









Targeted therapies in patients with newly diagnosed glioblastoma—A systematic meta-analysis of randomized clinical trials

Angelika Scherm¹ | Franziska Maria Ippen²  | Peter Hau¹  |
 Hansjörg Baurecht³  | Wolfgang Wick^{2,4}  | Jens Gempt⁵  | Helge Knüttel⁶  |
 Michael F. Leitzmann³  | Corinna Seliger² 

¹Wilhelm Sander-NeuroOncology Unit and Department of Neurology, Regensburg University Hospital, Regensburg, Germany

²Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany

³Institute of Epidemiology and Preventive Medicine, Regensburg University Hospital, Regensburg, Germany

⁴German Cancer Research Center (DKFZ) & German Cancer Center (DKTK), Heidelberg, Germany

⁵Department of Neurosurgery, Klinikum rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

⁶University Library, Regensburg University, Regensburg, Germany

Correspondence

Corinna Seliger, Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany.

Email: corinna.seliger-behme@med.uni-heidelberg.de

Abstract

Glioblastoma (GB) is the most common malignant primary brain tumor in adults. The standard of care for newly diagnosed GB involves surgical resection followed by radiochemotherapy with temozolomide, with or without tumor-treating fields. In recent years, various efforts have been made to identify suitable molecularly targeted treatment options for malignant brain tumors. This meta-analysis provides an overview of recently published randomized controlled trials (RCTs) with and without molecular stratification, analyzing targeted agents in patients with newly diagnosed GB. The Cochrane Library, MEDLINE (Ovid), ClinicalTrials.gov, WHO's International Clinical Trials Registry Platform, and Google Scholar were searched for RCTs on targeted therapies in patients with newly diagnosed glioblastoma. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were extracted and pooled in a random-effects meta-analysis. Twelve RCTs (n = 3941 patients) involving protein kinase inhibitors, proteasome and histone deacetylase inhibitors, anti-angiogenic approaches and poly (ADP-ribose) polymerase (PARP) inhibitors were included in the meta-analysis. None of the targeted agents achieved a significant benefit with regard to OS (HR = 0.98 [95% confidence interval (CI) 0.86-1.11, P = .7731]). By comparison, targeted therapy showed a benefit for PFS (HR = 0.83 [95% CI 0.74-0.94, P = .0037]), especially for patients with an unmethylated O6-methylguanine-DNA-methyltransferase (MGMT) promoter (0.75 [95% CI

Abbreviations: BBB, blood-brain-barrier; CDK, cyclin-dependent kinase; CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; EIAEDs, enzyme-inducing antiepileptic drugs; FGFR, fibroblast growth factor receptor; FLT1, Fms-related receptor tyrosine kinase 1; GB, glioblastoma; HDAC, histone deacetylase; HGFR, hepatocyte growth factor receptor; HR, hazard ratio; HR-QoL, health-related quality of life; IDH, isocitrate dehydrogenase; IGF-R, insulin-like growth factor receptor; KDR, kinase insert domain-containing receptor; MDM2, mouse double minute 2 homolog; MGMT, O6-methylguanine-DNA-methyltransferase; MMSE, Mini-Mental State Examination; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; OS, overall survival; OS-12, overall survival at 12 months; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PFS-12, progression-free survival at 12 months; PFS-6, progression-free survival at 6 months; PI3K, phosphatidylinositol-3 kinase; PKC β , protein kinase C- β ; RB1, retinoblastoma protein 1; RCT, randomized clinical trial; RPA, recursive partitioning analysis; RR, risk ratio; TGF- β , transforming growth factor beta; TMZ, temozolomide; TP53, tumor protein 53; VEGFR, vascular endothelial growth factor receptor.

Angelika Scherm and Franziska Maria Ippen contributed equally to this study.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *International Journal of Cancer* published by John Wiley & Sons Ltd on behalf of UICC.

0.56-0.99, $P = .0440$)). Prolongation of PFS was largely driven by VEGF inhibition with bevacizumab (HR = 0.70 [95% CI 0.61-0.80, $P = .0000$]). VEGF inhibition with bevacizumab prolonged PFS in patients with newly diagnosed glioblastoma compared to standard care. However, no improvement in OS was observed with any of the targeted agents.

KEYWORDS

glioblastoma, meta-analysis, newly diagnosed, randomized trials, targeted agents

What's new?

Recently, there has been an effort to identify targeted therapies for glioblastoma. Here, the authors conducted a meta-analysis of 12 recently conducted phase II and phase III randomized clinical trials to find out whether targeted therapies improve overall and progression-free survival. The analysis included trials of protein kinase inhibitors, proteasome and histone deacetylase inhibitors, anti-angiogenic approaches, and poly(ADP-ribose) polymerase (PARP) inhibitors. Targeted therapy showed a benefit for PFS, especially in patients with unmethylated MGMT promoter. However, no improvement in overall survival was seen.

1 | INTRODUCTION

Glioblastoma (GB) is the most common malignant primary brain tumor in adults, accounting for approximately 14.3% of all primary brain tumors¹ and up to 60%-70% of all malignant gliomas. Without therapy, patients with GB have a dismal prognosis, with a median survival of 3 to 4 months.² Currently, the standard of care for newly diagnosed GB consists of surgical resection or biopsy followed by radiochemotherapy with temozolomide³ with or without the addition of tumor-treating fields.⁴ Despite aggressive therapy, median overall survival (OS) only ranges between 15 and 26 months, highlighting the unmet need for effective treatment strategies.^{3,5}

Over the past decades, targeted therapies have gained increasing importance in the field of oncology.⁶ Targeted agents are directed against specific oncogenic pathways, including growth factor receptors, aberrant signaling pathways and cell cycle or immune checkpoints, and may therefore be more effective with fewer systemic side effects than traditional chemotherapeutic approaches.⁷ An improved understanding of the molecular pathology of gliomagenesis has enabled the development of a variety of targeted agents for glioblastoma therapy.⁸ For example, drugs have been designed to target the epidermal growth factor (receptor) [EGF(R)], for example, nimotuzumab,⁹ gefitinib and erlotinib,¹⁰ vascular endothelial growth factor receptor (VEGFR, eg, bevacizumab),¹¹ protein kinase C- β (PKC β , eg, enzastaurin),¹² mammalian target of rapamycin (mTOR, eg, temsirolimus and everolimus)¹³ and other vital intracellular signaling components such as the proteasome (eg, bortezomib),¹⁴ histone deacetylases (HDAC, eg, vorinostat),¹⁵ cyclin-dependent kinases (CDK, eg, palbociclib, abemaciclib)¹⁶ and phosphatidylinositol-3 kinase (PI3K, eg, BKM120).¹⁷

To date, various targeted agents have been evaluated or are currently being analyzed in clinical trials, but there are only few systematic data on the effectiveness of targeted treatments across different

targets vs the standard of care. In this most recent meta-analysis of randomized clinical trials on targeted therapies in patients with newly diagnosed GB, we aimed to provide the highest level of current evidence on the role of personalized therapies in these patients.

2 | MATERIALS AND METHODS

2.1 | Study design and systematic literature search

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, File S1).^{18,19}

The following databases and trial registries were searched from the date of inception to the present: MEDLINE (Ovid), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Protocols (Cochrane Library/Wiley), ClinicalTrials.gov (U.S. National Library of Medicine) and the WHO International Clinical Trials Registry Platform. Google Scholar was searched for additional reports, including gray literature. The search strategy combined the concepts "Patients with glioblastomas" and "Study type: randomized controlled trials" using the Boolean operator AND. For each of these concepts, we chose the relevant subject headings and text words. To maximize the sensitivity of the search and due to the wide variety of possible intervention terms, we did not limit the type of intervention in the searches.

We started with a primary search strategy developed for MEDLINE and adapted subject headings and syntax for other databases. In MEDLINE, we used two published search filters (combined with OR) to limit the study type: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), Ovid format and Filter P3 for Phase III Clinical Trials of Cooper et al.²⁰ No other limitations, such as

date period or language, were applied in the searches. Searches were updated by rerunning the strategies with the last search date on July 27, 2021 (ICTRP:2022-03-18). Although there was no opportunity for peer review of the search strategy, we strove to comply with the recommendations of the PRESS guidelines.²¹ The full search strategy for all sources is included in File S2. The PRISMA-S checklist²² is included in File S3. In addition to the database search, the reference lists of the included articles were scanned for additional studies.

Records from the database searches were imported into EndNote reference management software for deduplication and further processed according to a previously published method for deduplication of database search results for systematic reviews in EndNote by Brammer et al.²³ Two researchers (AS and FMI) independently screened the titles, followed by screening the previously extracted abstracts for their relevance. We obtained full texts of all records that either met the predefined inclusion criteria or in which the relevance to the topic remained uncertain. Ultimately, two researchers independently screened the full texts for eligibility. Disagreements were resolved by a third reviewer (CS). At the full-text stage, the reasons for exclusion of articles were recorded in a more detailed manner.

2.2 | Inclusion and exclusion criteria

Studies for systematic meta-analysis were defined as eligible if they analyzed patients with primary glioblastoma treated with targeted therapies vs standard of care. We considered only prospective randomized controlled trials (either phase II or phase III) that reported the following statistical outcome parameters for the systematic meta-analysis: median OS (mOS), median progression-free survival (mPFS), progression-free survival at 6 months (PFS-6), hazard ratio (HR) for death or HR for progression and 95% confidence intervals (CIs). Only RCTs were included in our meta-analysis to provide the highest level of evidence. Moreover, we excluded studies on patients under the age of 18 years, nonhuman research, and articles in a language other than English.

Targeted treatments included medications directed against growth factors and their receptors, for example, EGF(R), VEGF(R), (kinase insert domain-containing receptor [KDR] and Fms Related Receptor Tyrosine Kinase 1 [FLT1]), fibroblast growth factor receptor (FGF(R)), platelet-derived growth factor receptor (PDGF(R)), Met/hepatocyte growth factor receptor (HGF(R)/c-MET), insulin-like growth factor receptor (IGF-1 (R)), transforming growth factor beta (TGF- β), receptor tyrosine kinase c-kit; signaling pathways such as Ras/Raf/Mitogen-activated protein kinase/ERK kinase/extracellular-signal-regulated kinase (Ras/(B)Raf/MEK/MAPK(ERK), phosphatidylinositol-3 kinase (PI3K)/protein kinase B/mTOR (PI3K/Akt), PKC β ; cell cycle regulators/DNA repair mechanisms, for example, Mouse double minute 2 homolog (MDM2), tumor protein 53 (TP53), cyclin-dependent kinases Cdk4 and Cdk6 (CDK4/6), retinoblastoma protein 1 (RB1), poly(ADP-ribose) polymerase (PARP) and others (receptor tyrosine kinase RET, isocitrate dehydrogenase [IDH], transcription factor myc). Targeted drugs include small molecule kinase inhibitors, antibodies and vaccines. Intratumoral or topical

therapies (eg, gliadel wafers), oncolytic viral/antiviral/retroviral treatments (eg, TOCA 511/FC, ganciclovir, etc.), drugs that solely increase blood-brain-barrier (BBB) permeability (eg, RMP-7) or repurposed drugs not directly targeting cancer-associated pathways (eg, losartan) were excluded from further analysis. We excluded intratumoral or topical therapies to allow a reliable comparison of agents as local therapies have a clearly distinct application route and profile of side effects. Oncolytic viral, antiviral or retroviral treatments were excluded because they did not meet our criteria for specifically targeted agents.

2.3 | Data extraction

Two authors (AS, FMI) independently extracted data on substances, trial design (phase and randomization), drug regimen, target, number of patients, geographic region of the study, length of follow-up, mOS, overall survival at 12 months (OS-12), mPFS, PFS-6 and PFS-12, HR for death, HR for progression, CIs and histology or molecular subtype. If there were additional investigations of patient subgroups, data were also extracted.

2.4 | Statistical analysis

We interpreted HRs for death and HRs for tumor progression as relative risk (RR) estimates and computed the natural logarithm of the risk estimate $\log(RR_i)$ with the corresponding SE $s_i = d_i/1.96$, where d_i represents the maximum of $[\log(\text{upper } 95\% \text{ CI bound of } RR_i) - \log(RR_i)]$ and $[\log(RR_i) - \log(\text{lower } 95\% \text{ CI bound of } RR_i)]$.

We performed a random-effects meta-analysis²⁴ and calculated pooled RRs with 95% CIs of targeted agents compared to the standard of care among patients with primary glioblastoma. Heterogeneity among risk estimates was assessed using the Q-statistic and I^2 statistics.²⁵ Potential publication bias was evaluated using funnel plots, Begg's rank correlation test²⁶ and Egger's regression test.²⁷ All statistical analyses were carried out using the metafor, robumeta and dplyr packages in R 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical tests were two-sided and statistical significance was set at a 5% significance level.

3 | RESULTS

3.1 | Search results obtained from databases and registers

The PRISMA flow chart (see Figure 1) shows the proceedings of literature perusal. We received 14 051 results for evaluation, of which 10 957 remained after deduplication. A total of 10 430 references were excluded based on the title and abstract, and 527 articles were eligible for full-text evaluation. Of these, 515 were excluded because they did not meet the inclusion criteria. Ultimately, we included 12 studies in our meta-analysis of studies published between 2014

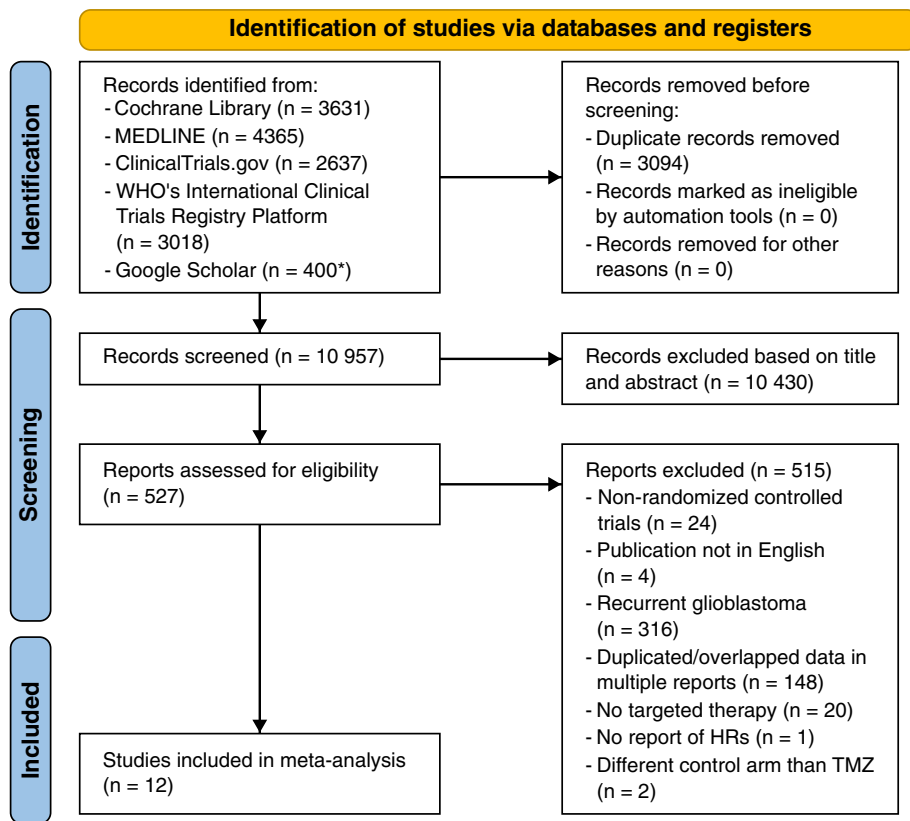


FIGURE 1 PRISMA flow diagram illustrating the flow of information through the processes of this systematic review. (*) Google Scholar: 200 records were downloaded for each one of the searches in 2019 and 2021 [Color figure can be viewed at wileyonlinelibrary.com]

and 2021. The search strategies based on a linear search algorithm are shown in File S2. File S3 displays the PRISMA-S-checklist, which summarizes the information sources and methods, as well as search strategies and management of the datasets.

3.2 | Characteristics of included studies

This meta-analysis included 3941 patients with newly diagnosed GB. In the meta-analysis, 2024 patients were assessed in the experimental arm and 1917 patients in the control arm. Of the studies included, five analyzed VEGF-inhibition (bevacizumab), one evaluated EGFR-inhibition (nimotuzumab), one considered EGFRVIII-directed immunotherapy (rindopepimut), two assessed mTOR-blockade (everolimus and temsirolimus), two evaluated $\alpha\text{v}\beta 3/\alpha\text{v}\beta 5$ integrin-inhibition (cilengitide) and one analyzed PARP inhibition (veliparib). All studies met the following inclusion criteria: randomized trials (either phase II or phase III) and treatment with targeted therapy alone or in combination with another medication (irinotecan or temozolomide) in the experimental arm vs temozolomide as the control group. All except one study²⁸ consisted of trials with two study arms. We focused on one arm of our study (standard dose cilengitide) in order to exclude bias due to overestimation of the respective control arm. In all but one study,²⁹ patients did not receive pretreatment prior to targeted therapy. In that study, the experimental agent was only used in the temozolomide maintenance phase after completion of standard radiochemotherapy, and patients were preselected based on their EGFRVIII

status. The basic characteristics of the studies included in the meta-analysis are presented in Table 1.

3.3 | Outcome parameters

3.3.1 | Overall survival

Eleven studies were eligible for the evaluation of OS. The phase II trial by Chaffert et al³⁰ was excluded because of a lack of data on HRs for OS. The random-effect meta-analysis showed a nonsignificantly reduced mortality risk of 0.98 [95% CI 0.86-1.11, $P = .7731$] for newly diagnosed GB patients treated with targeted therapy (N = 2024) compared to temozolomide (N = 1917; Figure 2). The moderate heterogeneity observed between studies ($I^2 = 58.36\%$) was statistically significant ($P = .0093$).

Next, we performed separate analyses for each molecular target, VEGF, EGFR, mTOR, $\alpha\text{v}\beta 3/\alpha\text{v}\beta 5$, and PARP. None of the targeted therapies showed a significant reduction in mortality risk compared to temozolomide (Figure 3). Of note, only one study was available on PARP inhibition. While therapies targeting VEGF (RR = 0.95 [95% CI 0.79-1.15, $P = .6006$]), EGFR (RR = 0.89 [95% CI 0.75-1.05, $P = .1563$]) and $\alpha\text{v}\beta 3/\alpha\text{v}\beta 5$ (RR = 0.86 [95% CI 0.58-1.25, $P = .4241$]) tended to show a positive effect on survival compared to standard therapy, treatment of the mTOR pathway showed a significantly increased risk of death = 1.43 [95% CI 1.03-1.97, $P = .0318$]. Study heterogeneity was significantly reduced by stratified analyses, with

TABLE 1 Characteristics of the included studies

Substance	Author	Year	Study name	Phase	Targets	Intervention		Number		mOS (months)		OS-12 (%)		mPFS (months)		PFS-6 (%)	
						Ex	Co	Ex	Co	Ex	Co	Ex	Co	Ex	Co	Ex	Co
Bevacizumab	Chauffert	2014	TEMAVIR	II	VEGF	Bevacizumab/Irinotecan	TMZ	60	60	11.1	11.1	43.3	46.7	7.1	5.2	61.7	41.7
Bevacizumab	Gilbert	2014	RTOG-0825	III	VEGF	Bevacizumab/Temozolomide	TMZ	312	309	15.7	16.1	64.1	62.1	10.7	7.3	77	52.7
Bevacizumab	Chinot	2014	AVAgllo	III	VEGF	Bevacizumab/Temozolomide	TMZ	458	463	16.8	16.7	72.4	66.3	10.6	6.2	79.9	53.3
Bevacizumab	Herrlinger	2016	GLARIUS	II	VEGF	Bevacizumab/Irinotecan	TMZ	116	54	16.6	17.5	86.8	77.8	9.7	5.99	79.3	42.6
Bevacizumab	Balana	2016	GENOM 009	II	VEGF	Bevacizumab/Temozolomide	TMZ	48	45	10.6	7.7	48.9	29.6	4.8	2.2	40	20
Cilengitide	Stupp	2014	CENTRIC	II	$\alpha\text{v}\beta3/\alpha\text{v}\beta5$	Cilengitide/Temozolomide	TMZ	272	273	26.3	26.3	80.1	77.7	10.6	7.9	59.9	56
Cilengitide	Nabors	2015	CORE	II	$\alpha\text{v}\beta3/\alpha\text{v}\beta5$	Cilengitide/Temozolomide	TMZ	88	89	16.3	13.4	62.5	70.7	5.6	4.1	35.2	28.1
Everolimus	Chinnaiyan	2018	RTOG-0913	II	mTOR	Everolimus/Temozolomide	TMZ	88	83	16.5	21.2	57.9	68.7	8.2	10.2	65.9	60.2
Nimotuzumab	Westphal	2015	OSAG101-BSA-05	III	EGFR	Nimotuzumab/Temozolomide	TMZ	71	71	22.3	19.6	78.6	79.1	7.7	5.8	53	49
Rindopepimut	Weller	2017	ACT IV	III	EGFR/VEGF	Rindopepimut/Temozolomide	TMZ	371	374	17.4	17.4	72	74	7.1	5.6	NA	NA
Tensirolimus	Wick	2016	EORTC 26082	II	mTOR	Tensirolimus	TMZ	56	55	14.8	16	69.6	72.2	5.4	6	38.7	50
Velparib	Sim	2021	VERTU	II	PARP	Velparib followed by Velparib/TMZ	TMZ	84	41	12.7	12.8	NA	NA	5.7	4.2	46	31

Abbreviations: Co, control; EGFR, epidermal growth factor receptor; Ex, experimental; mOS, median overall survival; mPFS, median progression-free survival; mTOR, mechanistic target of rapamycin; PARP, poly(ADP-ribose) polymerase; TMZ, temozolomide; VEGF, vascular endothelial growth factor; $\alpha\text{v}\beta3/\alpha\text{v}\beta5$, $\alpha\text{v}\beta3/\alpha\text{v}\beta5$ integrin.

little or minor heterogeneity among the EGFR ($I^2 = 0.0\%$; $P = .8837$) and mTOR subgroups ($I^2 = 25.81\%$; $P = .2456$) and moderate heterogeneity among the $\alpha\text{v}\beta3/\alpha\text{v}\beta5$ ($I^2 = 70.84\%$; $P = .0641$) and VEGF ($I^2 = 64.57\%$; $P = .0309$) subgroups.

3.3.2 | Progression-free survival

All 12 studies including 3941 patients mentioned above were included. The random-effects meta-analysis yielded a 17% significant reduction in the risk of disease progression with targeted therapy (RR = 0.83 [95% CI 0.74-0.94, $P = .0037$]; Figure 4). Moderate heterogeneity was observed among the included studies ($I^2 = 60.02\%$; $P = .0024$).

Stratified analyses with regard to molecular targets showed a significant reduction in the risk of disease progression only for therapies targeting VEGF (RR = 0.70 [95% CI 0.61-0.80, $P < .001$]). Although not statistically significant, therapies targeting EGFR, $\alpha\text{v}\beta3/\alpha\text{v}\beta5$ and PARP tended to be beneficial, whereas therapies targeting mTOR tended to increase the risk of disease progression (Figure 5). Again, only one study was available on PARP inhibition. The study heterogeneity was low ($I^2 = 0\%$ -32.21% $P > .2489$).

3.3.3 | Subgroup analyses

Further stratification was carried out based on biomarkers and patient characteristics: methylated/unmethylated O6-methylguanine-DNA-methyltransferase (MGMT) status, sex, biopsy vs gross total resection, use of steroids, ethnicity, Mini-Mental State Examination (MMSE) score, recursive partitioning analysis (RPA) class and use of enzyme-inducing antiepileptic drugs (EIAEDs).

Regarding OS, there was no significant benefit in any of the subgroups examined (Figure S1). A statistically nonsignificant benefit was observed for patients with unmethylated MGMT status compared to those with methylated MGMT status. No statistical difference was observed between men and women, and similar results were obtained regarding steroid use, ethnicity and RPA class. Patients with complete resection seemed to benefit most from treatment with targeted agents compared to biopsy, especially with respect to bevacizumab in the AVAGlio trial,³¹ although the trend was not statistically significant. Patients with an MMSE score ≥ 27 tended to have a more favorable outcome than those with an MMSE score < 27 , although studies of the MMSE ≥ 27 group were highly heterogeneous ($I^2 = 98.44\%$).

For PFS, we found no significant benefit for patients with methylated MGMT (0.87 [95% CI 0.73-1.03, $P = .1085$]), whereas for patients with unmethylated MGMT, we noted a significant benefit for the targeted drug (0.75 [95% CI 0.56-0.99, $P = .0440$]). A significant improvement in PFS was observed for patients using EIAEDs compared to patients who did not receive EIAEDs. Unfortunately, there was no sufficient information in the primary studies on which AEDs were used and reasons for the observed association are speculative including potential drug interactions between the targeted agents and

Targeted Therapy vs. Temozolomide - Overall Survival

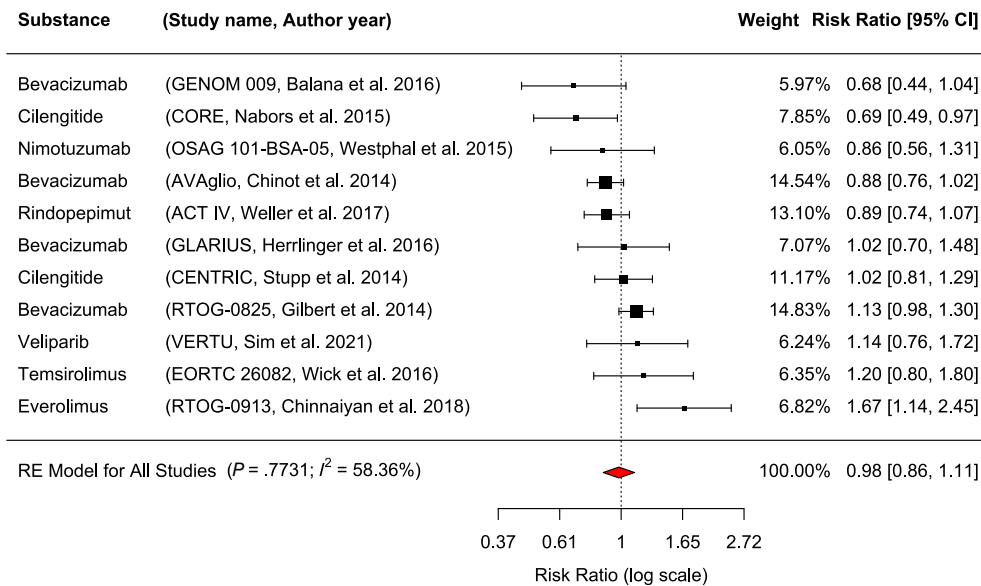


FIGURE 2 Forest plot of the pooled estimated risk ratio (red diamond) for overall survival across 11 RCTs of treatment of newly diagnosed GBMs with targeted therapy vs temozolomide. RE, risk estimate [Color figure can be viewed at wileyonlinelibrary.com]

Subgroups by Target - Overall Survival

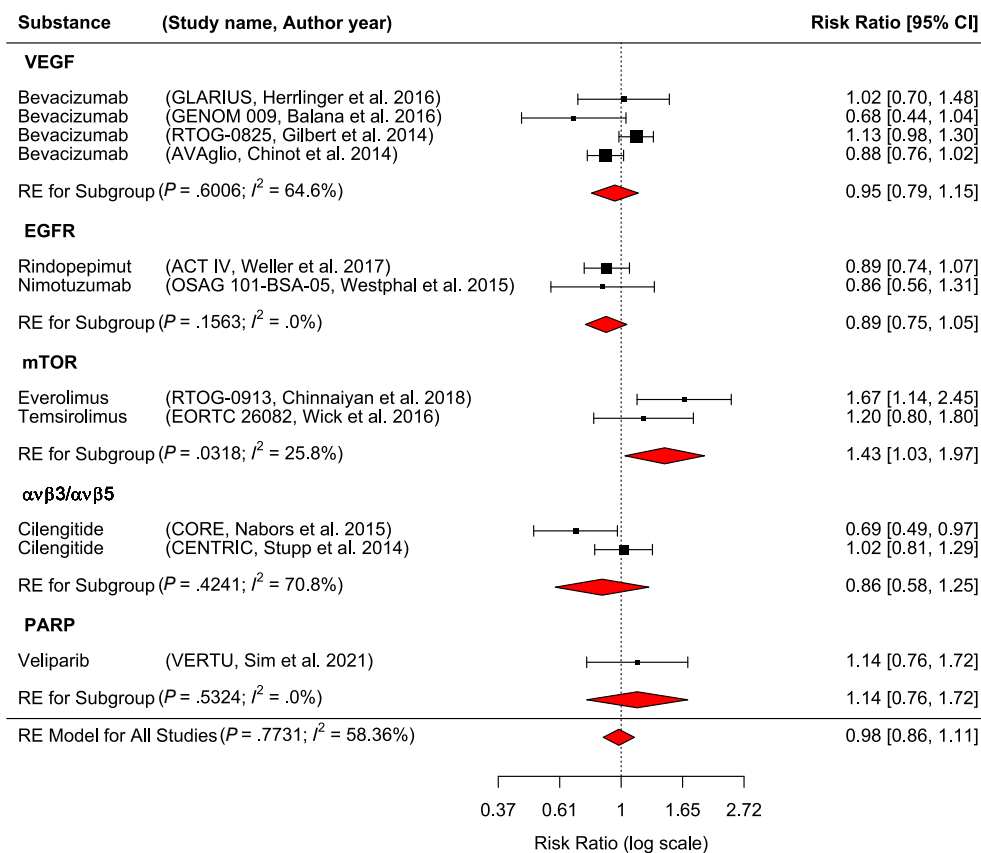


FIGURE 3 Forest plot displaying the subsequent subgroup analysis by target of the pooled estimated risk ratio (red diamond) for overall survival. EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin; PARP, poly(ADP-ribose) polymerase; RE, risk estimate; VEGF, vascular endothelial growth factor; $\alpha\text{v}\beta\text{3}/\alpha\text{v}\beta\text{5}$, $\alpha\text{v}\beta\text{3}/\alpha\text{v}\beta\text{5}$ integrin [Color figure can be viewed at wileyonlinelibrary.com]

EIAEDs. All other subgroups showed a significant reduction in the risk of tumor progression when the targeted agent was administered (Figure S2).

Only one study reported HRs for patient subgroups stratified by molecular biomarkers (mTOR).³² p-mTOR^{Ser2448} positive patients who

received temsirolimus as compared to temozolomide showed a non-significant improvement in survival (HR, 0.62 [95% CI 0.26-1.47, $P = .27$]). In p-mTOR^{Ser2448} negative patients, survival was longer with standard therapy than with temsirolimus as an experimental treatment (HR 1.77 [95% CI 0.95-3.29, $P = .07$]). This shows that targeted

FIGURE 4 Forest Plot of the pooled estimated risk ratios for progression-free survival across 12 RCTs of treatment of newly diagnosed GBMs with targeted therapy vs temozolomide. RE, risk estimate [Color figure can be viewed at wileyonlinelibrary.com]

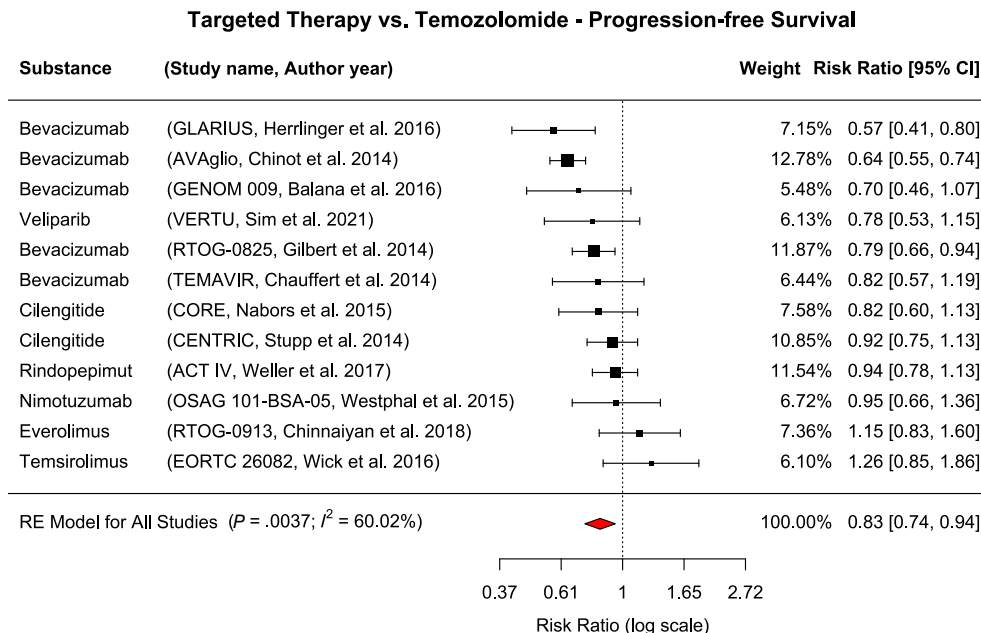
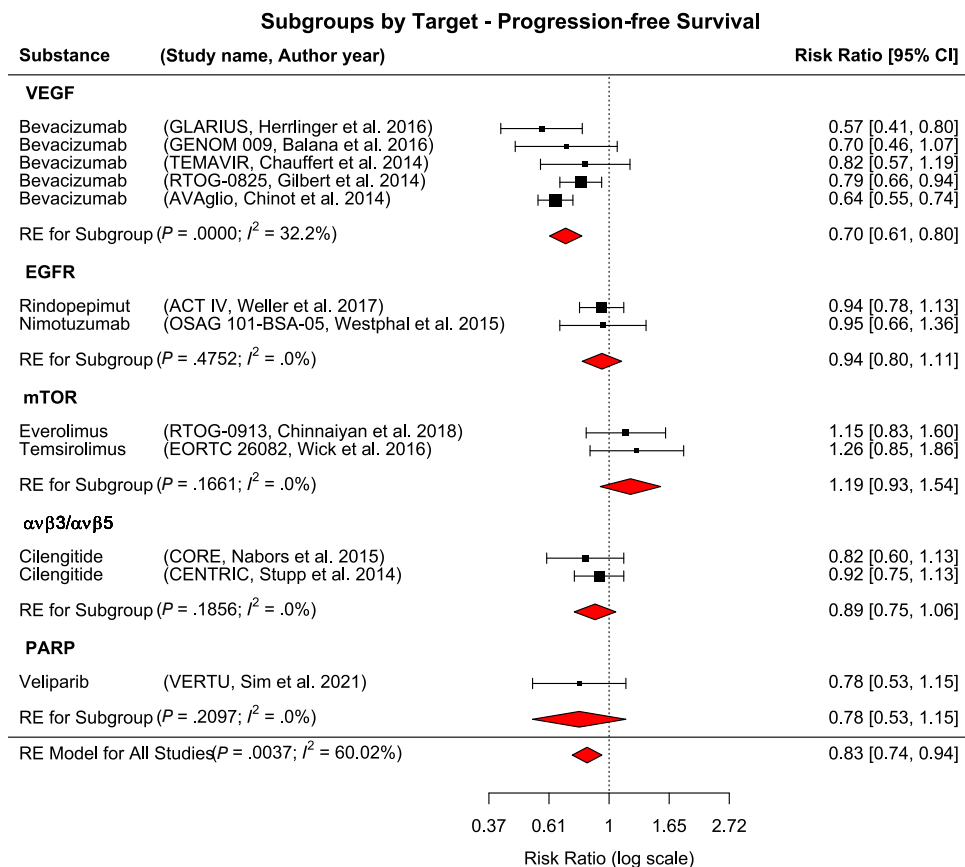


FIGURE 5 Forest plot of subgroup analysis by target for progression-free survival. EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin; PARP, poly(ADP-ribose) polymerase; VEGF, vascular endothelial growth factor; $\alpha\beta3/\alpha\beta5$, $\alpha\beta3/\alpha\beta5$ integrin [Color figure can be viewed at wileyonlinelibrary.com]



therapy in an unselected population may also have a negative impact on survival. One study preselected patients according to EGFRvIII status.²⁹ Among the patients with EGFRvIII mutation, there was a non-significant benefit for both OS (HR 0.89 [95% CI 0.74-1.07, $P = .22$]) or PFS (0.94 [95% CI 0.79-1.13, $P = .51$]) for treatment with rindopepimut compared to standard therapy. Unfortunately, no stratifications

could be carried out according to the IDH status of the patients, because only the study from Sim et al reported this data.

The funnel plots for the risk of OS and disease progression (Figure S3a,b) displayed an almost symmetrical distribution, indicating no publication bias. This was corroborated by high P values of Begg's ($P = .8793$ and $.8406$) and Egger's ($P = .8901$ and $.5068$) tests.

4 | DISCUSSION

In recent years, substantial efforts have been made to find suitable targeted therapies to improve the survival of glioblastoma patients. Thus far, the use of targeted agents in patients with newly diagnosed glioblastoma remains a matter of ongoing research.

To the best of our knowledge, this is the first in-field meta-analysis of targeted agents in newly diagnosed glioblastoma patients, comparing different therapeutic targets and their effects on overall and PFS. To assess the highest possible therapeutic evidence, we included only randomized controlled trials of phases II or III.

The target most frequently used in the trials analyzed here was the VEGF/VEGFR pathway, followed by integrin inhibition (targeting $\alpha v \beta 3 / \alpha v \beta 5$ with cilengitide), EGFR inhibition (eg, nimotuzumab, rindopepimut and vandetanib) and PARP-inhibition.

The VEGF/VEGFR pathway plays a crucial role in angiogenesis in GB, mediating tumor progression and general outcomes.³³ Although either the combination of bevacizumab with TMZ or irinotecan yielded a substantial improvement in PFS, inhibition of the VEGF/VEGFR pathway failed to show an extension of OS.^{11,31,34-36} The results of our analysis regarding VEGF/VEGFR-inhibition with bevacizumab are in line with previously published meta-analyses³⁷⁻³⁹ confirming a significant advantage in PFS. Likewise, in these meta-analyses, bevacizumab failed to show a considerable extension of OS. The reasons for this discrepancy between OS and PFS results have been extensively discussed and include, among others, the phenomenon of bevacizumab-associated pseudo-response due to closure of the blood-brain barrier or secondary resistance mechanisms.^{40,41} However, we would like to emphasize that a prolongation of PFS can be meaningful for the patient, an assumption that led to the approval of bevacizumab in the US and other countries. This is corroborated by health-related quality of life (HR-QoL) analyses, which show improvements in patients treated with bevacizumab in comparison to controls.^{42,43}

It has been shown that $\alpha v \beta 3 / \alpha v \beta 5$ integrin expression on the cell surface is induced by transforming growth factor beta (1) (TGF-beta (1)) and TGF-beta(2), promoting glioma cell motility.⁴⁴ Unfortunately, although there was a trend toward improved OS for patients receiving cilengitide in the CORE trial conducted by Nabors et al,²⁸ this trend did not reach statistical significance. Furthermore, no significant improvement in PFS was detected in patients receiving cilengitide in either the CORE or the CENTRIC-trial.^{5,28}

The effect of EGFR inhibition on PFS and OS did not reach significance, regardless of the underlying mechanism of pathway inhibition (tyrosine kinase inhibitors, monoclonal antibodies or vaccines). These results are supported by a recent meta-analysis by Lee et al⁴⁵ exclusively focused on EGFR-targeted treatments in patients with GB and showed nonsignificant reductions in the risks of death and disease progression.

Regarding the molecular characteristics, only a subgroup calculation for promoter methylation status was feasible in our meta-analysis. For OS, we found no significant benefit for patients with methylated or unmethylated MGMT. Regarding PFS, we found no

significant benefit in patients with methylated MGMT, whereas, for patients with unmethylated MGMT, we noted a significant benefit for the targeted drug.

Very little or no data were available for analyses stratified by EGFRVIII, mTOR and IDH mutations. Data for patients with EGFRVIII mutations were only available in the publication by Weller et al.²⁹ Among patients with an EGFRVIII mutation, there was a nonsignificant benefit in both OS and PFS for treatment with rindopepimut compared to standard therapy. Likewise, only the study by Wick et al³² addressed a possible therapeutic advantage of an mTOR inhibitor in the presence of a phosphorylated or nonphosphorylated mTOR status. With respect to OS, p-mTOR^{Ser2448} positive patients who received temsirolimus as compared to those who received temozolomide showed a nonsignificant improvement in survival. In p-mTOR^{Ser2448} negative patients, survival tended to be longer with standard therapy than with temsirolimus. Umbrella trials, in which the patient is administered a substance that best corresponds to their molecular profile, meet an urgent need in neuro-oncology. One of these trials, the N2M2 study, evaluating targeted treatment options in patients with newly diagnosed glioblastoma is currently ongoing (NCT03158389).

In addition to the substances analyzed in this meta-analysis, there are a number of other targeted drugs, such as farnesyltransferase inhibitors,^{46,47} CDK 4,6, CDKN2A/B inhibitors (palbociclib: NCT03158389), PI3K inhibitors (paxalisib: NCT03522298) or other PARP inhibitors,⁴⁸ whose efficacy and tolerability have been and are still being tested in nonrandomized and randomized clinical trials (eg, veliparib: NCT03581292; tipifarnib: NCT00058097), and the results are eagerly awaited.

This meta-analysis had several limitations. As we conducted a study-level meta-analysis, we only included full-text articles on randomized controlled trials reporting both PFS as well as OS data. Therefore, recent studies on targeted substances have not been included. One study⁴⁵ was excluded because of lack of data. Furthermore, the clinical heterogeneity between studies, such as the different numbers of study participants (ranging from 93 to 921), should be considered when assessing the results. Moreover, only limited data are available on molecular markers, resection status, sex, ethnicity, steroid use, MMSE and RPA class due to the lack of reported hazard ratios, making a more detailed subgroup analysis challenging. More specifically, only two studies were available for subgroup analysis, and the subanalysis of RPA-class IV and V was based on bevacizumab trials only. Lastly, we were unable to translate the WHO classification systems of 2006 and 2017, which were used for the design of inclusion criteria in the analyzed trials, to the recently published WHO Classification of Tumors of the Central Nervous System of 2021.⁴⁹ Parts of the “glioblastomas” included here would have been reclassified as diffuse astrocytoma CNS-WHO-Grades 2, 3 or 4 in the new classification. However, it was not possible to select “true” glioblastomas from the available data, which could lead to an under- or overestimation of effects, as reported here.

Our study has several strengths. We explored the data from numerous studies using different drugs and various mechanisms of

action. Only completed clinical trials with the highest available evidence level were selected for this meta-analysis, securing a high level of study design, data processing, statistics and data reporting. In addition, most of the trials were registration trials, adding an additional level of quality assurance provided by the involved study groups, industry and competent authorities alike.

In summary, in this meta-analysis of targeted therapies in patients with newly diagnosed glioblastoma, we provide the currently highest evidence for the possible effects of targeted agents on PFS and OS. None of the investigated substances provided a significant improvement in OS, although a potentially clinically meaningful extension in PFS has been demonstrated with regard to VEGF/VEGFR blockade. The findings of our study confirm the general notion of published guidelines that targeted therapies should only be used in the context of clinical trials. Our study further highlights the need for a personalized design of randomized trials, including a careful selection of patient populations that should focus on molecular markers that may predict the response to the specific agents used in the trial.

AUTHOR CONTRIBUTIONS

Angelika Scherm, Franziska Maria Ippen, Corinna Seliger: Conceptualization; **Helge Knüttel, Hansjörg Baurecht, Corinna Seliger:** Methodology; **Angelika Scherm, Hansjörg Baurecht:** Software; **Corinna Seliger, Franziska Maria Ippen:** Validation; **Angelika Scherm, Franziska Maria Ippen, Hansjörg Baurecht:** Formal analysis; **Angelika Scherm, Franziska Maria Ippen, Helge Knüttel:** Investigation; **Angelika Scherm, Franziska Maria Ippen, Helge Knüttel, Corinna Seliger:** Resources; **Angelika Scherm, Hansjörg Baurecht:** Data curation; **Angelika Scherm, Franziska Maria Ippen:** Writing – Original Draft; **Corinna Seliger, Peter Hau, Hansjörg Baurecht, Wolfgang Wick, Jens Gempt, Helge Knütte, Michael F. Leitzmann:** Writing – Review & Editing; **Angelika Scherm, Franziska Maria Ippen:** Visualization; **Corinna Seliger:** Supervision; **Corinna Seliger:** Project administration; **Corinna Seliger:** Funding acquisition. The work reported in this article has been performed by the authors, unless clearly specified in the text.

CONFLICT OF INTEREST

All authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data extracted from the sources mentioned above and the study protocol are available upon request from the corresponding author.

ETHICS STATEMENT

All procedures performed in the primary studies meta-analyzed here involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

ORCID

Franziska Maria Ippen  <https://orcid.org/0000-0001-6870-1784>

Peter Hau  <https://orcid.org/0000-0003-3894-5053>

Hansjörg Baurecht  <https://orcid.org/0000-0002-9265-5594>

Wolfgang Wick  <https://orcid.org/0000-0002-6171-634X>

Jens Gempt  <https://orcid.org/0000-0003-4123-4690>

Helge Knüttel  <https://orcid.org/0000-0002-2654-6517>

Michael F. Leitzmann  <https://orcid.org/0000-0002-0371-2789>

Corinna Seliger  <https://orcid.org/0000-0002-4923-4495>

REFERENCES

- Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. *Neuro Oncol.* 2021;23:iii1-iii105.
- Omuro A, DeAngelis LM. Glioblastoma and other malignant gliomas: a clinical review. *JAMA.* 2013;310:1842-1850.
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
- Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA.* 2017;318:2306-2316.
- Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2014;15:1100-1108.
- Lau D, Magill ST, Aghi MK. Molecularly targeted therapies for recurrent glioblastoma: current and future targets. *Neurosurg Focus.* 2014;37:E15.
- Omuro AM, Faivre S, Raymond E. Lessons learned in the development of targeted therapy for malignant gliomas. *Mol Cancer Ther.* 2007;6:1909-1919.
- Wang H, Xu T, Jiang Y, et al. The challenges and the promise of molecular targeted therapy in malignant gliomas. *Neoplasia.* 2015;17:239-255.
- Solomon MT, Selva JC, Figueredo J, et al. Radiotherapy plus nimotuzumab or placebo in the treatment of high grade glioma patients: results from a randomized, double blind trial. *BMC Cancer.* 2013;13:299.
- Peereboom DM, Shepard DR, Ahluwalia MS, et al. Phase II trial of erlotinib with temozolomide and radiation in patients with newly diagnosed glioblastoma multiforme. *J Neurooncol.* 2010;98:93-99.
- Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med.* 2014;370:699-708.
- Butowski N, Chang SM, Lamborn KR, et al. Phase II and pharmacogenomics study of enzastaurin plus temozolomide during and following radiation therapy in patients with newly diagnosed glioblastoma multiforme and gliosarcoma. *Neuro Oncol.* 2011;13:1331-1338.
- Chinnaiyan P, Won M, Wen PY, et al. A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: results of NRG oncology RTOG 0913. *Neuro Oncol.* 2018;20:666-673.
- Kong XT, Nguyen NT, Choi YJ, et al. Phase 2 study of bortezomib combined with temozolomide and regional radiation therapy for upfront treatment of patients with newly diagnosed glioblastoma multiforme: safety and efficacy assessment. *Int J Radiat Oncol Biol Phys.* 2018;100:1195-1203.
- Galanis E, Anderson SK, Miller CR, et al. Phase I/II trial of vorinostat combined with temozolomide and radiation therapy for newly diagnosed glioblastoma: results of Alliance N0874/ABTC 02. *Neuro Oncol.* 2018;20:546-556.
- Taylor JW, Parikh M, Phillips JJ, et al. Phase-2 trial of palbociclib in adult patients with recurrent RB1-positive glioblastoma. *J Neurooncol.* 2018;140:477-483.

17. Wen PY, Touat M, Alexander BM, et al. Buparlisib in patients with recurrent glioblastoma harboring phosphatidylinositol 3-kinase pathway activation: an open-label, multicenter, multi-arm, phase II trial. *J Clin Oncol*. 2019;37:741-750.
18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol*. 2021;74:790-799.
20. Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. *J Clin Epidemiol*. 2019;112:12-19.
21. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol*. 2016;75:40-46.
22. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. *Syst Rev*. 2021;10:39.
23. Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. Deduplication of database search results for systematic reviews in EndNote. *J Med Libr Assoc*. 2016;104:240-243.
24. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med*. 1999;18:321-359.
25. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088-1101.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
28. Nabors LB, Fink KL, Mikkelsen T, et al. Two cilengitide regimens in combination with standard treatment for patients with newly diagnosed glioblastoma and unmethylated MGMT gene promoter: results of the open-label, controlled, randomized phase II CORE study. *Neuro Oncol*. 2015;17:708-717.
29. Weller M, Butowski N, Tran DD, et al. Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. *Lancet Oncol*. 2017;18:1373-1385.
30. Chauffert B, Feuvret L, Bonnetain F, et al. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMAVIR study from ANOCEF. *Ann Oncol*. 2014;25:1442-1447.
31. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370:709-722.
32. Wick W, Gorlia T, Bady P, et al. Phase II study of radiotherapy and Temsirolimus versus Radiochemotherapy with temozolomide in patients with newly diagnosed glioblastoma without MGMT promoter hypermethylation (EORTC 26082). *Clin Cancer Res*. 2016;22:4797-4806.
33. Chi AS, Sorensen AG, Jain RK, Batchelor TT. Angiogenesis as a therapeutic target in malignant gliomas. *Oncologist*. 2009;14:621-636.
34. Balana C, De Las PR, Sepulveda JM, et al. Bevacizumab and temozolomide versus temozolomide alone as neoadjuvant treatment in unresected glioblastoma: the GENOM 009 randomized phase II trial. *J Neurooncol*. 2016;127:569-579.
35. Chauffert B, Feuvret L, Bonnetain F, et al. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMAVIR study from ANOCEF dagger. *Ann Oncol*. 2014;25:1442-1447.
36. Herrlinger U, Schafer N, Steinbach JP, et al. Bevacizumab plus irinotecan versus temozolomide in newly diagnosed O6-methylguanine-DNA methyltransferase nonmethylated glioblastoma: the randomized GLARIUS trial. *J Clin Oncol*. 2016;34:1611-1619.
37. Liao KL, Huang S, Wu YP. The prognosis for patients with newly diagnosed glioblastoma receiving bevacizumab combination therapy: a meta-analysis. *Oncol Targets Ther*. 2018;11:3513-3520.
38. Su J, Cai M, Li W, et al. Molecularly targeted drugs plus radiotherapy and temozolomide treatment for newly diagnosed glioblastoma: a meta-analysis and systematic review. *Oncol Res*. 2016;24:117-128.
39. Wang WL, Aru N, Liu Z, et al. Prognosis of patients with newly diagnosed glioblastoma treated with molecularly targeted drugs combined with radiotherapy vs temozolomide monotherapy: a meta-analysis. *Medicine*. 2019;98:e17759.
40. Mar N, Desjardins A, Vredenburg JJ. CCR 20th anniversary commentary: bevacizumab in the treatment of glioblastoma—the progress and the limitations. *Clin Cancer Res*. 2015;21:4248-4250.
41. Wen PY, Junck L. Bevacizumab for glioblastoma. *Neurology*. 2014;82:1670-1671.
42. Henriksson R, Bottomley A, Mason W, et al. Progression-free survival (PFS) and health-related quality of life (HRQoL) in AVAglio, a phase III study of bevacizumab (Bv), temozolomide (T), and radiotherapy (RT) in newly diagnosed glioblastoma (GBM). *J Clin Oncol*. 2013;31:2005.
43. Schäfer N, Proescholdt M, Steinbach JP, et al. Quality of life in the GLARIUS trial randomizing bevacizumab/irinotecan versus temozolomide in newly diagnosed, MGMT-nonmethylated glioblastoma. *Neuro-Oncology*. 2018;20:975-985.
44. Platten M, Wick W, Wild-Bode C, Aulwurm S, Dichgans J, Weller M. Transforming growth factors beta(1) (TGF-beta(1)) and TGF-beta(2) promote glioma cell migration via up-regulation of alpha(V)beta(3) integrin expression. *Biochem Biophys Res Commun*. 2000;268:607-611.
45. Lee EQ, Kaley TJ, Duda DG, et al. A multicenter, phase II, randomized, noncomparative clinical trial of radiation and temozolomide with or without vandetanib in newly diagnosed glioblastoma patients. *Clin Cancer Res*. 2015;21:3610-3618.
46. Lustig R, Mikkelsen T, Lesser G, et al. New approaches to brain tumor therapy CNSC. Phase II preradiation R115777 (tipifarnib) in newly diagnosed GBM with residual enhancing disease. *Neuro Oncol*. 2008;10:1004-1009.
47. Nghiemphu PL, Wen PY, Lamborn KR, et al. A phase I trial of tipifarnib with radiation therapy, with and without temozolomide, for patients with newly diagnosed glioblastoma. *Int J Radiat Oncol Biol Phys*. 2011;81:1422-1427.
48. Blakeley JO, Grossman SA, Mikkelsen T, et al. Phase I study of iniparib concurrent with monthly or continuous temozolomide dosing schedules in patients with newly diagnosed malignant gliomas. *J Neurooncol*. 2015;125:123-131.
49. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23:1231-1251.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Scherm A, Ippen FM, Hau P, et al. Targeted therapies in patients with newly diagnosed glioblastoma—A systematic meta-analysis of randomized clinical trials. *Int J Cancer*. 2023;1-10. doi:10.1002/ijc.34433