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

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Running title: Targeted agents in newly diagnosed glioblastoma
Keywords: glioblastoma, meta-analysis, newly diagnosed, targeted agents, randomized trials

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Appropriate article category: Research article

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-Methylguanin-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-6, progression-free survival at 6 months; PFS-12, progression-free survival at 12 months; PI3K, phosphatidylinositol-3 kinase; PKCß, protein kinase C-β; RB1, retinoblastoma protein 1; RCT, randomized clinical trial; RPA, recursive partitioning analysis; RR, risk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.34433

ratio; TGF-ß, transforming growth factor beta; TMZ, temozolomide; TP53, tumor protein 53; VEGFR, vascular endothelial growth factor receptor;

Novelty and Impact:

This meta-analysis provides an overview of recently published randomized controlled trials analyzing the effect of targeted agents on overall and progression-free survival in patients with newly diagnosed glioblastoma. Only phase II and phase III trials were included, ensuring to analyze the highest level of evidence. The results are of high translational relevance, suggesting that targeted agents might be beneficial especially for patients with unmethylated MGMT-promotor, which usually only show limited responses to standard chemotherapy.

Word count: 3,549 words
Total number of figures and tables: 5 figures, 1 table, 3 supplementary figures, and 3 supplementary files

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=3,941 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=0.7731]. By comparison, targeted therapy showed a benefit for PFS (HR=0.83 [95% CI 0.74-0.94, p=0.0037], especially for patients with an unmethylated *O6-Methylguanin-DNA-methyltransferase* (*MGMT)* promoter (0.75 [95% CI 0.56-0.99, p=0.0440]). Prolongation of PFS was largely driven by VEGF inhibition with bevacizumab (HR=0.70 [95% CI 0.61-0.80, p=0.0000]). VEGF inhibition with bevacizumab prolonged PFS in patients with newly diagnosed glioblastoma compared with standard care. However, no improvement in OS was observed with any of the targeted agents.

1. Introduction

Glioblastoma (GB) is the most common malignant primary brain tumor in adults, accounting for approximately 14.3% of all primary brain tumors [1] 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 temozolomide[3] with or without the addition of tumor-treating fields.[4] Despite aggressive therapy, median overall survival only ranges between 15-26 months, highlighting the unmet need for effective treatment strategies.[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, e.g., bevacizumab) [11], protein kinase C-β (PKCß, e.g., enzastaurin),[12] mammalian target of rapamycin (mTOR, e.g., temsirolimus and everolimus)[13] and other vital intracellular signaling components such as the proteasome (e.g., bortezomib),[14] histone deacetylases (HDAC, e.g., vorinostat),[15] cyclin-dependent kinases (CDK, e.g., palbociclib, abemaciclib)[16] and phosphatidylinositol-3 kinase (PI3K, e.g., BKM120).[17]

To date, various targeted agents have been evaluated or are currently being analyzed in clinical trials, but there are only a few systematic data on the effectiveness of targeted treatments across different targets versus 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. Material 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, Supplementary File 1).[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 grey 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

2021-07-27 (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 Supplementary File 2. The PRISMA-S checklist[22] is included in Supplementary File 3. 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 Bramer 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 versus 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 overall survival (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, non-human research, and articles in a language other than English.

Targeted treatments included medications directed against growth factors and their receptors, e.g., 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-ß), 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), PKCß; cell cycle regulators/DNA repair mechanisms, e.g. 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 (e.g., gliadel wafers), oncolytic viral/antiviral/retroviral treatments (e.g., TOCA 511/FC, ganciclovir, etc.), drugs that solely increase blood-brain-barrier (BBB) permeability (e.g., RMP-7), or repurposed drugs not directly targeting cancer-associated pathways (e.g., 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, progression-free survival at 6 months (PFS-6) and 12 months (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 standard error $s_i=d_i/1.96$, where d_i represents the maximum of [log(upper 95% CI bound of RR_i)–$\log(RR_i)$] and [$\log(RR_i)$–log(lower 95% CI bound of RR_i)].

We performed a random-effects meta-analysis [24] 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 test,[26] 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 and 2021. The search strategies based on a linear search algorithm are shown in Supplementary File 2. Supplementary File 3 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 3,941 patients with newly diagnosed GB. In the meta-analysis, 2,024 patients were assessed in the experimental arm and 1,917 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 $\alpha v\beta 3/\alpha v\beta 5$ 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 versus temozolomide as the control group. All except one study [28] consisted of trials with two study arms. We focused on one arm of this 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.

Outcome parameters

3.2.1 Overall survival (OS)

Eleven studies were eligible for the evaluation of overall survival. The phase II trial by Chauffert et al. [30] was excluded because of a lack of data on HRs for OS. The random-effect meta-analysis showed a non-significantly reduced mortality risk of 0.98 (95% CI 0.86-1.11, p=0.7731) for newly diagnosed GB patients treated with targeted therapy (N=2,024) compared to temozolomide (N=1,917) (Figure 2). The moderate heterogeneity observed between studies (I^2=58.36%) was statistically significant (p=0.0093).

Next, we performed separate analyses for each molecular target, VEGF, EGFR, mTOR, αvβ3/αvβ5, and PARP. None of the targeted therapies showed a significant reduction in mortality risk compared with 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=0.6006]), EGFR (RR=0.89 [95% CI 0.75-1.05, p=0.1563]) and αvβ3/αvβ5 (RR=0.86 [95% CI 0.48-1.25, p=0.4241]) 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=0.0318]. Study heterogeneity was significantly reduced by stratified analyses, with little or minor heterogeneity among the EGFR (I^2=0.0%; p=0.8837) and mTOR subgroups (I^2=25.81%; p=0.2456) and moderate heterogeneity among the αvβ3/αvβ5 (I^2=70.84%; p=0.0641) and VEGF (I^2=64.57%; p=0.0309) subgroups.

3.2.1.Progression-free survival (PFS)

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=0.0037)]) (Figure 4). Moderate heterogeneity was observed among the included studies (I^2=60.02%; P =0.0024).

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<0.001]). Although not statistically significant, therapies targeting EGFR, αvβ3/αvβ5, 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>0.2489).

3.2.2.Subgroup analyses

Further stratification was carried out based on biomarkers and patient characteristics: *methylated/unmethylated O6-Methylguanin-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 (Supplementary Figure 1). A statistically non- significant 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 with 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=0.1085]), whereas for patients with unmethylated *MGMT*, we noted a significant benefit for the targeted drug (0.75 [95% CI 0.56-0.99, p=0.0440]). 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 EIAEDs. All other subgroups showed a significant reduction in the risk of tumor progression when the targeted agent was administered (Supplementary Figure 2).

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=0.27]). 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=0.07]). This shows that targeted 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 0.75 - 1.07, p=0.22]) or PFS (0.94 [95% CI 0.79 - 1.13, p=0.51]) 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 overall survival and disease progression (Supplementary Figures 3a and b) displayed an almost symmetrical distribution, indicating no publication bias. This was corroborated by high P-values of Begg`s (P=0.8793 and 0.8406) and Egger`s (P=0.8901 and 0.5068) 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 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 progression-free survival. 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 (for example, 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 progression-free survival, inhibition of the VEGF/VEGFR pathway failed to show an extension of overall survival.[11, 31, 34-36] The results of our analysis regarding VEGF/VEGFR-inhibition with bevacizumab are in line with previously published meta-analyses [37-39] 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 αvβ3/αvβ5 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 towards 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 al.[45] exclusively focused on EGFR-targeted treatments in patients with GB and showed non-significant 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 non-significant benefit in both OS and PFS for treatment with rindopepimut compared to standard therapy. Likewise, only the study by Wick et al.[46] addressed a possible therapeutic advantage of an mTOR inhibitor in the presence of a phosphorylated or non-phosphorylated mTOR status. With respect to OS, p-mTOR^{Ser2448} positive patients who received temsirolimus as compared to those who received temozolomide showed a non-significant 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,[47,48] CDK 4,6, CDKN2A/B inhibitors (palbociclib: NCT03158389), PI3K inhibitors (paxalisib: NCT03522298), or other PARP inhibitors,[49] whose efficacy and tolerability have been and are still being tested in non-randomized and randomized clinical trials (e.g., 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 progression-free as well as overall survival data. Therefore, recent studies on targeted substances have not been included. One study[45] 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 sub-analysis 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.[50] 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 overall survival, although a potentially clinically meaningful extension in progression-free survival 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.

Conflict of Interest

All authors declare no potential conflicts of interest.

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.

Author Contributions: Conceptualization (AS, FMI, CS); Methodology (HK, HB, CS); Software (AS, HB); Validation (CS, FMI); Formal analysis (AS, FMI, HB); Investigation (AS, FMI, HK); Resources (AS, FMI, HK, CS); Data Curation (AS, HB); Writing - Original Draft (AS, FMI); Writing - Review & Editing (CS, PH, HB, WW, JG, HK, MFL); Visualization (AS, FMI); Supervision (CS); Project administration (CS); Funding acquisition (CS). The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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

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Figure and Table Legends

Table 1: Characteristics of the included studies

Abbreviations: mOS: median overall survival; mPFS: median progression-free survival; Ex: Experimental; Co: Control; TMZ: Temozolomide; VEGF=Vascular endothelial growth factor, EGFR=Epidermal Growth Factor Receptor, mTOR=mechanistic Target of Rapamycin, PARP= Poly(ADP-ribose) polymerase; αvβ3/αvβ5: αvβ3/αvβ5 integrin

Figure 1:

PRSIMA 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 in 2021.

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 versus temozolomide.

Abbreviation: RE= risk estimate

Figure 3:

Forest plot displaying the subsequent subgroup analysis by target of the pooled estimated risk ratio (red diamond) for overall survival.

Abbreviations: RE= risk estimate, VEGF=Vascular endothelial growth factor, EGFR=Epidermal Growth Factor Receptor, mTOR=mechanistic Target of Rapamycin, PARP= Poly(ADP-ribose) polymerase; αvβ3/αvβ5: αvβ3/αvβ5 integrin

Figure 4:

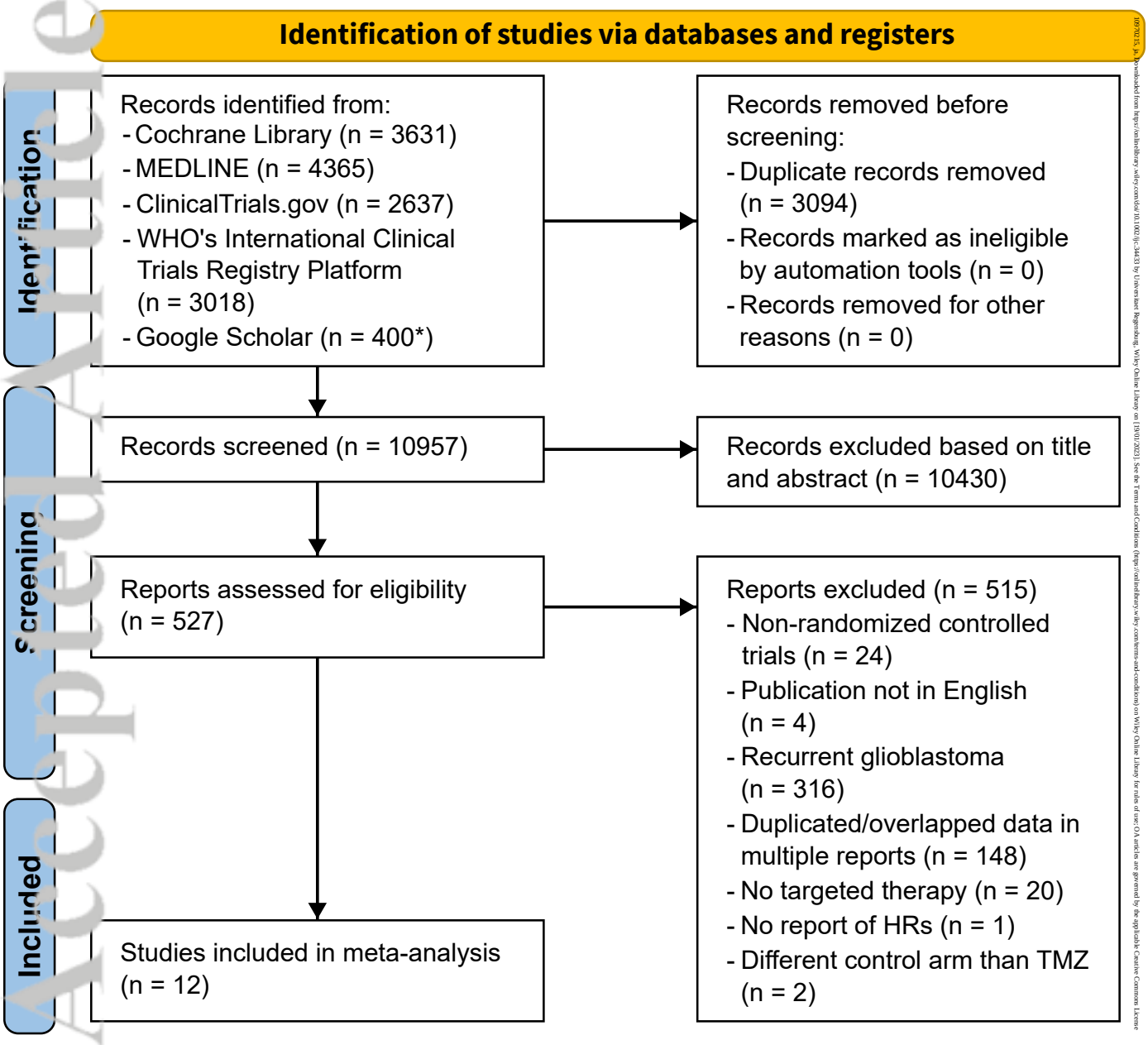
Forest Plot of the pooled estimated risk ratios for progression-free survival across 12 RCTs of treatment of newly diagnosed GBMs with targeted therapy versus temozolomide.

Abbreviation: RE= risk estimate

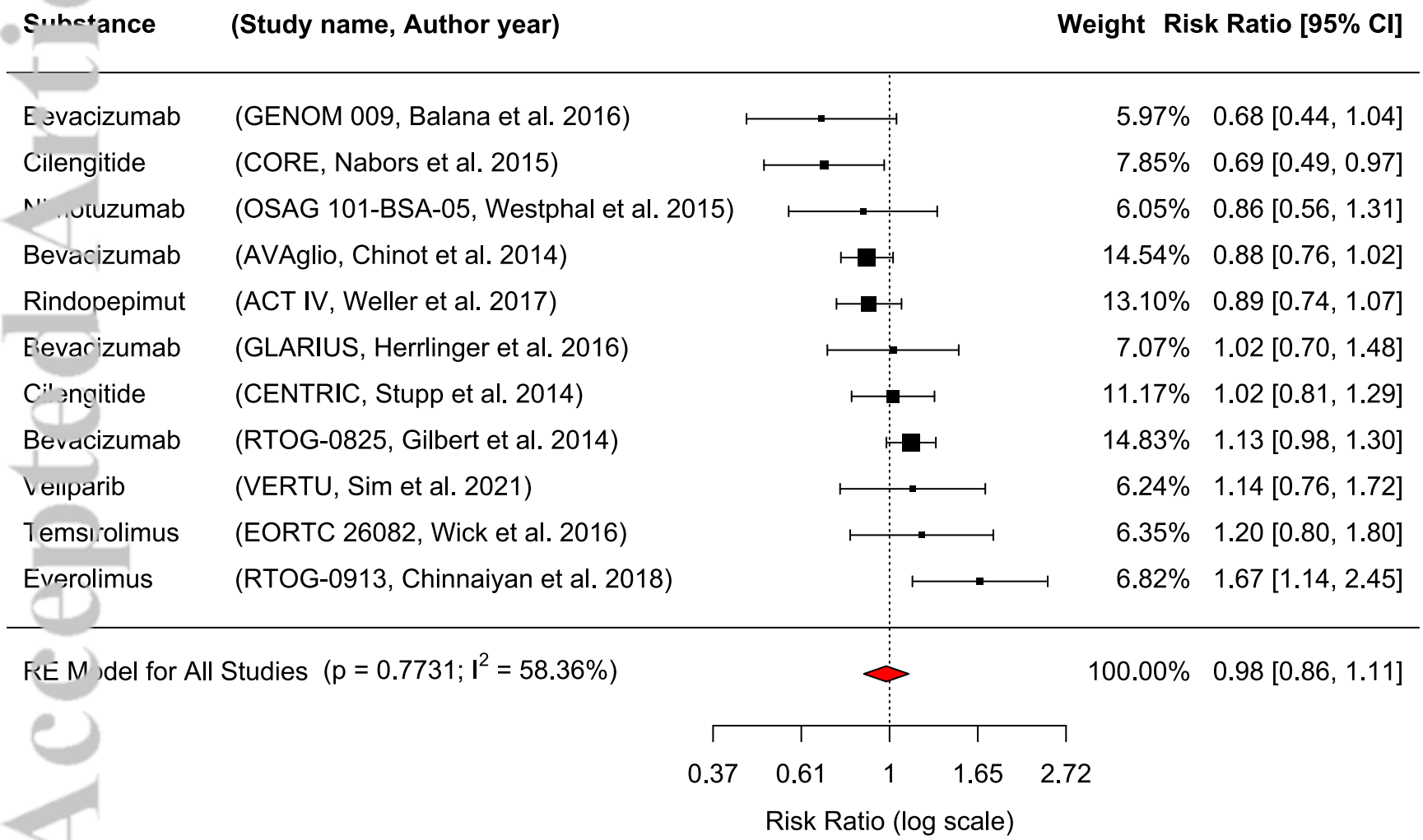
Figure 5:

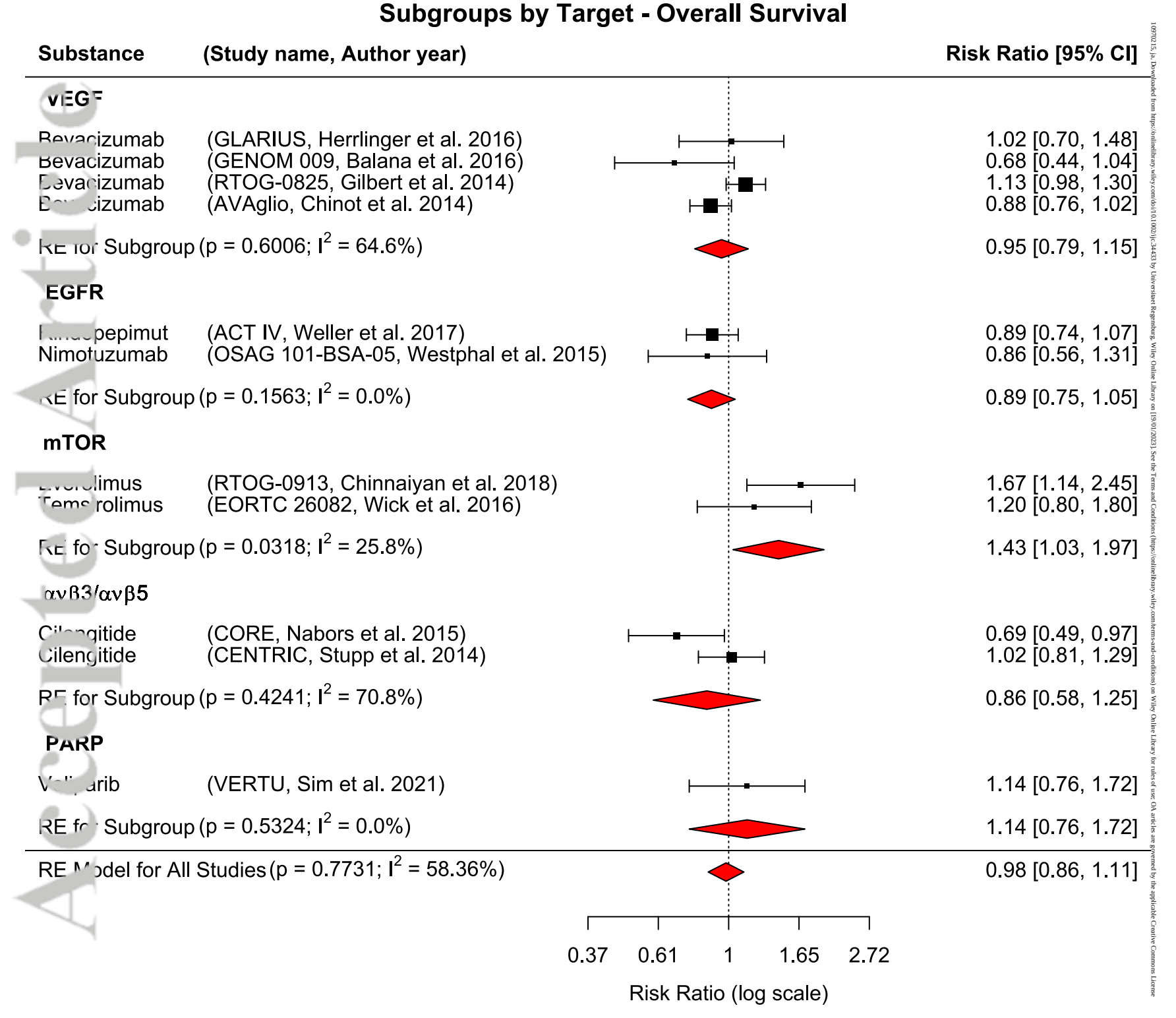
Forest Plot of subgroup analysis by target for progression-free survival.

Abbreviations: VEGF=Vascular endothelial growth factor, EGFR=Epidermal Growth Factor Receptor, mTOR=mechanistic Target of Rapamycin; PARP= Poly(ADP-ribose) polymerase; αvβ3/αvβ5: αvβ3/αvβ5 integrin

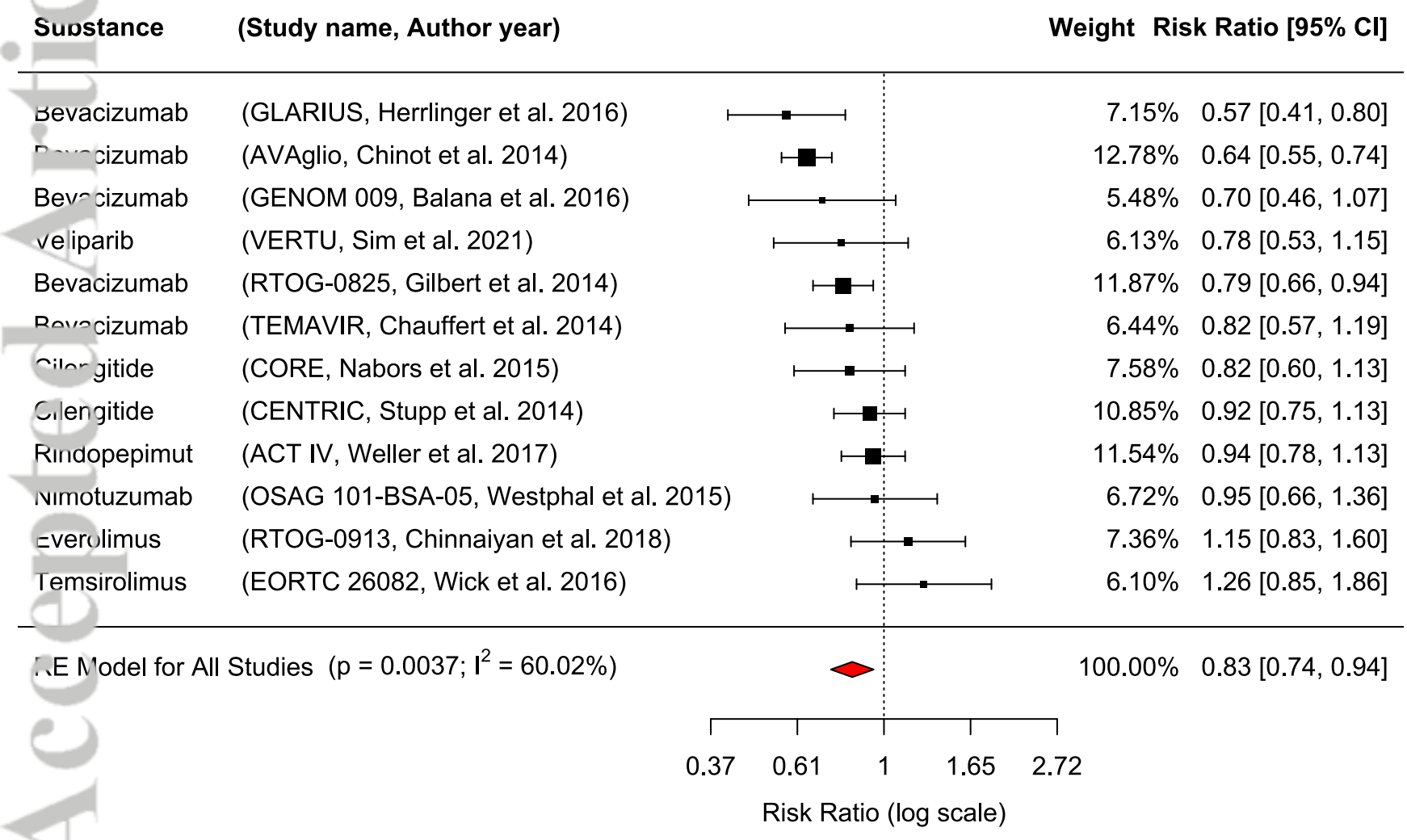


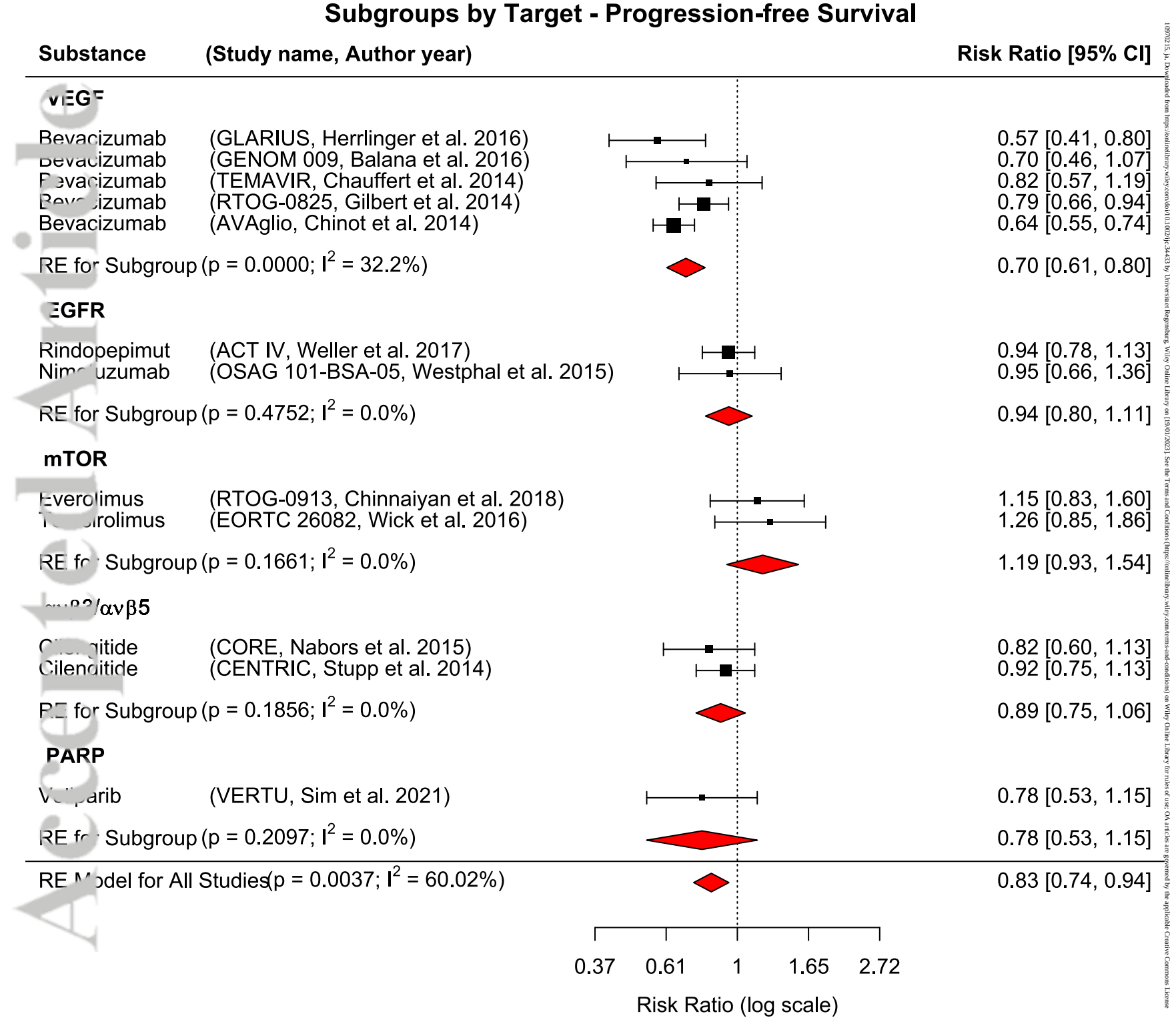
Targeted Therapy vs. Temozolomide - Overall Survival





Targeted Therapy vs. Temozolomide - Progression-free Survival





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	AVAglio	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	$\alpha\nu\beta3/\alpha\nu\beta5$	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	$\alpha\nu\beta3/\alpha\nu\beta5$	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	EGFRvIII	Rindopepimut/ Temozolomide	TMZ	371	374	17.4	17.4	72	74	7.1	5.6	NA	NA
Temsirolimus	Wick	2016	EORTC 26082	II	mTOR	Temsirolimus	TMZ	56	55	14.8	16	69.6	72.2	5.4	6	38.7	50
Veliparib	Sim	2021	VERTU	II	PARP	Veliparib followed by Veliparib/TMZ	TMZ	84	41	12.7	12.8	NA	NA	5.7	4.2	46	31