	—	—	—
Reardon 2020 Clin Can Res	2nd	II	Yes	2	Rindopepimut + Bevacizumab vs Bevacizumab	Multicenter	73	59, 55	6-month PFS	No	—	—	100.0, 100.0

Abbreviations: LD, low dose; ORR, objective response rates; OS, overall survival; PFS, progression-free survival; RT, radiotherapy.

rest were 2nd-line trials. In all studies, patients had previously received temozolomide. Bevacizumab, alone or in combination, was the most common therapeutic agent adopted. Previous administration was clearly allowed only in 4 studies,[35,39,43,55] in 2 (50.0%) of these a bevacizumab-containing regimen was assessed, in another 1 (25.0%) a tyrosine kinase inhibitor (TKI) with anti-angiogenic activity (ie, regorafenib) was tested. In one study, previous bevacizumab administration status was not specified, but most patients (80.6%) were treated with a bevacizumab-containing regimen at their first relapse, suggesting most had not received it, yet.[42] To note, to include NovoTTF-100A in the networks, the active control in Stupp et al was assumed to be bevacizumab monotherapy, considering that this was the most frequent therapeutic option adopted in the trial.[43]

MGMT methylation, *IDH*1/2 mutations, and EGFRvIII expression, which are all currently well-known glioblastoma molecular prognostic and/or predictive biomarkers, had been assessed in 9 (37.5%),[31,42,44,49,51,52,54,55,60] 8 (33.3%),[28,31,42,44,53-55,60] and 2 (8.3%)[60,61] studies, respectively. The median percentage of *MGMT* promoter methylated glioblastoma was 23.4% (IQR: 19.1-43.8%). The median percentage of *IDH*-mutant glioblastoma was 6.9% (IQR: 2.9%-10.2%). In Reardon et al all glioblastoma had to be positive for EGFRvIII, either in the primary or the relapsing tumor,[61] while in Cloughesy et al approximately 20% of cases were EGFRvIII-positive.[60]

Study characteristics are resumed in Table 1.

Primary endpoint: overall survival

For the OS network, a fixed-effect model turned out to be the best-fitting model based on DIC. Overall, 23 different treatments were compared (Figure 2).

When taking lomustine monotherapy as a common comparator, we observed that only regorafenib (HR: 0.50, 95%CrI: 0.33-0.75) was likely to be significantly superior in terms of OS (Figure 3). Regorafenib was likely to be significantly superior to 16 (69.6%) regimens, including NovoTTF-100A (HR: 0.53, 95%CrI: 0.28-0.98), nivolumab (HR: 0.44, 95%CrI: 0.24-0.79), bevacizumab monotherapy (HR: 0.46, 95%CrI: 0.26-0.80) or combined with lomustine (HR: 0.54, 95%CrI: 0.34-0.86), carboplatin (HR: 0.39, 9%CrI: 0.20-0.75), or re-irradiation (HR: 0.47, 95%CrI: 0.24-0.90). The TKI was the best treatment choice according to the SUCRA-based ranking (Figure 3). According to SUCRA, lomustine ranked 5th when considering only approved therapies, and was superior to bevacizumab monotherapy (Figure 3). The direct comparison between the 2 therapies did not show a significantly different association with OS (HR: 0.83, 95%CrI: 0.61-1.14). To note, besides regorafenib, no other regimen among those approved for the clinical practice showed any significant superiority/inferiority to others, including bevacizumab monotherapy (not shown). There was no relevant inconsistency in the OS network model based on DIC.

Secondary endpoint: progression-free survival and overall response rates

For the PFS and the ORR networks, a random effect model turned out to be the best-fitting model based on DIC. Respectively, 21 and 26 different regimens were compared in the former and latter networks (Figure 2). No treatment was significantly superior to lomustine monotherapy in PFS and in ORR (Figure 4). Furthermore, no treatment was likely to be

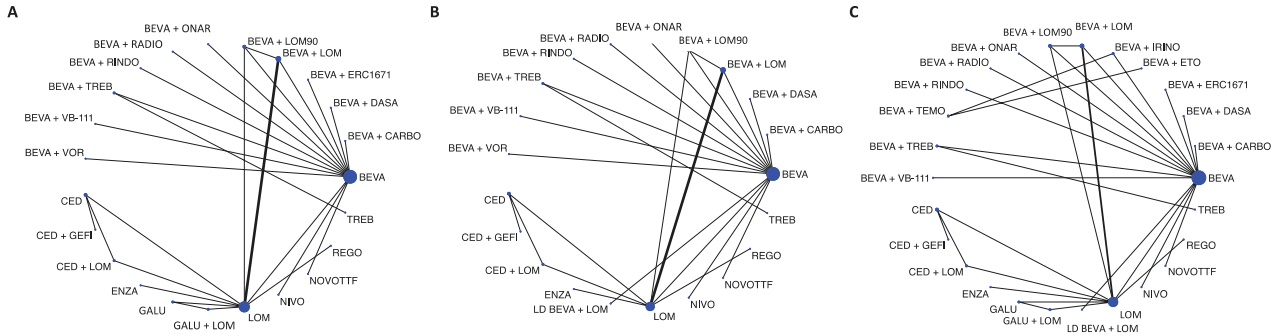


Figure 2. Treatment networks of OS, PFS, and ORR. Direct comparisons are represented by the black lines connecting the treatments. Line width is proportional to the number of trials including every pair of treatments, whereas circle size is proportional to the total number of patients difference in the proportion of patients for each treatment in the network. (A) OS network; (B) PFS network; (C) ORR network. Abbreviations: BEVA, bevacizumab; CARBO, carboplatin; CED, cediranib; DASA, dasatinib; ENZA, enzastaurin; ERC1671, sitoiganap; ETO, etoposide; GALU, galunisertib; GEFI, gefitinib; IRINO, irinotecan; LD, low dose; LOM, lomustine; LOM90, lomustine at a dose of 90mg/m^2; NIVO, nivolumab; NOVOTTF, NovoTTF-100A; ONAR, onartuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RADIO, radiotherapy; REGO, regorafenib; RINDO, rindopepimut; TEMO, temozolomide; TREB, trebananib; VB-111, ofranergene obadenovec; VOR, vorinostat.

significantly superior to the others regarding both endpoints (not shown). According to SUCRA values, the top 5 regimens approved for clinical practice that were likely to improve most PFS when compared to lomustine monotherapy (SUCRA: 0.41) and all other regimens, were bevacizumab + lomustine in 3 different schedules (SUCRA: 0.65 and 0.58), bevacizumab + re-irradiation (SUCRA: 0.58) and NovoTTF-100A (SUCRA: 0.56) (Supplementary Figure S1). Regorafenib and bevacizumab monotherapy provided similar results in terms of PFS, which reflected in a similar SUCRA value (SUCRA: 0.52 and 0.51, respectively). The top 5 regimens approved for clinical practice that were likely to provide higher ORR compared to lomustine (SUCRA: 0.31) and all other regimens, were bevacizumab + carboplatin, lomustine, re-irradiation, or irinotecan (SUCRA: 0.66, 0.64, 0.63, and 0.62, respectively) and NovoTTF-100A (SUCRA: 0.66) (Supplementary Figure 2). There was no relevant inconsistency in both PFS and ORR network models, based on DIC (Supplementary Results).

Risk of bias analysis

Overall, the included studies presented with low risk of bias for most domains (Figure 5). Globally, the highest risk was observed for the performance and detection biases, since 9 (37.5%) studies were open-label and the blinding of the outcome assessment was uncertain in 10 (41.6%) studies and absent in 5 (20.8%) (Supplementary Figure 3).

Discussion

We conducted a systematic literature search and Bayesian NMA to identify the best therapeutic option in terms of OS, PFS, and ORR for refractory/relapsing glioblastoma. We detected 24 prospective interventional phase II or III trials, almost all randomized, which compared 27 different treatment regimens. Lomustine was used as a common comparator to show the main results, being a treatment generally available worldwide and frequently used in the setting of relapsing/refractory glioblastoma. To note, bevacizumab is the preferred option in some countries. Overall, the anti-angiogenic TKI regorafenib proved to be the best therapeutic option in terms of OS. No other treatment was significantly superior to lomustine or bevacizumab, nor to regorafenib. In terms of PFS and ORR, no specific treatment was significantly superior to lomustine, or to the others.

Defining a standard-of-care for relapsing/refractory glioblastoma already pre-treated with temozolomide is a non-trivial endeavor. Many treatments have been tested so far, without showing significant PFS and OS improvements, with few exceptions.[24-68] For this reason, the only approaches currently recommended by main international guidelines are surgery or re-irradiation with palliative purposes, temozolomide rechallenges (not studied in randomized trials), nitrosureas (lomustine, fotemustine, or carmustine) in monotherapy, or in combination (eg, PCV) or platinum agents.[3,5,69] In fact, the most recent ASCO guidelines pose no specific recommendation for or against any therapeutic strategy in this setting, recommending that patients with recurrent glioblastoma should be referred for participation in a clinical trial whenever possible.[5] Evidence for chemotherapy agents typically came from clinical trials in which the currently recommended regimens were used as control arms. Since no significant improvements in PFS/OS were observed with the experimental treatments, these control regimens were deemed to be an appropriate benchmark. Differently, regorafenib provided superior OS than lomustine in the REGOMA trial,[55] whereas bevacizumab added to lomustine showed superior PFS (but no OS) than lomustine in the EORTC26101 trial.[49] Nonetheless, bevacizumab failed to provide superior outcomes than control regimens in other studies, either in monotherapy or in combination.[44,46,51] However, bevacizumab has a proven steroid-sparing effect, which can effectively improve patients' quality of life, and is a usually well-tolerated drug. Hence, it was ultimately approved by the US Food and Drug Administration (FDA) in monotherapy or combination for the treatment of recurrent glioblastoma.[5] Still, available data have been considered insufficient so far by many other regulatory agencies, including the European Medicine Agency.

Regorafenib, was recently added as a preferred regimen at recurrence in the NCCN guidelines.[4] The drug was also approved in several European countries and recommended by national guidelines. However, its availability worldwide is limited. This is because the OS improvement observed in the REGOMA trial was counterbalanced by the extremely poor

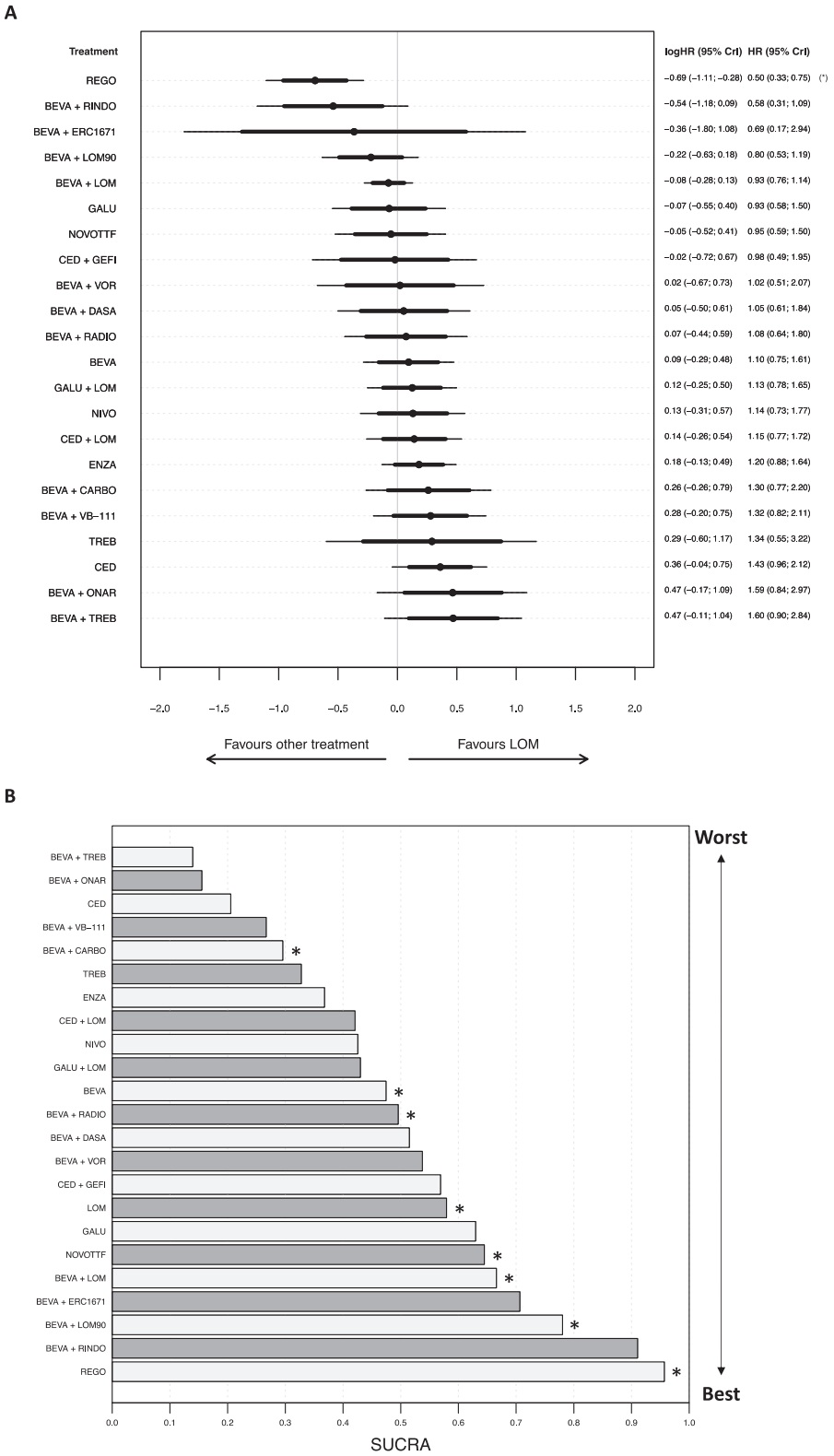


Figure 3. Forest plot of OS of all included regimens for relapsed/refractory glioblastoma compared to lomustine monotherapy and treatment ranking based on SUCRA. (A) A forest plot including the logHR of OS of each treatment vs lomustine monotherapy. Central dots represent posterior medians; thin lines represent 95%CrI, while thicker ones represent 80% CrI. Log scale was adopted to graphically represent the 95% CrI. The first column of values on the right reports the logHR with 95%CrI, the second column reports HR for OS with 95%CrI. Statistically significant results according to Bayesian posterior medians and 95%CrI are highlighted by asterisks. (B) Treatment ranking according to the OS endpoint, based on SUCRA values. Bar plot displaying SUCRA values for treatments analyzed in a Bayesian network meta-analysis. Each bar represents a treatment, with the height of the bar corresponding to its SUCRA value, which indicates the probability of a treatment being among the most effective options. Higher bars denote higher SUCRA values, suggesting greater effectiveness relative to other treatments. The y-axis lists the treatments, and the x-axis shows the SUCRA values as percentages. Abbreviations: BEVA, bevacizumab; CARBO, carboplatin; CED, cediranib; CrI, credible interval; DASA, dasatinib; ENZA, enzastaurin;

outcomes of the lomustine control arm likely due to the worse prognostic features of this cohort, which made the study results controversial. Additionally, some non-trivial grade (G) 3-4 toxicities like hand-foot skin reaction (10%) or neutropenia (5%) and frequent G1-2 toxicities like fatigue (24%), hypertension (22%), diarrhea (15%), and skin rash/desquamation (12%) were associated to the TKI. Our results, shed light on the performance of regorafenib when compared also to bevacizumab-based regimens and chemotherapies other than lomustine. In this perspective, our analysis seems to support a potential role for regorafenib in recurrent glioblastoma, despite the limitations previously exposed. Furthermore, regorafenib is likely less toxic than combination chemotherapies that are also administered in the refractory scenario, such as PCV, to which it could not be compared in this NMA. At the same time, regorafenib recent performance in the GBM AGILE adaptive phase II/III trial (NCT03970447) was disappointing at best, posing serious questions on its therapeutic efficacy in this context.[70]

According to these NMA results, bevacizumab, both in monotherapy or in combination with chemotherapy or re-irradiation, seemed not to be significantly inferior, nor superior to other treatments on all endpoints. Only in terms of OS, bevacizumab was significantly inferior to regorafenib. Noteworthy, no bevacizumab-based combination was significantly superior to bevacizumab monotherapy, despite showing a better SUCRA ranking position on all endpoints. Consequently, taking into account its potential steroid-sparing role, the availability of biosimilar drugs that significantly reduced its costs, the potential PFS benefit, and the mild toxicity profile in comparison to most single-agent chemotherapies, bevacizumab alone might be a reasonable therapeutic option in the refractory scenario, especially for patients unfit for chemotherapy or regorafenib. Less clear remains its role in combination with chemotherapy, since no specific advantages can be clearly detected. Importantly, bevacizumab sequential use after regorafenib has not been studied, whereas in the REGOMA trial bevacizumab therapy previous to regorafenib administration was allowed,[55] suggesting the feasibility of this sequence.

Interestingly, NovoTTF-100A, an FDA-approved medical device based on the use of electric fields applied to the tumor mass to destroy brain cancer cells, not subject to common mechanisms of antineoplastic resistance, showed in its pivotal trial comparable efficacy and activity with chemotherapy regimens commonly used for refractory/recurrent glioblastoma. Moreover, toxicity and quality of life clearly favored NovoTTF-100A over systemic anticancer agents.[43] In this NMA, NovoTTF-100A was the 2nd best option in the SUCRA ranking for the ORR, despite being less performing in terms of PFS and OS as compared to regorafenib and bevacizumab-based regimens. Therefore, taking into account this evidence, but also considering that this NMA is ultimately inconclusive for the lack of statistically significant results and that the same pivotal trial had the important limitation of non-centralized imaging evaluation for assessing tumor responses, we suggest that NovoTTF-100A might be an alternative option only for selected cases, for example, when objective responses are required for symptomatic palliation.

Recent preliminary evidences show that in glioblastoma with melanoma-like *BRAF* mutations (occurring in ~3% adult cases), anti-BRAF/MEK combinations might be active therapeutic options,[71] which are also recommended by the NCCN guidelines as off-label treatment.[4] Several phase I and/or II studies are currently ongoing in this setting.[71] Moreover, in 1%-2% glioblastoma cases, aberrant *NTRK* fusions can be targeted with TKI entrectinib or larotrectinib, following their tumor-agnostic approval based on 2 patient-level pooled analyses of non-randomized, non-comparative phase I and II trials.[4,5,72,73] Unfortunately, we could not compare the performance of all these regimens, since no comparative data are available and the proportion of *BRAF*V600-mutant or NTRK-fusion-positive glioblastoma in all studies included in our networks is unknown. In any case, besides these limited successful examples, the vast majority of molecularly-driven therapeutic strategies hardly proved some benefit in glioblastoma. To promote more effective personalized treatment strategies, numerous efforts have been made in recent years to improve our knowledge concerning glioblastoma biology. The Cancer Genome Atlas Research Network described recurrent genomic abnormalities in glioblastoma in 2008 and the methylation of *MGMT* promoter was found to be associated with sensitivity to alkylating agents.[74] A subsequent seminal work from Verhaak et al identified a robust gene expression-based molecular classification that subdivided glioblastoma into proneural, neural, classical, and mesenchymal subtypes, with differential response to intensive treatments and proneural glioblastoma showing a trend toward longer survival.[75] However, the identification of reliable predictive biomarkers of response for glioblastoma is still elusive.

Conducting RCTs in patients affected by glioblastoma is a hard task because this tumor is infrequent and its rarity contributes to a paucity of funding for developing new drugs.[76] Furthermore, cognitive and motor impairment due to the disease itself makes it more difficult than for other cancers to enroll patients and make them strictly adhere to study protocols. Additionally, most available treatments prevent patients from entering many studies on recurrent glioblastoma, due to their exclusion criteria. Thus, the main strength of this NMA is that it provides evidence of comparisons of different therapeutic options which were mostly not (and likely will not be) compared in RCTs. At the same time, the major limitation is that we could not include some treatments that are conventionally used in relapsing/refractory glioblastoma (eg, PVC or platinum-based regimens), because approximately half of the initially selected studies were not linkable, due to heterogeneity in treatment strategies or unavailability of data required for statistical analyses. The latter issue is not surprising, considering that a significant number of trials were of phase II, and these trials are often underpowered and/or not designed to assess survival endpoints such as OS. However, restricting our search only to phase III trials would have significantly limited the possibility of developing an adequate network for our analyses. A possible solution might have been to have no

ERC1671, sitoiganap; GALU, galunisertib; GEFI, gefitinib; HR, hazard ratio; LOM, lomustina; LOM90, lomustine at a dose of 90mg/m^2; NIVO, nivolumab; NOVOTTF, NovoTTF-100A; ONAR, onartuzumab; OS, overall survival; RADIO, radiotherapy; REGO, regorafenib; RINDO, rindopepimut; SUCRA, surface under the cumulative ranking curve; TREB, trebananib; VB-111, ofranergene obadenovec; VOR, vorinostat. The ranking also includes regimens that are currently not approved or no longer in active development. *Identify regimens potentially available in clinical practice, although geographical restrictions exist due to heterogeneous approvals and reimbursement worldwide.

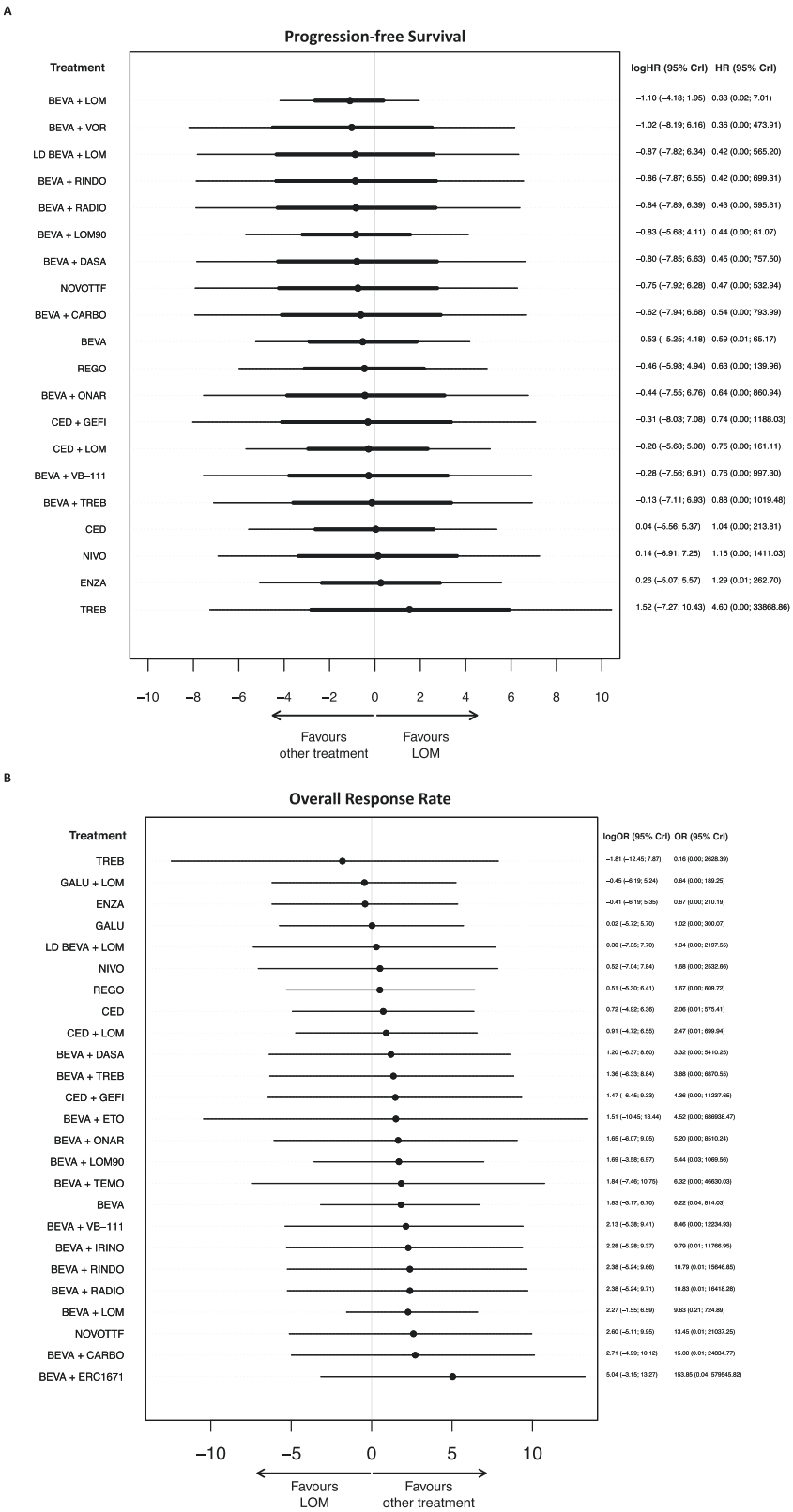


Figure 4. Forest plots of PFS and ORR of all included regimens for relapsed/refractory glioblastoma compared to lomustine monotherapy. (A) A forest plot including the logHR of PFS of each treatment vs lomustine monotherapy. Central dots represent posterior medians; thin lines represent 95%CrI, while thicker ones represent 80% CrI. Log scale was adopted to graphically represent the 95% CrI. The first column of values on the right reports the logHR with 95%CrI, the second column reports HR for PFS with 95%CrI. Statistically significant results according to Bayesian posterior medians and 95%CrI are highlighted by asterisks. (B) A forest plot including the logOR for ORR of each treatment vs lomustine monotherapy. Central dots represent posterior medians; lines represent 95% CrI. Log scale was adopted to graphically represent the 95% CrI. The first column of values on the right reports the logOR with 95% CrI, and the second column reports OR with 95% CrI. Statistically significant results according to Bayesian posterior medians and 95% CrI are highlighted by asterisks. Abbreviations: BEVA, bevacizumab; CARBO, carboplatin; CED, cediranib; CrI, credible interval; DASA, dasatinib; ENZA, enzastaurin; ERC1671, sitoiganap; ETO, etoposide; GALU, galunisertib; GEFI, gefitinib; HR, hazard ratio; IRINO, irinotecan; LD, low dose; LOM, lomustina; LOM90, lomustine at a dose of 90mg/m^2; NIVO, nivolumab; NOVOTTF, NovoTTF-100A; ONAR, onartuzumab; OR, odds ratio; ORR, overall response rate; PFS, progression-free survival; RADIO, radiotherapy. REGO, regorafenib; RINDO, rindopepimut; TEMO, temozolomide; TREB, trebananib; VB-111, ofranergene obadenovec; VOR, vorinostat.

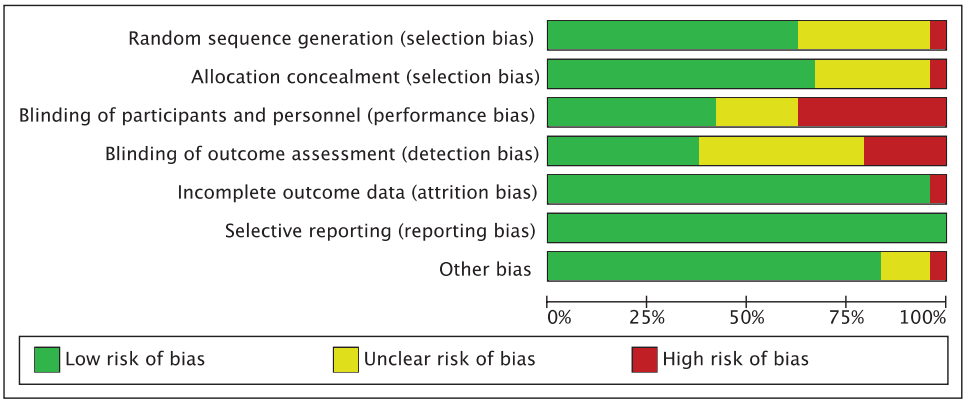


Figure 5. Global risk of bias analysis.

restriction for first-line setting trials, however, we chase to conduct our analyses in a more homogeneous setting, which is, by contrast, an important strength of our NMA. Another important limitation derives from WHO reclassifying CNS tumors in 2021. Since then, the *IDH*1/2-mutant entities are no longer considered as GB.[77] The most relevant consequence is the fact that many trial results are partially affected by the presence of IDH-mutant disease. Nonetheless, the approval of currently available therapeutic choices is based on the results of studies conducted before this paradigmatic change, including the ones that could be included in this NMA. Moreover, in 29.2% of the included studies, the mutational status was known and the proportion of IDH-mutant cases went from none to 18.1%, with a median of 6.9%. Considering the general low proportion of cases and their better prognosis compared to pure glioblastoma, it is unlikely that our results could be dramatically affected by this specific issue. However, it should be also considered that for most studies the population had not been molecularly characterized with respect to *MGMT* promoter methylation and EGFRvIII status. As a consequence, some population heterogeneity has to be considered when analyzing this study's results. Another limitation is that we could not provide a network for toxicities due to the heterogeneity of side effects reporting in distinct clinical trials. Finally, we also point out that NMA shares the same limitations as standard pairwise meta-analyses.[78]

To the best of our knowledge, while this is not the first NMA in the setting of relapsing/refractory glioblastoma, it is the most updated, also including immune-checkpoint inhibitor nivolumab, which was missing in previous studies, as well as the only published randomized study testing re-irradiation in a refractory scenario.[79,80] No significant inconsistency was found in our analytical models, the internal validity of the eligible studies was successfully assessed with the most appropriate risk of bias analysis[81] and results were methodologically reliable, being also coherent with previous efforts.[79,80] However, we believe that where our study mostly succeeds, is in pointing out the intrinsic limitations of published literature in glioblastoma, where most studies are underpowered, have varying inclusion criteria and primary endpoints, and are no longer adapted to the most updated WHO classification. Hence, given all these considerations, the poor response, and the scarce OS improvements provided by all of the available therapeutic options, recruiting in clinical trials should be always considered the preferential approach. Furthermore, the incorporation of next-generation sequencing and proteomic platforms in clinical trials for patient selection or stratification, or the development of clinical trials with Bayesian adaptive design to expedite the identification of promising drugs, as elegantly done with the GBM AGILE trial,[70] might represent a paradigmatic change that we strongly need, in order to develop more effective treatments to tackle refracting/relapsing glioblastoma.

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Author contributions

All authors conceived the study. Francesco Schettini and Victoria Buché independently performed the literature search and Daniele Generali was consulted in case of controversy. Francesco Schettini and Victoria Buché collected the data from retrieved studies. Sergio Venturini digitalized the Kaplan-Meier curves and calculated the hazard ratios for the survival endpoints when unavailable from published abstracts or articles. Francesco Schettini and Daniele Generali approved the final list of included studies. Sergio Venturini built the networks and performed the statistical analyses. Francesco Schettini, Sergio Venturini, Estela Pineda, and Daniele Generali wrote the first manuscript draft. All authors revised and accepted the final version of the manuscript.

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Conflicts of interest

Francesco Schettini reports honoraria from Novartis, Gilead, and Daiichy-Sankyo for educational events/materials, advisory

role for Pfizer, and travel expenses from Novartis, Gilead and Daiichy-Sankyo. Daniele Generali declares personal fees for educational events by Novartis, Lilly, Pfizer, Daiichy-Sankyo, and Roche; research funds from AstraZeneca, Novartis, and LILT. The authors have declared no conflict of interest.

Data availability

The data used for the analyses reported in this study are publicly available from published literature. No proprietary codes were used in the statistical analyses.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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