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Protein kinase inhibitors as targeted therapy for glioblastoma: a meta-analysis of randomized controlled clinical trials

José Pinto-Fraga [a], Celia García-Chico [a], Simone Lista [a], Pedro Miguel Lacal [b], Giuseppe Carpenzano [c], Maurizio Salvati [c], Alejandro Santos-Lozano [a,d], Grazia Graziani [e,*], Claudia Ceci [e]

[a] i+HeALTH Strategic Research Group, Miguel de Cervantes European University, Valladolid 27038, Spain
[b] Laboratory of Molecular Oncology, IDI-IRCCS, Rome, Italy
[c] Department of Neurosurgery, Policlinico Tor Vergata, University of Rome Tor Vergata. Rome, Italy
[d] Research Institute of the Hospital 12 de Octubre ('1mas12' [PaHerg Group]), Madrid 28041, Spain
[e] Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

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ABSTRACT

Glioblastoma (GBM) is the most common and lethal primary brain tumor. The standard treatment for newly diagnosed GBM includes surgical resection, when feasible, followed by radiotherapy and temozolomide-based chemotherapy. Upon disease progression, the anti-vascular endothelial growth factor-A (VEGF-A) monoclonal antibody bevacizumab, can be considered.

Given the limited efficacy of pharmacological treatments, particularly for the recurrent disease, several molecularly targeted interventions have been explored, such as small-molecule protein kinase inhibitors (PKIs), inhibiting tyrosine kinase growth factor receptors and downstream signaling pathways involved in GBM angiogenesis and infiltrative behavior.

This meta-analysis, based on searches in PubMed and Web Of Science, evaluated 12 randomized controlled trials (RCTs) examining PKIs in patients with newly diagnosed or recurrent GBM. Pooled analysis of shared clinical outcomes - progression-free survival (PFS) and overall survival (OS) - revealed a lack of significant improvements with the use of PKIs. In newly diagnosed GBM, no significant differences were observed in median [-1.02 months, 95 % confidence interval (CI), −2.37–0.32, $p = 0.14$] and pooled [hazard ratio (HR) = 1.13, 95 % CI, 0.95–1.35, $p = 0.17$) OS, or in median (0.34 months, 95 % CI, −0.9–1.58, $p = 0.60$) and pooled (HR = 0.98, 95 % CI, 0.76–1.27, $p = 0.89$) PFS, when comparing PKI addition to standard chemo-radiotherapy *versus* chemo-radiotherapy alone. In recurrent GBM, three different analyses were conducted: PKI *versus* other treatments, PKI combined with other treatments *versus* those treatments alone, PKI *versus* PKI combined with other treatments. Also, across these analyses, no significant clinical benefits were found. For instance, when comparing PKI treatment with other treatments, median OS and PFS showed no significant difference (-0.78 months, 95 % CI, −2.12–0.55, $p = 0.25$; −0.23 months, 95 % CI, −0.79–0.34, $p = 0.43$, respectively), and similar non-significant results were observed in the pooled analyses (OS: HR = 0.89, 95 % CI, 0.59–1.32, $p = 0.55$; PFS: HR = 0.83, 95 % CI, 0.63–1.11, $p = 0.21$).

Abbreviations: AIFA, Italian Medicines Agency; BBB, blood-brain barrier; BCRP/ABCG2, Breast Cancer Resistance Protein; CDK4/6, cyclin-dependent kinase 4 and 6; CI, confidence interval; CNS, central nervous system; DNA-PK, DNA-dependent protein kinase; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FDA, Food and Drug Administration; FGFR, fibroblast growth factor receptor; GBM, glioblastoma; GCN2, General Control Non-derepressible 2; GSCs, glioblastoma stem cells; HR, hazard ratio; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Status; MGMT, O^6-methylguanine-DNA methyltransferase; mTor, mammalian target of rapamycin; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PDGFR, platelet derived growth factor receptor; PFS, progression-free survival; P-gp/ABCB1, P-glycoprotein; PICO, population, intervention, comparison, outcome; PKI, protein kinase inhibitor; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; PROSPERO, International Prospective Register of Systematic Reviews; ROB 2, Risk of Bias 2; RANO, Response Assessment in Neuro-Oncology; RTK, receptor tyrosine kinase; SD, standard deviation; TGFβR, transforming growth factor-β receptor; TMZ, temozolomide; VEGF-A, vascular endothelial growth factor-A; VEGFR, vascular endothelial growth factor receptor; WHO, World Health Organization.

* Correspondence to: Department of Systems Medicine, University of Rome Tor Vergata, Via Montpellier 1, Rome 00133, Italy.
E-mail address: graziani@uniroma2.it (G. Graziani).

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Veliparib (PubChem CID: 11960529).

Despite these overall negative findings, some data indicate improved clinical outcomes in a subset of GBM patients treated with certain PKIs (i.e., regorafenib) and encourage further research to identify PKIs with better blood-brain barrier penetration and lower risk for resistance development.

1. Introduction

Glioblastoma (GBM) is the most aggressive primary brain tumor, deriving from non-neuronal/glial cells (such as astrocytes, oligodendrocytes, microglial, and ependymal cells) [1] and accounting for about 14 % of the overall glioma cases. Among all malignancies, GBM has the worst prognosis, being the median survival less than 15 months [2].

Traditionally, the World Health Organization (WHO) classified GBM as a grade IV glioma based on histological criteria [3]. However, recent WHO guidelines established the absence of mutations in the *isocitrate dehydrogenase 1/2* (*IDH*-wild type) and *histone 3* (*H3*-wild type) genes as requisite for the diagnosis of GBM. Such classification has improved prognosis definition, by upgrading histologically lower-grade, *IDH*-wild type astrocytoma to GBM [4].

The invasive nature and resistance to therapies are peculiar properties of GBM contributing to the frequently observed recurrence after standard treatment, represented by surgical resection (when feasible) followed by radiation with concurrent and maintenance temozolomide (TMZ)-based chemotherapy [5].

For recurrent GBM, in 2009, the Food and Drug Administration (FDA) granted accelerated approval to bevacizumab, an anti-vascular endothelial growth factor-A (VEGF-A) monoclonal antibody targeting angiogenesis [6,7]. Conversion to a full approval was obtained in 2017 based on the results of a phase 3 study, reporting that bevacizumab, in combination with lomustine-based chemotherapy, reduced the risk of disease progression or death by 48 %. However, the addition of bevacizumab to lomustine did not improve overall survival (OS), health-related quality of life, and neurocognitive function, and increased systemic toxicity [8]. Due to lack of evidence of OS and risk/benefit ratio improvement, the European Medicines Agency (EMA) rejected the indication of bevacizumab for recurrent GBM, although in many countries it is administered off-label. Also in the case of newly diagnosed GBM, the combination of bevacizumab with first-line chemo--radiotherapy did not improve OS and was associated with a higher rate of adverse effects, compared to placebo [9–11].

Among alternative treatments being explored, re-irradiation has emerged as a promising strategy for recurrent GBM resistant to bevacizumab monotherapy, although further studies are needed to optimize its use [10]. Other approaches, like immune checkpoint inhibitors, have been also explored in combination with re-irradiation and bevacizumab [12]. Among targeted agents, protein kinase inhibitors (PKIs) have gained attention as putative therapeutic agents able to affect multiple pathways associated with GBM [13,14]. Indeed, receptor tyrosine kinase (RTK) signaling pathways have been identified as crucial for tumor cell proliferation, survival, metabolism, metastasis, and their dysregulation has been recognized as critical for GBM initiation and progression in over 80 % of cases [13,14]. In detail, gene alterations affecting specific RTKs, such as epidermal growth factor receptor (*EGFR*), platelet derived growth factor receptor (*PDGFR*), fibroblast growth factor receptor (*FGFR*), are common in GBM. *EGFR* amplification is detected in approximately 50 % (45–57 %) of GBMs [15,16] and the most common *EGFR* mutation (in-frame deletion of exon 2–7, defined as EGFRvIII) occurs in ~50 % of all *EGFR*-amplified GBM cases [17]. *PDGFR* is amplified in 10–20 % of GBM cases [16,18], while mutated *PDGFR* has been detected in 11 % of GBM samples, and limited to the proneural GBM subtype [19]. In regard to *FGFR*, the oncogenic gene fusion with *TACC* (transforming acidic coiled-coil containing proteins) occurs in about 3 % of GBM patients [20]; other *FGFR* mutations/amplifications are generally less frequent, occurring in about 1 % or even less cases [21]. Such advances in understanding GBM biological/molecular features are paralleled by an extensive preclinical exploration of PKI-based new therapeutic strategies in several GBM models [22].

To date, ~80 FDA-approved PKIs are available targeting about two dozen protein kinases, most of which are inhibitors of RTKs [23,24]. Nevertheless, currently there is not any FDA- and/or EMA-approved PKI for treating GBM. An exception is represented by regorafenib, a PKI targeting VEGF-A receptors (VEGFRs) approved in 2019 by the Italian Medicines Agency (AIFA) in the setting of recurrent GBM [25].

Clinical trials conducted to test PKIs activity in GBM, based on their efficacy in various other tumors, have been largely unsuccessful, showing limited efficacy [13], attributed to poor blood-brain barrier (BBB) permeability and lack of tumor specificity.

However, no meta-analyses have been published specifically focusing on the therapeutic efficacy of PKIs in GBM patients. The only systematic meta-analysis to be mentioned was conducted on 12 recent randomized studies evaluating the use of certain targeted therapies, not limited to PKIs, on patients with newly diagnosed GBM [26]. In detail, the meta-analysis by Scherm at al. included antiangiogenic approaches (bevacizumab and cilengitide), anti-EGFR agents (nimotuzumab and rindopepimut), the poly(ADP-ribose) polymerase (PARP) inhibitor veliparib, and everolimus and temsirolimus as only examples of PKIs, acting on the mammalian target of rapamycin (mTor) serine/threonine kinase signal transduction pathway [26]. Results suggested a significantly prolonged progression-free survival (PFS) in patients with newly diagnosed GBM, compared to standard care, only in the case of VEGF-A inhibition with bevacizumab, but confirmed no improvement in OS with bevacizumab and any other targeted agent [26]. This evidence is in line with the results of other meta-analyses, indicating an enhancement of PFS with bevacizumab, and only modest or no improvement in OS [27–30].

Current preclinical research is focused on investigating drug delivery strategies (liposomes, polymeric nanoparticles/micelles, albumin nanoparticles, inorganic nanocarriers, lipid nanocapsules) able to overcome the weakness of PKIs due to limited BBB permeability, and several new inhibitors are still currently moving from preclinical to clinical investigation [22]. In this perspective, we think that a conclusive overview on the available “first generation” clinical studies evaluating PKIs in GBM patients during the last decade may be useful, to be consulted by both clinicians and researchers. Therefore, the present study aims to provide the first comprehensive meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy of PKIs in recurrent and newly diagnosed GBM patients, by focusing on OS and PFS as primary outcomes. Three different analyses were performed on a pool of recurrent GBM patients, i.e. comparisons of, *i*) PKI *versus* other treatments (not PKI), *ii*) PKI in combination with other treatments *versus* other treatments (not PKI), and *iii*) PKI *versus* PKI in combination with other treatments. An additional analysis was performed on studies enrolling newly diagnosed GBM patients by comparing PKI in combination with other treatments *versus* other treatments (standard chemo-radiotherapy).

2. Methods

The conduct and reporting of the current meta-analysis conform to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [31] and the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024591769).

2.1. Search strategy

Two researchers independently conducted a systematic search (CC, GG). Studies published in English were identified in PubMed using the keywords *Glioblastoma Kinase Inhibitor,* with the filter *Randomized Controlled Trial* selected through the Article Type tool, up to June 2024. A similar search was conducted on the Web of Science using the same keywords, and this was supplemented by a manual review of reference lists from relevant publications to find additional studies on the subject. The full texts of the studies that met the inclusion criteria were independently assessed by four authors (CC, GG, CGC, JPF).

2.2. Study selection

The study selection criteria were established in terms of PICO (population, intervention, comparison, outcome) and study design framework [32].

Only RCTs were included, i.e., prospective studies that evaluate the effects of an intervention and are considered as the standard of reference for studying causal relationships of such intervention [33].

The selection criteria for including a RCT in the meta-analysis were the following: *i*) enrollment of patients with a confirmed diagnosis of GBM, newly diagnosed and not previously subject to treatment with chemotherapy or radiation, or recurrent and showing progression following prior surgery, radiation therapy, and TMZ; evaluation of *ii*) a PKI compared to another treatment, or *iii*) a PKI plus another treatment, in comparison with the other treatment alone or PKI alone, in recurrent GBM, receiving prior standard treatment with surgery and TMZ-based chemo-radiotherapy; evaluation of *iv*) a PKI plus standard treatment with surgery and TMZ-based chemo-radiotherapy in newly diagnosed GBM. Non-randomized, phase 1, and discontinued studies were excluded, as well as studies assessing other targeted agents (monoclonal antibodies, antibody-drug conjugates, antisense oligonucleotides) acting on protein kinases, or not evaluating survival outcomes.

2.3. Quality assessment and data collection

The risk of bias in individual studies was assessed based on seven criteria using the Risk of Bias 2 tool (ROB 2) [34]: sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other biases. The Cochrane Collaboration tool was used for this evaluation. Each criterion was rated as low risk, unclear risk, or high risk. Quality assessments were conducted independently by two authors (JPF and CGC), with any disagreements resolved through discussion with a third author (ASL).

Data were collected by one investigator (JPF), who extracted information on median OS, median PFS, hazard ratio (HR) for OS, and HR for PFS. When data were not directly provided, the software WebPlotDigitizer [Rohatgi, A., 2021. WebPlotDigitizer (version 4.2 Computer software). Pacifica, CA, (Updated August, 2021) available from: https://automeris.io/webplotdigitizer] and the Parmar method [35] were used to estimate the values from Kaplan-Meier curves.

2.4. Statistical analyses

The pooled effect of PKIs in patients with GBM was estimated through a random-effects model meta-analysis [36] when at least three studies used the same outcome. Depending on the nature of the variable, each outcome was analyzed using the proportions or the effect sizes. The weight assigned to each study included in the meta-analysis was defined by the standard deviation (SD) of the variables and the sample size. When direct comparisons between treatment groups were not available within the evaluated studies, an indirect comparison method was used to estimate HR for OS and PFS. Specifically, the Bucher method was used, which allows for the calculation of an indirect HR by leveraging available direct comparisons between each treatment and a common control group [37].

The Begg's test was used to determine the presence of publication bias, and the I^2 statistic was used to assess heterogeneity across studies.

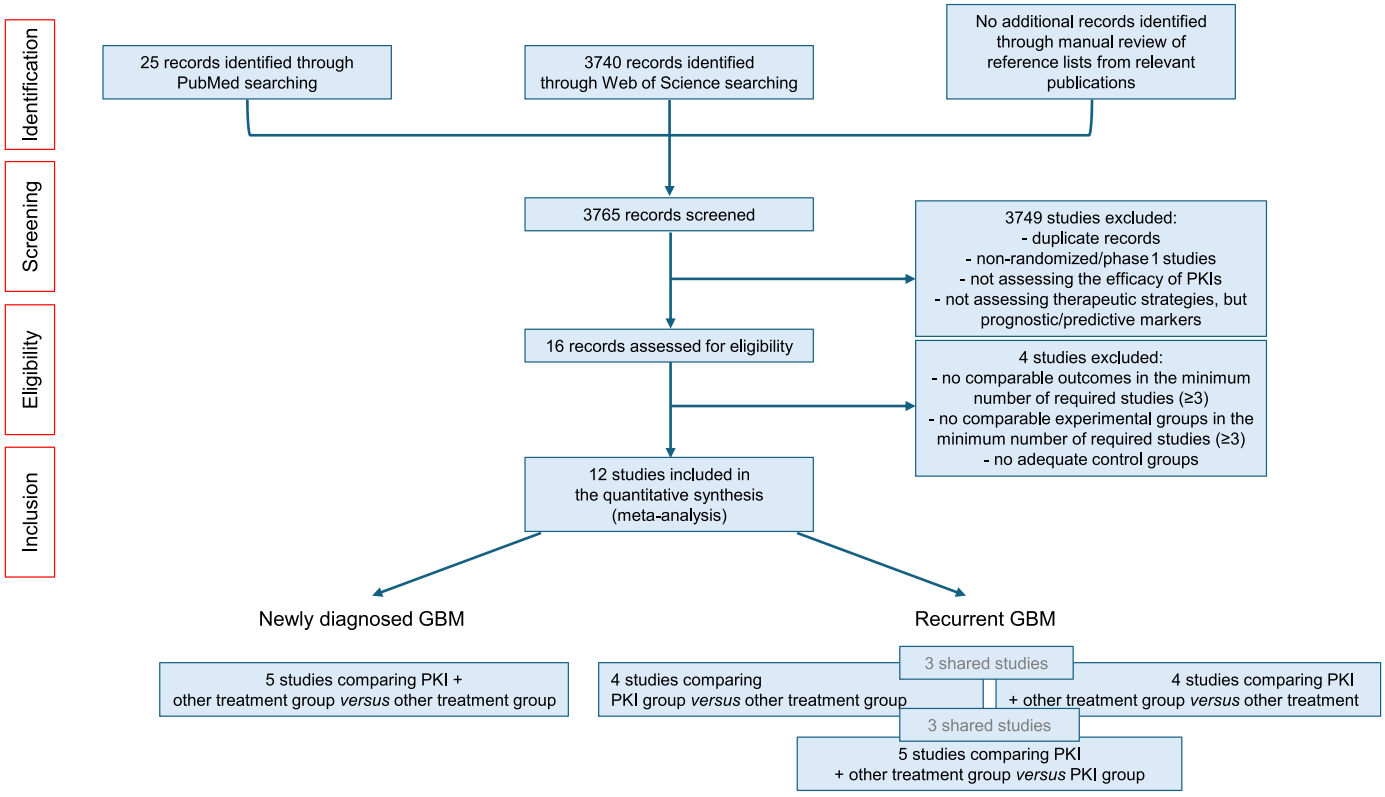

Fig. 1. PRISMA flow diagram detailing the search strategy based on the keywords *Glioblastoma and Kinase Inhibitor* and the selection of eligible RCTs.

Table 1
Characteristics summary of the studies included in the meta-analysis.

Randomized studies on RECURRENT GBM and PKIs as intervention

First author (Year)	Sample characteristics	Intervention	Outcomes	Main results
Lombardi et al. (2019) Regorafenib [25]	**EG1 (n = 59)** **Gender (%)**: male (69); female (31) **Median age (range)**: 54.8 (46.8–61.3) **Diagnosis**: histologically confirmed GBM with first progression after surgery + radiotherapy + TMZ	**Effective EG1 (n = 59)** **Regorafenib** **Intervention characteristics**: - regorafenib 160 mg orally, once daily during 3 weeks of each 4-weeks cycle	- **Primary:** OS *(Kaplan-Meier method)* - **Secondary:** PFS; proportion of patients achieving an objective response *(%, RANO criteria)* - **Safety:** reported toxicities; adverse events *(percentage)*; laboratory abnormalities; vital sings; electrocardiography	↑ OS in EG1 *versus* EG2 ↑ PFS in EG1 *versus* EG2 ↑ Occurrence of grades 3–4 drug-related adverse events in EG1 than in EG2
	EG2 (n = 60) **Gender (%)**: male (72); female (28) **Median age (range)**: 58.9 (51.8–65.2) **Diagnosis**: histologically confirmed GBM with first progression after surgery + radiotherapy + TMZ	**Effective EG2 (n = 60)** **Lomustine** **Intervention characteristics**: - lomustine 110 mg/m^2 orally, on day 1 of every 6-week cycle until disease progression, death, unacceptable toxicity, or discontinuation		
Reardon et al. (2015) Afatinib [39]	**EG1 (n = 39)** **Gender (%)**: male (64.1); female (35.9) **Mean age + SD**: 56.9 + 10.62 **Diagnosis**: histologically confirmed grade 4 malignant glioma at first recurrence after TMZ chemoradiotherapy	**Effective EG1 (n = 39)** TMZ **Intervention characteristics**: - TMZ 75 mg/m^2/day, orally, for 21/28 days	- **Primary:** 6-months PFS - **Secondary:** median PFS *(Kaplan Meier method)*; Disease Control Rates (DCR); biomarkers: EGFR, EGFRvIII, PTEN, PAKT, MGMT *(immunohistochemistry)*; EGFR, PTEN *(FISH)*; OS *(Kaplan-Meier method)* - **Safety:** reported toxicities; adverse events *(percentage)*; laboratory abnormalities; vital sings; electrocardiography	↓ 6-months PFS, median PFS, and DCR in EG2 *versus* EG1 ↑ Median PFS in EG2 participants with EFGRvIII-positive tumors *versus* EGFRvIII-negative tumors ↑ Frequency of adverse events in EG2 and EG3 *versus* EG1
	EG2 (n = 41) **Gender (%)**: male (65.9); female (34.1) **Mean age + SD**: 56.6 + 9.44 **Diagnosis**: histologically confirmed grade 4 malignant glioma at first recurrence after TMZ chemoradiotherapy	**Effective EG2 (n = 41)** Afatinib **Intervention characteristics**: - afatinib 40 mg/day orally, for 21/28 days		
	EG3 (n = 39) **Gender (%)**: male (53.8); female (46.2) **Mean age + SD**: 56.6 + 9.44 **Diagnosis**: histologically confirmed grade 4 malignant glioma at first recurrence after TMZ chemoradiotherapy	**Effective EG3 (n = 39)** Afatinib + TMZ **Intervention characteristics**: - afatinib 40 mg/day, orally - TMZ 75 mg/m^2, orally, for 21/28 days		
Duerinck et al. (2018) Axitinib [47]	**EG1 (n = 50)** **Gender (%)**: male (66); female (34) **Median age (range)**: 55 (27–79) **Diagnosis:** GBM with tumor recurrence or progression following prior treatment with surgery, radiation therapy, and TMZ	**Effective EG1 (n = 50)** Axitinib **Intervention characteristics**: - axitinib 5 mg, orally, twice daily	- **Primary:** 6-months PFS - **Secondary**: best overall response rate; median OS (*Kaplan-Meier method*); molecular analysis: *MGMT* promoter methylation - **Safety:** reported toxicities; adverse events *(percentage)*	PFS and OS not significantly different between EG1 and EG2 ↑ PFS and OS in patients with *MGMT* promoter hypermethylation and not on steroid treatment at baseline in both EGs ↑ Incidence of grade 3–4 adverse events (thrombocytopenia and neutropenia) in EG2 *versus* EG1
	EG2 (n = 31) **Gender (%)**: male (58); female (42) **Median age (range)**: 56 (28–75)	**Effective EG2 (n = 29)** Axitinib + Lomustine **Intervention**		

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Table 1 (*continued*)

Randomized studies on RECURRENT GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
	Diagnosis: GBM with tumor recurrence or progression following prior treatment with surgery, radiation therapy, and TMZ	**characteristics**: - axitinib 5 mg, orally, twice daily - lomustine 90 mg/m^2, orally, every 6 weeks		
Galanis et al. (2019) Dasatinib [43]	**EG1 (n = 83)** **Gender (%)**: male (57.9); female (42.1) **Mean age + SD**: 52.5 + 14.1 **Diagnosis:** histologically confirmed GBM, including variant gliosarcoma, with up to 2 prior chemotherapy regimens (≤1 regimen for recurrent disease) but not including angiogenesis inhibitors or dasatinib	**Effective EG1 (n = 83)** Bevacizumab + Dasatinib **Intervention characteristics**: - bevacizumab 10 mg/kg, intravenously, on day 1 of each 14-day cycle - dasatinib 100 mg, orally, twice-daily from day 1–14 of each 14-day cycle	- **Primary:** 6-months PFS - **Secondary:** objective response (OR, *RANO criteria)*; OS *(Kaplan-Meier method);* time to disease progression (TTP) - **Safety:** reported toxicities; adverse events *(percentage);* patient-reported quality of life - **Exploratory:** molecular analysis of Src pathway activation and correlation with outcomes	No statistically significant differences in PFS between EG1 and EG2 No statistically significant differences in OR, OS, TTP between EG1 and EG2 No statistically significant increase of grade ≥ 3 toxicities incidence in EG1 *versus* EG2 No difference in quality of life between EG1 and EG2 No significant interactions between outcomes and biomarkers IHC values
	EG2 (n = 38) **Gender (%)**: male (63.6); female (36.4) **Mean age + SD**: 55.5 + 12.1 **Diagnosis:** histologically confirmed GBM, including variant gliosarcoma, with up to 2 prior chemotherapy regimens (≤1 regimen for recurrent disease) but not including angiogenesis inhibitors or dasatinib	**Effective EG2 (n = 38)** Bevacizumab + Placebo **Intervention characteristics**: - bevacizumab 10 mg/kg, intravenously, on day 1 of each 14-day cycle - placebo, orally, twice-daily from day 1–14 of each 14-day cycle		
Brandes et al. (2016) Galunisertib [41]	**EG1 (n = 39)** **Gender (%)**: male (59.1); female (40.9) **Mean age ± SD**: 56,6 ± 10,9 **Diagnosis**: recurrent, histologically confirmed GBM (progression determined by RANO criteria following standard chemoradiation)	**Effective EG1 (n = 39)** Galunisertib **Intervention characteristics**: - galunisertib 300 mg/day, orally, for 14 days followed by 14 days off in a 28-day cycle	- **Primary:** comparison of OS between EG3 and EG2 (*Bayesian augmented control design*) - **Secondary:** OS and PFS (*Kaplan-Meier estimates and the log-rank test*); OR (*RANO criteria*) - **Pharmacokinetic analysis** (*LC-MS/MS methods*) - **Pharmacodynamic analysis** (*IHC* on tumor tissue samples for *IDH1* mutation and CD3 + T-cell infiltrates; *ELISA* on plasma samples for TGF-b1 levels*; flow cytometry* for levels of CD4 + and CD8 +, CD4 +CD25 +CD1272/ LOFOXP3 + T cell subsets; *epigenetic T cell assay* for percentage of FOXP3 and CD3 in whole blood) - **Safety:** adverse events (*CTCAE version 4.0*), dose-limiting toxicities, laboratory changes, changes in ECOG PS, electrocardiogram, and echocardiography/Doppler	No statistically significant changes in OS between EGs No statistically significant changes in PFS and response rates between EGs Improved prognosis associated with bevacizumab given post-discontinuation of the experimental therapy, small tumors, high baseline levels of macrophage-derived chemokine (MDC/ CCL22), high baseline eosinophil counts, high CD4 +CD25 +CD1272/LOFOXP3 + , high percentage in CD3 + and FOX P3 ↑ OS in patients with a phenotype of regulatory T cells (i.e., high CD4 +CD25 +CD1272/ LOFOXP3 + and MDC levels) Unchanged galunisertib PK profile across both treatment arms and comparable to previous assessments No notable differences among the 3 treatment arms for health outcome measurement
	EG2 (n = 40) **Gender (%)**: male (52,4); female (47.6) **Mean age ± SD**: 56,9 ± 10,2 **Diagnosis**: recurrent, histologically confirmed GBM (progression determined by RANO criteria following standard chemoradiation)	**Effective EG2 (n = 40)** Placebo + Lomustine **Intervention characteristics**: - placebo, orally - lomustine, first dose at 100 mg/m^2 and thereafter (at the discretion of investigator) orally once every 6 weeks at 100–130 mg/m^2		
	EG3 (n = 79) **Gender (%)**: male (52,4); female (47.6) **Mean age ± SD** = 57,5 ± 9,3	**Effective EG3 (n = 79)** Galunisertib + Lomustine		

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Table 1 (*continued*)

Randomized studies on RECURRENT GBM and PKIs as intervention

First author (Year)	Sample characteristics	Intervention	Outcomes	Main results
	Diagnosis: recurrent, histologically confirmed GBM (progression determined by RANO criteria following standard chemoradiation)	**Intervention characteristics**: - galunisertib 300 mg/day, orally, at intermittent dosing; each cycle = 14 days on/14 days off - lomustine first dose as 100 mg/m^2 after 7 days of galunisertib treatment and thereafter (at the discretion of investigator) orally once every 6 weeks at 100–130 mg/m^2		
Brown et al. (2016) Cediranib/gefitinib [42]	**EG1 (n = 19)** **Gender (%)**: male (73.7); female (26.3) **Mean age**: 61 (range 40–69) **Diagnsis**: histologically confirmed recurrent/progressive GBM, following surgery, cranial radiotherapy and chemotherapy with concurrent and adjuvant TMZ	**Effective EG1 (n = 19)** Cediranib + Placebo **Intervention characteristics**: - cediranib 30 mg, orally, every day, - daily oral dose of matched placebo	- **Primary:** PFS (*RANO criteria*) - **Secondary:** OS rate, PFS at 6 months, OS at 12 months (*RANO criteria*) - **Safety:** Quality of Life (*EORTC QLQ-C30 and the EORTC brain tumor module BN−20);* adverse events (*CTCAE version 4.03*)	PFS, OS, and response rates favor the combination of cediranib and gefitinib, without statistical significance 16 patients (89 %) in EG2 reported a grade 3 or 4 adverse event, compared to 68 % in EG1 No significant differences between EG1 and EG2 in quality of life analyses In the whole population, increasing age and resection for recurrent disease were associated with significantly lower PFS
	EG2 (n = 19) **Gender (%)**: male (68.4); female (31.6) **Mean age**: 55 (range 30–71) **Diagnosis**: histologically confirmed recurrent/progressive GBM, following surgery, cranial radiotherapy and chemotherapy with concurrent and adjuvant TMZ	**Effective EG2 (n = 18)** Cediranib + Gefitinib **Intervention characteristics**: - cediranib 30 mg, orally, every day, - gefitinib, 500 mg orally, every day		
Batchelor et al., 2013 Cediranib [38]	**EG1 (n = 131)** **Gender (%)**: male (-); female (-) **Median age**: 54 **Diagnosis**: recurrent GBM receiving prior treatment with a TMZ-containing chemotherapy and radiation	**Effective EG1 (n = 128)** Cediranib **Intervention characteristics**: - cediranib 30 mg, given orally once daily	- **Primary:** PFS (*centralized, radiographic review, log-rank test, stratified by resection status and age*) - **Secondary:** OS, radiographic response rate, proportion of patients alive and progression-free at 6months (APF6), time to deterioration in neurologic status (TTNS), safety, and tolerability (adverse events recorded according to *CTCAE v 3.0*) - **Exploratory:** time to deterioration in KPS, changes from baseline in the levels of solublemarkers of angiogenesis and tumor growth (VEGF, sVEGFR2, and bFGF in plasma samples)	Not significantly different PFS between EG1, EG2, and EG3 No significant difference in the secondary end point of OS between EG1, EG2, and EG3 No differences in the radiographic response rates between EG1 and EG2 Not significant effect of baseline VEGF levels on either PFS or OS outcome Higher incidence of toxicities, especially hematologic adverse effects in EG2, compared with EG1 and EG3
	EG2 (n = 129) **Gender (%)**: male (-); female (-) **Median age**: 54 **Diagnosis**: recurrent GBM receiving prior treatment with a TMZ-containing chemotherapy and radiation	**Effective EG2 (n = 123)** Cediranib + Lomustine **Intervention characteristics**: - cediranib 20 mg given orally once daily - lomustine 110 mg/m^2, given once daily every 6 weeks as oral capsules		
	EG3 (n = 65) **Gender (%)**: male (-); female (-) **Median age**: 54 **Diagnosis**: recurrent GBM receiving prior treatment with a TMZ-containing chemotherapy and radiation	**Effective EG3 (n = 64)** Lomustine + Placebo **Intervention characteristics**: - lomustine 110 mg/m^2		

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Table 1 (*continued*)

Randomized studies on RECURRENT GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
		given as oral capsules once every 6 weeks - cediranib-matched placebo, given orally once daily		

Randomized studies on NEWLY DIAGNOSED GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
Lee et al. (2015) Vandetanib [48]	**EG1 (n = 36)** **Gender (%)**: male (47.2); female (52.8) **Median age (range)**: 55 (23–73) **Diagnosis:** histologically confirmed newly diagnosed GBM or gliosarcoma (no prior chemotherapy or radiation)	**Effective EG1 (n = 29)** Radiation + TMZ **Intervention characteristics:** - radiation (daily fractions of 180–200 cGy, to a planned total dose to the tumor of ~6000 cGy), and concurrent TMZ (75 mg/m^2, orally), daily for 6 weeks - 4–6 weeks rest - TMZ (150 mg/m^2/day, orally, on days 1–5 of the first 28-day cycle; if well tolerated → 200 mg/m^2/day, orally, on days 1–5 of each subsequent 28-day cycle. (tot. 12 cycles)	- **Primary:** median OS *(Kaplan-Meier method)* - **Secondary:** median PFS, 12-months PFS - **Safety:** reported toxicities; adverse events *(percentage)* - **Exploratory:** pharmacokinetics; changes in tissue and plasma angiogenic biomarkers	Not significantly different median OS and PFS between EG1 and EG2 Unacceptable toxicity for 23 patients (33 %) in EG2, compared with 3 patients (10 %) in EG1 In EG2 (treatment vs baseline): ↑ VEGF (at day 22) ↓ PIGF (at 4 hours) ↑ PIGF (at days 2, 8, 22) ↓ sVEGFR2 (at 4 hr, 2, 8, 22 days) ↓ sTie2 (at 4 hours) ↓ SDF1α (at 4 hours) ↑ SDF1α (at day 22)
	EG2 (n = 70) **Gender (%)**: male (62.9); female (37.1) **Median age (range)**: 59 (23–83) **Diagnosis:** histologically confirmed newly diagnosed GBM or gliosarcoma (no prior chemotherapy or radiation)	**Effective EG2 (n = 69)** Vandetanib + Radiation + TMZ **Intervention characteristics**: - vandetanib 100 mg, orally, daily from 5 to 7 days prior radiation till study finish - radiation (daily fractions of 180–200 cGy, to a planned total dose to the tumor of ~6000 cGy), and concurrent TMZ (75 mg/m^2, orally), daily for 6 weeks - 4–6 weeks rest - TMZ (150 mg/m^2/day, orally, on days 1–5 of the first 28-day cycle; if well tolerated → 200 mg/m^2/day, orally, on days 1–5 of each subsequent 28-day cycle (tot. 12 cycles)		

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Table 1 (*continued*)

Randomized studies on NEWLY DIAGNOSED GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
Wick et al. (2020) (phase 2a) Galunisertib [40]	**EG1 (n = 40)** **Gender (%):** male (55); female (45) **Mean age ± SD**: 58,7 ± 8,9 years **Diagnosis**: newly diagnosed, histologically confirmed GBM	**Effective EG1 (n = 40)** Galunisertib + RTX/TMZ **Intervention characteristics:** - galunisertib 300 mg/day, orally, on an intermittent dose regimen of 14 days on/14 days off for a 28-day cycle - RTX: 30 fractions at 1.8–2.0 Gy/dose (5 days a week for 6 weeks) - TMZ, 75 mg/m^2 orally, once daily, followed by 6 cycles of adjuvant TMZ 150–200 mg/m^2 once daily for 5 days in 28-day cycles	- **Primary:** tolerability; pharmacodynamic effect on T-cells (changes in response biomarkers and their relationship to OS; *Kaplan-Meier method*) - **Secondary:** PFS, time-to-treatment failure, time-to-tumor progression, duration-to-tumor response, ORR, clinical benefit rate (*RANO criteria*) - **Exploratory**: pharmacodynamics of biomarkers on tumor tissue and blood samples (*IHC, clinical laboratory tests, ELISA, multi-analyte immunoassay panel, flow cytometry*) - **Safety analysis:** adverse events rates (*CTCAE version 4.0);* laboratory and non-laboratory changes, physical examination, other safety observations *(cardiac safety: echocardiography/Doppler, chest CT scan, and cardiac plasma markers*)	↑ Overall disease control rate in EG1 compared to EG2 ↑ Percentage of grade 3–4 drug-related adverse events in EG1 compared to EG2 No association between baseline Tregs and OS/PFS analysis across baseline biomarkers ↑ Ratio of CD4/CD8, favoring EG1 treatment compared to EG2 treatment, but not statistically significant ↓ CD4, CD8, and Treg cells, between baseline and Day 42, in EG1
	EG2 (n = 16) **Gender (%):** male (68.8); female (31.2) **Mean age ± SD**: 57,8 ± 11,6 years **Diagnosis**: newly diagnosed, histologically confirmed GBM	**Effective EG2 (n = 16)** RTX/TMZ **Intervention characteristics**: - RTX: 30 fractions at 1.8–2.0 Gy/dose (5 days a week for 6 weeks) - TMZ 75 mg/m^2 orally, once daily, followed by 6 cycles of adjuvant TMZ 150–200 mg/m^2 once daily for 5 days in 28-day cycles		
Rahman et al., 2023 Neratinib [44]	**EG1 (n = 71)** **Gender (%)**: male (61); female (39) **Median age**: 59 (range 24 – 75) **Diagnosis**: newly diagnosed and untreated intracranial GBM or gliosarcoma	**Effective EG1 (n = 68)** Control Arm **Intervention characteristics**: - radiation to 60 Gy in 30 fractions - TMZ 75 mg/m^2 orally, once daily, followed by 6 cycles of adjuvant TMZ 150–200 mg/m^2 once daily for 5 days in 28-day cycles	- **Primary:** OS (*proportional hazards model in full population and biomarker-specific subpopulations – EGFR, CDK, PI3K biomarker status*) - **Exploratory:** evaluation of the impact of adaptive randomization of the EG4	No significant improvement in OS between EG2 and EG1; significantly longer PFS in EG2 compared to EG1; significantly longer PFS in EG2 biomarker subgroup with EGFR-positive patients, compared to EG1 No significant improvement in OS between EG3 and EG1; significantly longer PFS in EG3 compared to EG1 No significant improvement in OS and PFS between EG4 and EG1
	EG2 (n = 81) **Gender (%)**: male (66); female (34) **Median age**: 56 (range 29 – 77) **Diagnosis**: newly diagnosed and untreated intracranial GBM or gliosarcoma	**Effective EG2 (n = 72)** Neratinib **Intervention characteristics**: - radiation to 60 Gy in 30 fractions - TMZ 75 mg/m^2 orally, once daily		

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Table 1 (*continued*)

Randomized studies on NEWLY DIAGNOSED GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
		- adjuvant neratinib, orally at 240 mg once daily in 28-day cycles		
	EG3 (n = 73) **Gender (%)**: Male (57); female (43) **Median age**: 60 (range 24 – 78) **Diagnosis**: newly diagnosed and untreated intracranial GBM or gliosarcoma	**Effective EG3 (n = 71)** Abemaciclib **Intervention characteristics**: - radiation to 60 Gy in 30 fractions - TMZ, 75 mg/m^2 orally, once daily - adjuvant abemaciclib at 150 mg, orally, twice daily in 28-day cycles		
	EG4 (n = 12) **Gender (%)**: Male (92.5); female (7.5) **Median age**: 64 (range 33 – 74) **Eligibility**: newly diagnosed and untreated intracranial GBM or gliosarcoma	**Effective EG4 (n = 12)** CC−115 **Intervention characteristics:** - CC−115 10 mg, orally, twice daily in combination with radiotherapy and adjuvantly as monotherapy		
Chinnaiyan et al., 2018 Everolimus [45]	**EG1 (n = 89)** **Gender (%)**: male (55.4); female (44.6) **Age (%)**: ≤ 49:27.7 / 50–59:32.5 / 60–69: 24.1 / ≥ 70:15.7 **Diagnosis**: centrally reviewed newly diagnosed, unifocal, supratentorial GBM; no prior chemotherapy, treatment with an mTOR inhibitor, or radiation	**Effective EG1 (n = 83)** Chemoradiation therapy **Intervention characteristics:** - radiation therapy (60 Gy in 30 fractions of 2 Gy each) - daily TMZ (75 mg/m^2, orally), followed by adjuvant TMZ (150–200 mg/m^2) on days 1–5 every 28 days for up to 12 cycles beginning 4 weeks after the completion of radiation therapy	**- Primary**: PFS (*Kaplan–Meier method*) **- Secondary:** OS (*Kaplan–Meier method*), treatment related toxicity, correlation between *MGMT* methylation status and survival outcomes (*Kaplan–Meier method*)	No significant difference in PFS between EG1 and EG2 No significant treatment and *MGMT* status interaction effects on the survival outcomes Increased toxicity in EG2 compared to EG1
	EG2 (n = 92) **Gender (%)**: male (63.6); female (36.4) **Age (%)**: ≤ 49:21.6 / 50–59:21.6 / 60–69: 39.8 / ≥ 70:17 **Diagnosis**: centrally reviewed newly diagnosed, unifocal, supratentorial GBM; no prior chemotherapy, treatment with an mTOR inhibitor, or radiation	**Effective EG2 (n = 88)** Chemoradiation therapy + Everolimus **Intervention characteristics:** - radiation therapy (60 Gy in 30 fractions of 2 Gy each) - daily TMZ (75 mg/m^2, orally), followed by		

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Table 1 (*continued*)

Randomized studies on NEWLY DIAGNOSED GBM and PKIs as intervention				
First author (Year)	**Sample characteristics**	**Intervention**	**Outcomes**	**Main results**
		adjuvant TMZ ($150–200\ mg/m^2$) on days 1–5 every 28 days for up to 12 cycles beginning 4 weeks after the completion of radiation therapy - daily everolimus (10 mg, orally) during concurrent chemoradiation and adjuvant TMZ		
Wick et al., 2016 Temsirolimus [46]	**EG1 (n = 55)** **Gender (%)**: male (65.5); female (34.5) **Median age**: 57.7 (range 24.4 – 76) **Diagnosis**: newly diagnosed GBM harboring an unmethylated *MGMT* promoter	**Effective EG1 (n = 55)** Chemoradiation therapy **Intervention characteristics:** - standard chemoradiotherapy (TMZ/RT → TMZ) = radiotherapy plus continuous daily temozolomide ($75\ mg/m^2$ per day, orally, 7 days per week from the first to the last day of radiotherapy, followed by six cycles of adjuvant temozolomide ($150–200\ mg/m^2$ orally, for 5 days during each 28-day cycle)	- **Primary**: OS at 12 months (OS12, *Kaplan–Meier method*) - **Secondary**: PFS (*Macdonald criteria*, estimated using the *Kaplan–Meier method*), OS, safety (*CTCAE version 3*), assessment of prognostic, and predictive biomarkers of the mTOR pathway (*tissue microarray, IHC, FISH EGFR*)	No significant difference in OS12, OS24, and median PFS between arms Phosphorylation of mTORSer2448 in the pretreatment tumor tissue may define a subgroup benefitting from mTOR inhibition
	EG2 (n = 56) **Gender (%)**: male (62.6); female (37.5) **Median age**: 54.9 (range 28.2 – 74.7) **Diagnosis**: newly diagnosed GBM harboring an unmethylated *MGMT* promoter	**Effective EG2 (n = 56)** Radiation therapy + Temsirolimus **Intervention characteristics:** - standard fractionated radiotherapy - concomitant temsirolimus (standard dose of 25 mg intravenously, weekly beginning at day −7 from the start of radiotherapy, continued until disease progression)		

Abbreviations: EG, experimental group.

Table 2
General properties of PKIs included in the present meta-analysis.

PKI	Target	Type[a]	Approval Status	Adverse Effects	Ref.
Cediranib	VEGFR−1, −2,−3, c-KIT	n.c.	Not approved	Nausea, vomiting, diarrhea, taste disturbances, hoarseness, fatigue, hypertension, hypothyroidism	[49]
Galunisertib	TGFβR1	n.c.	Not approved	Neutropenia, leukopenia, fatigue	[50]
Gefitinib	EGFR, PDGFR	I	FDA approval (first accelerated approval in 2003, full approval in 2015) and EMA marketing authorization (2009), for Non-Small Cell Lung Cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 substitutions	Skin rash, dry skin pruritus, stomatitis diarrhea, nausea, vomiting, anorexia	[51]
Axitinib	VEGFR−1,−2,−3, PDGFRβ, c-KIT	IIA	FDA and EMA approval (first in 2012) for advanced renal cell carcinoma	Diarrhea, nausea, anorexia, dehydration, dysphonia, hypertension, fatigue, hand-foot syndrome, dyspnea, headache, hemoptysis, stomatitis, erythema, limb pain, arthralgia, myalgia	[52]
Dasatinib	BCR-ABL, Src, PDGFRβ, c-KIT, EPHA2	I/I½A	FDA and EMA approval (first in 2006) for Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia	Myelosuppression, anemia, neutropenia, thrombocytopenia, hemorrhage, fluid retention, pericardial effusion, skin rash, abdominal pain, nausea, vomiting, diarrhea, fatigue, headache, skin rash, dyspnea, infection, myalgia, arthralgia	[53]
Regorafenib	VEGFR−1,−2,−3, TIE−2, PDGFRα/β, FGFR, BCR-ABL, c-KIT, RET, Raf−1, BRAF, EPHA2	IIA	FDA and EMA approval for colorectal cancer (2012); FDA (2013) and EMA (2014) approval for gastrointestinal stromal tumors; FDA and EMA approval for hepatocellular carcinoma (2017); AIFA approval for recurrent GBM (2019)	Anemia, thrombocytopenia, proteinuria, diarrhea, nausea, stomach pain, anorexia, weight loss, hypertension, fever, infections, abnormal liver function tests, fatigue, hand–foot skin reaction	[54]
Afatinib	EGFR, HER2, HER4	VI	FDA and EMA approval for late stage NSCLC (2013) and Squamous Cell Carcinoma of the Lung (2016)	Diarrhea, nausea, vomiting, anorexia, transaminase increase, skin rash/acne, dry skin, stomatitis, paronychia	[55]
Vandetanib	VEGFR−2, TIE2, EGFR, RET, EPHR, Src	I	FDA (2011) and EMA (2012) approval for advanced medullary thyroid cancer	Hypertension, QT prolongation, proteinuria, skin rash, diarrhea, stomach pain, nausea, loss of appetite, headache, fatigue	[56]
Neratinib	EGFR, HER2, HER4	VI	FDA approval for early stage (2017) and metastatic (2020) HER2+ breast cancer; EMA approval as extended adjuvant therapy for patients with early-stage HRc+, HER2+ breast cancer (2018)	Diarrhea, nausea, abdominal pain, fatigue, vomiting, skin rash, stomatitis, decreased appetite, weight loss, urinary tract infection, headache	[57]
Everolimus	mTor, FKBP12	IV	FDA and EMA approval for advanced renal cell carcinoma (2009), advanced HER2- breast cancer (2012), progressive, nonfunctional gastrointestinal and lung neuroendocrine tumors (2016); approval for pancreatic neuroendocrine tumors (FDA, 2011; EMA 2016)	Diarrhea, nausea, vomiting, anorexia, weight loss, taste disturbances, epistaxis, dry skin, dizziness, headache	[58]
Temsirolimus	mTor, FKBP12	IV	FDA and EMA approval for advanced kidney cancer (2007)	Anemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, asthenia, skin rash, mucositis, dyspnea, cough, diarrhea, stomach pain, upset stomach, vomiting, headache, muscle or joint pain, pyrexia	[59]

[a] Classification based on the structure of the enzyme-bound antagonist complex [60].
I = inhibitors bind reversibly to the ATP-binding pocket of kinase active conformation (*DFG-Asp in*, *C-helix in*)
I/I½A = inhibitors bind reversibly to the ATP-binding pocket of the inactive *DFG-Asp in* conformation of target kinase
IIA = inhibitors bind reversibly to the inactive *DFG-Asp out* conformation of target protein kinase
IV = allosteric inhibitors bind reversibly to sites distant from the substrate binding sites
VI = inhibitors bind covalently (irreversibly) to their target enzyme
n.c. = not classified
Abbreviations: HER2 + , human epidermal growth factor receptor 2 positive; HER2-, human epidermal growth factor receptor 2 negative; HRc+ , hormone receptor positive; NSCLC, Non-Small Cell Lung Cancer.

Thus, I^2 values $\geq 30\,\%$ and $< 50\,\%$, $\geq 50\,\%$ and $< 75\,\%$, or $\geq 75\,\%$ were considered indicative of moderate, substantial, or high heterogeneity across studies, respectively [https://training.cochrane.org/handbook/current/chapter-10]. The level of significance was set at 0.05. All analyses were performed using Review Manager 5.4.1 software (Cochrane Library Software, Oxford, UK) and MIX 2.0 Pro for Excel program (BiostatXL, Mountain View, CA, USA).

3. Results

3.1. Study selection

The PRISMA flow chart (Fig. 1) outlines the literature evaluation process. Our search identified 3765 records across PubMed and Web of Science. After removing duplicates and excluding non-randomized,

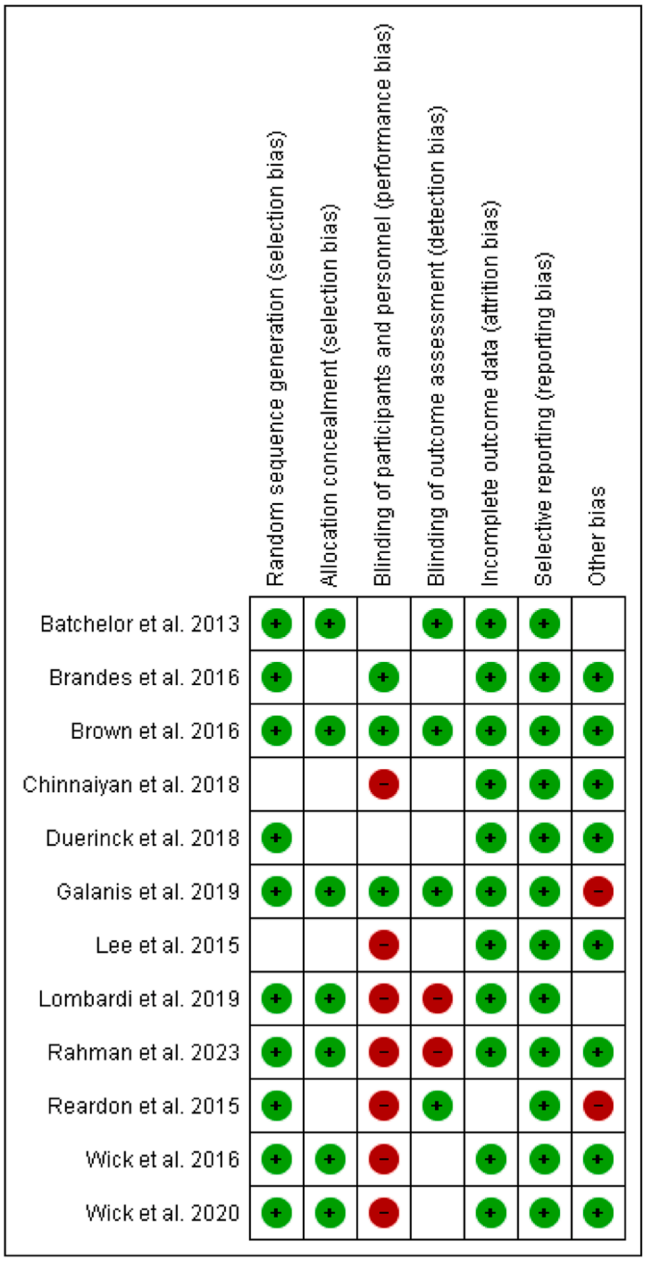


Fig. 2. Risk of bias assessment: review authors' judgements about each risk of bias item for each included study using the ROB 2 tool.

phase 1 studies, and trials focused on agents other than PKIs or RTKs as prognostic/predictive markers, 16 records were deemed eligible for the meta-analysis. Of these, 12 studies (total number of patients enrolled =1652) were included in the final meta-analysis after excluding those with non-comparable outcomes or insufficient experimental group data. In total, 7 studies on recurrent GBM (number of patients enrolled =961), published since 2013, and 5 studies on newly diagnosed GBM (number of patients enrolled =691), published since 2015, were analyzed, comparing the efficacy of PKIs in various treatment combinations.

3.2. Study characteristics

The characteristics of the studies included in the systematic review and of the PKIs investigated in the same studies are detailed in Tables 1 and 2, respectively.

Only multicenter RCTs were selected: a single phase 3 placebo-controlled trial [38], two phase 1/2 comparative trials that only contributed with data from the randomized part 2 of the study [39,40], and nine phase 2 studies, among which placebo-controlled [41–44], comparative [25,45,46], and non-comparative [47,48] trials. Most studies were 2-arms [25,40,42,43,45–48], three studies were 3-arms [38,39,41], a single study was 4-arms [44]. Most studies were open-label [25,39,40,44–48], a single study was partially blinded [38], three studies were double-blinded [41–43]. The number of randomized patients was in the range between the 38 patients of the study that evaluated gefitinib/cediranib combination, in comparison with cediranib plus placebo [42], and the 325 patients enrolled in the only phase 3, 3-arms study, comparing cediranib with the combinations cediranib plus lomustine and lomustine plus placebo [38].

All the studies included both male and female patients, whose relative percentage was only missing in the study by Batchelor et al. 2013 [38]. With the only exception of the control group (radiation plus TMZ arm) of the study that investigated vandetanib in newly diagnosed GBM patients [48], in all the study groups the percentage of men was higher than that of women. The median age was between 52 and 64 years.

For studies enrolling newly diagnosed GBM patients as baseline condition, inclusion was dependent upon a histologically confirmed diagnosis of GBM and adult age ($\geq$ 18 years), with no prior chemotherapy or radiation, and surgery not performed more than six weeks before enrollment. In the case of vandetanib, the experimental treatment was extended to patients with diagnosis of gliosarcoma [48], and in the case of neratinib, the presence of unmethylated O^6-methylguanine-DNA methyltransferase (MGMT) promoter was required for eligibility [44].

For studies enrolling recurrent GBM patients, inclusion criteria included adult age ($\geq$ 18 years), previous surgery, TMZ, and radiotherapy (concluded by 12 weeks), at first relapse, or, only in one case, with no limit to the number of prior recurrences [47]. Gliosarcoma variant was considered eligible in the treatment with dasatinib [43].

For both newly diagnosed and recurrent GBM patients, enrollment required the evaluation of Karnofsky Performance Status (KPS, no lower than 70 or 60 for eligibility) or Eastern Cooperative Oncology Group Performance Status (ECOG PS, generally established to be lower or equal to 1).

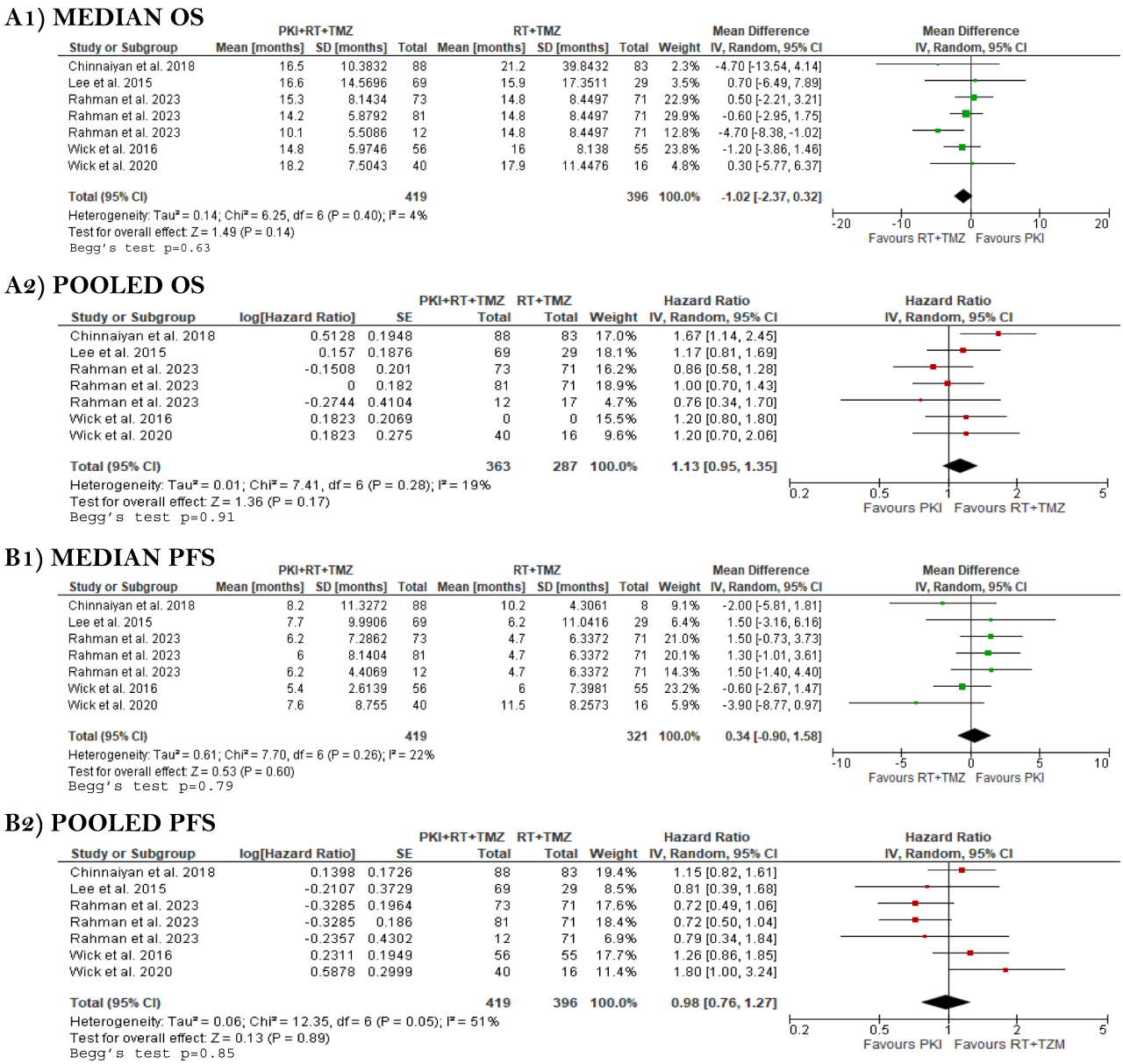
All the studies reported exclusion criteria represented by prior experimental treatments with congeners of the drug under investigation, comorbidity conditions, including liver, renal, cardiovascular diseases, or multi-drug regimens, for instance the co-administration of cytochrome P450 enzyme-inducing anti-seizure drugs [42].

Locations of the clinical centers involved in the studies were in North America [38,39,43–45,48], Europe [25,42,46,47], or both continents [40,41]. Enrollments expanded from 2008 to 2021.

The studies assessed one or two PKIs, targeting various RTKs and intracellular protein kinases, including EGFRs [i.e., EGFR1 (or HER1), HER2, and HER4], vascular endothelial growth factor receptors (VEGFRs, including VEGFR-1, VEGFR-2, and VEGFR-3), PDGFR, transforming growth factor-β receptor (TGFβR), FGFR, KIT, mTor, Raf, and Src. None of the PKIs are approved by FDA or EMA for GBM, although most of them (i.e., vandetanib, regorafenb, afatinib, axitinib, dasatinib, gefitinib, neratinib, everolimus, temsirolimus) are approved for other indications.

Control arm for studies on newly diagnosed GBM was standard chemo-radiotherapy (radiation in daily fractions of 2 Gy and concurrent TMZ at the dosage of 75 mg/m^2, followed by adjuvant TMZ at 150 mg/m^2 on days 1–5 of 28-days cycle, for a maximum of 12 cycles). In the experimental arm, the PKI was added to concurrent chemo-radiotherapy. The cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor abemaciclib and the mTor and DNA-dependent protein kinase (DNA-PK) dual inhibitor CC-115 were used as comparator treatments sharing a common control arm with neratinib [44]; all the three agents were administered twice daily with concurrent chemo-radiotherapy, and as adjuvant drugs in monotherapy.

For recurrent GBM, comparator treatments included temozolomide [39], lomustine [25,38,41,47], or bevacizumab [43]. A single study



Main finding: in newly diagnosed GBM, no signficant differences were found for OS and PFS in the comparison "PKI plus standard chemo-radiotherapy *versus* standard chemo-radiotherapy alone"

Fig. 3. Forest plot illustrating the comparisons between the addition of PKIs to standard chemo-radiotherapy (radiotherapy plus TMZ) and standard chemo-radiotherapy alone, in a population study represented by patients with newly diagnosed GBM. Panel A1) shows the mean difference in median OS, Panel A2) displays the HR for pooled OS, Panel B1) presents the mean difference in median PFS, and Panel B2) depicts the HR for pooled PFS. RT, radiotherapy.

compared a PKI, i.e., cediranib, with its combination with another PKI, such as gefitinib [42].

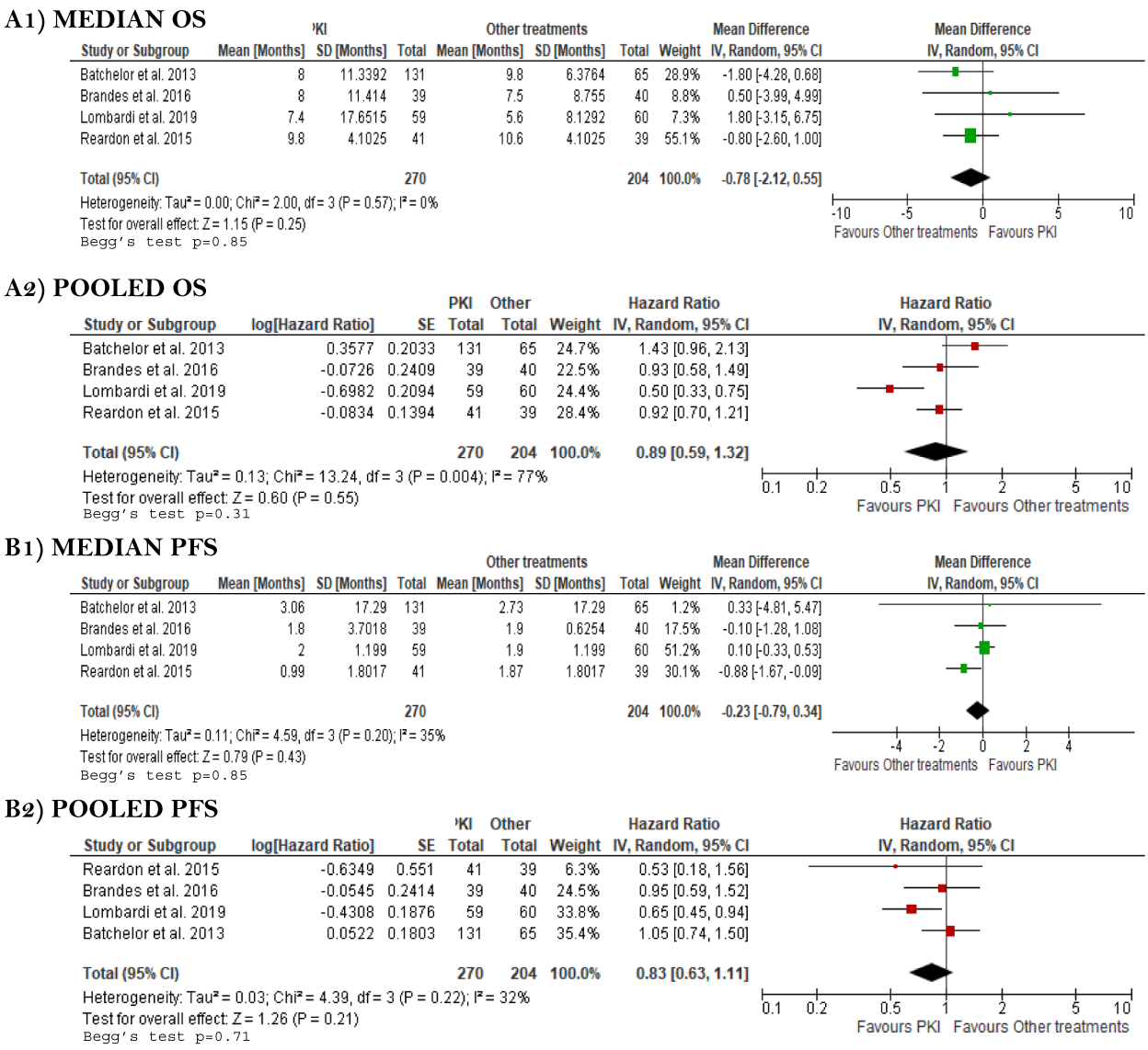
PFS (evaluated as median, after 6 months, or after 12 months) and OS (median or at 12 months) were commonly assessed across all studies, as primary or secondary clinical outcomes, evaluated through the Kaplan Meier method and according to the Response Assessment in Neuro-Oncology (RANO) criteria, alongside safety and treatment-related toxicity. Common side effects included rash, diarrhea, fatigue, anemia, and leukopenia. In a subset of studies, exploratory outcomes, including pharmacokinetic profiles and predictive/prognostic biomarkers, were also evaluated [38,41,43,44,48].

A low grade of heterogeneity in terms of study design, population, interventions, and outcomes is detectable among the included studies on newly diagnosed GBM patients; a pooled study with clear contribution to heterogeneity is the only 4-arms trial evaluating neratinib in comparison with abemaciclib, CC-115, and a common control arm [44].

Higher grade of heterogeneity can be found between the pooled studies on recurrent GBM patients. Factors contributing to reduce heterogeneity can be different and related to design (e.g., open-label, single-blinded, or double-blinded), interventions (e.g., monotherapies or combination therapies, with or without a control group, distributed in two or three arms).

3.3. *Risk of bias assessment*

The majority of studies showed a low risk of bias across most domains (see Fig. 2). Specifically, some studies [38–44,46,47] exhibited low risk of bias in all assessed domains. However, some studies



Main finding: in recurrent GBM, no significant differences were found for OS and PFS in the comparison "PKI *versus* other treatments" - Regoranefib was the only PKI significantly improving both OS and PFS

Fig. 4. Forest plot showing the comparisons between PKI and other treatments, as investigational therapeutic approaches tested on patients with recurrent GBM. Panel A1) shows the mean difference in median OS, Panel A2) displays the HR for pooled OS, Panel B1) presents the mean difference in median PFS, and Panel B2) depicts the HR for pooled PFS.

presented concerns in specific areas. For instance, the studies by Chinnaiyan et al. [45] and Lee et al. [48] showed high risk of bias related to unblinding of treatment assignment to participants and personnel (performance bias), potentially influencing the outcomes. Similarly, the study by Lombardi et al. [25] displayed a high risk of bias due to incomplete outcome data (attrition bias). Additionally, selective reporting (reporting bias) was noted in the studies by Galanis et al. [43] and Wick et al. (2016) [46], indicating that not all pre-specified outcomes may have been fully reported.

3.4. Outcomes

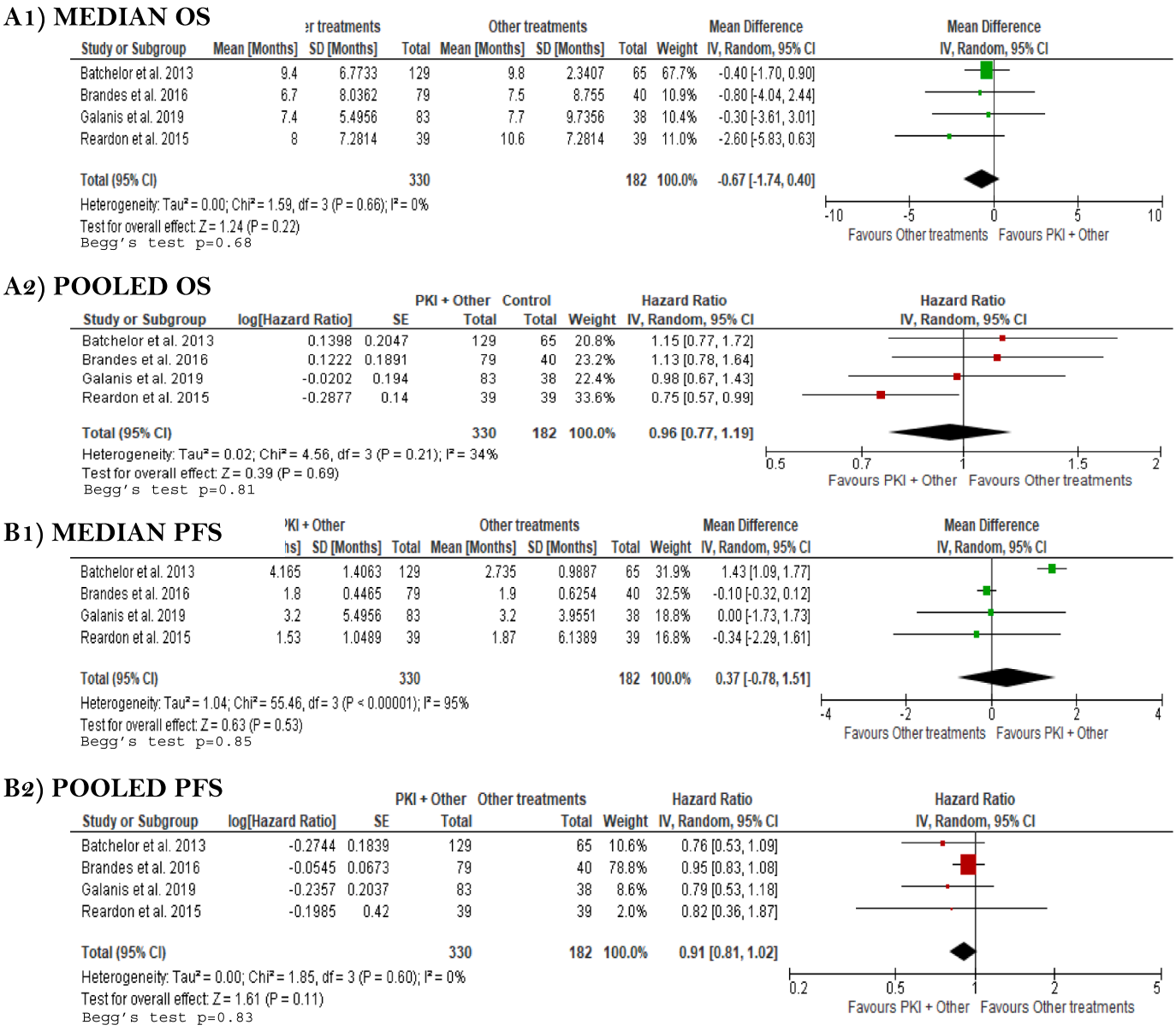
The OS and the PFS were analyzed based on reported HRs, medians, and their respective confidence intervals (CI).

A meta-analysis was conducted on data from newly diagnosed GBM patients to compare outcomes between addition of a PKI to TMZ-based standard chemo-radiotherapy and standard chemo-radiotherapy alone.

For recurrent GBM, three separate analyses were performed: a) PKI *versus* other treatment, b) PKI combined with other treatment *versus* the other treatment alone, and c) PKI alone *versus* PKI combined with another treatment.

3.4.1. *PKI plus standard chemo-radiotherapy versus standard chemo-radiotherapy in newly diagnosed GMB*

No significant differences were observed in the median OS between the PKI plus standard chemo-radiotherapy regimen and standard chemo-radiotherapy alone in newly diagnosed GBM patients (-1.02 months, 95 % CI, −2.37–0.32, $p = 0.14$), with no evidence of publication bias (Begg's test $p = 0.63$) or heterogeneity ($I^2 = 4$ %, $p = 0.40$) (Fig. 3 A1). Similarly, no differences were found in the median PFS between these groups (0.34 months, 95 % CI, −0.9–1.58, $p = 0.60$), with no publication bias (Begg's test $p = 0.79$) and no significant



Main finding: in recurrent GBM, no significant differences were found for OS and PFS in the comparison "PKI plus other treatments *versus* other treatments"

Fig. 5. Forest plot showing the comparisons between PKIs in combination with other treatments and other treatments alone, as investigational therapeutic approaches tested on patients with recurrent GBM. Panel A1) shows the mean difference in median OS. Panel A2) displays the HR for pooled OS, Panel B1) presents the mean difference in median PFS, and Panel B2) depicts the HR for pooled PFS.

heterogeneity ($I^2 = 22$ %, $p = 0.26$) (Fig. 3 B1).

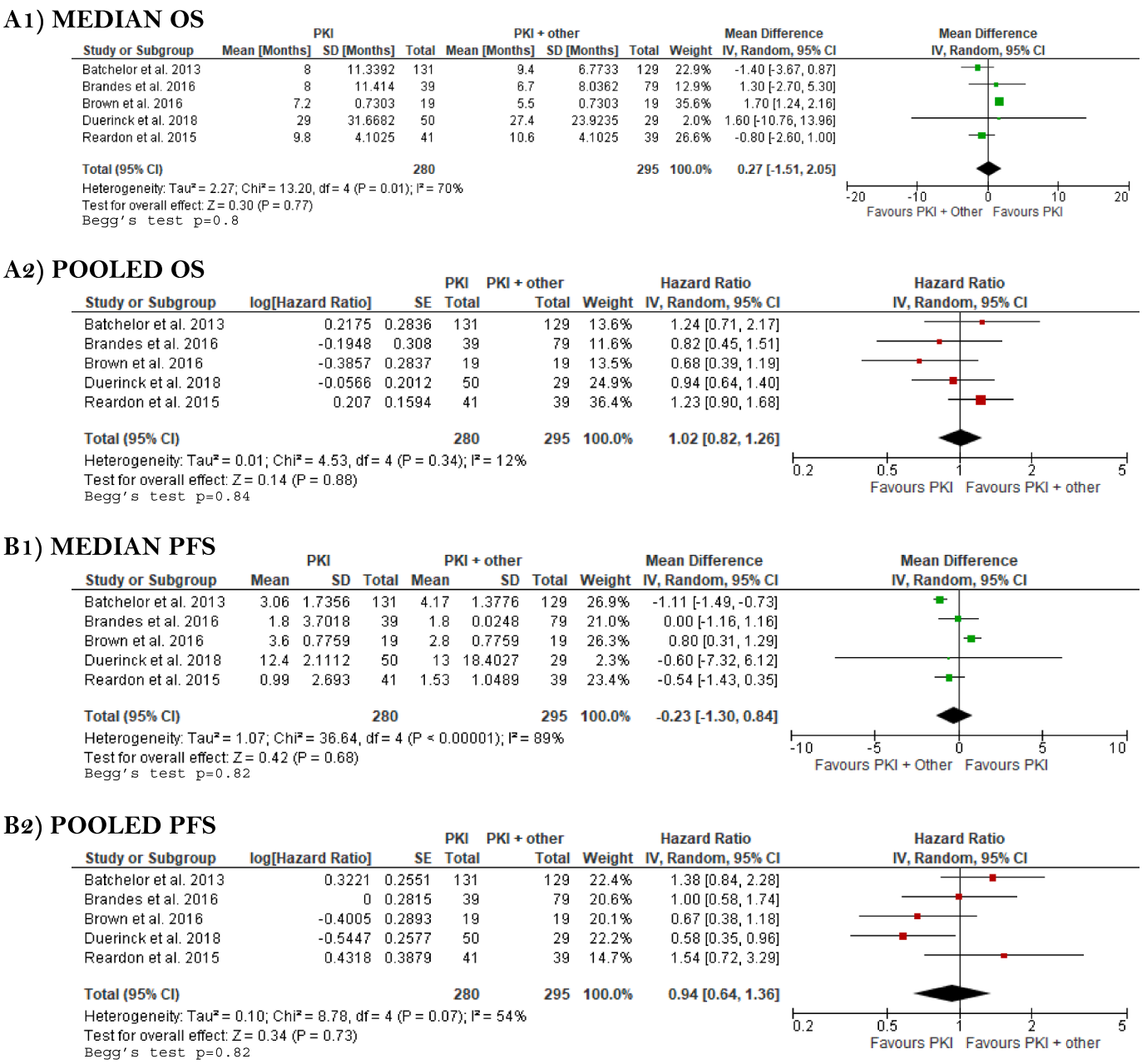
When analyzing pooled OS and PFS in recurrent GBM patients, similar results were observed. For the pooled OS (Fig. 3 A2) there were no differences between PKI *versus* other treatments (HR = 1.13, 95 % CI, 0.95–1.35, $p = 0.17$), with no publication bias (Begg's test $p = 0.91$) or heterogeneity ($I^2 = 19$ %, $p = 0.28$). Likewise, in the pooled PFS analysis (Fig. 3 B2), no differences were found between these groups (HR = 0.98, 95 % CI, 0.76–1.27, $p = 0.89$), with no publication bias (Begg's test $p = 0.85$) but with significant heterogeneity ($I^2 = 51$ %, $p = 0.05$).

3.4.2. *PKI versus other treatments in recurrent GBM*

When evaluating median OS (Fig. 4 A1), no significant differences were found between patients treated with PKIs and those who received alternative treatments (-0.78 months, 95 % CI, −2.12–0.55 $p = 0.25$). The analysis indicated no publication bias (Begg's test $p = 0.85$) and no heterogeneity across studies ($I^2 = 0$ %, $p = 0.57$). Similarly, the median PFS comparison (Fig. 4 B1) revealed no significant differences between the groups (-0.23 months, 95 % CI, −0.79–0.34, $p = 0.43$), with no publication bias (Begg's test $p = 0.85$) and no significant heterogeneity ($I^2 = 35$ %, $p = 0.20$).

Further analysis of pooled OS (Fig. 4 A2) showed no significant differences between patients treated with PKIs and the control groups (HR = 0.89, 95 % CI, 0.59–1.32, $p = 0.55$). Although no publication bias was detected (Begg's test $p = 0.31$), substantial heterogeneity was observed ($I^2 = 77$ %, $p < 0.001$).

For PFS (Fig. 4 B2), the comparison between PKI and control groups



Main finding: in recurrent GBM, no significant differences were found for OS and PFS in the comparison "PKI plus other treatments *versus* PKI alone"

Fig. 6. Forest plot showing the comparisons between PKIs and PKIs in combination with other treatments, as investigational approaches tested on patients with recurrent GBM. Panel A1) shows the mean difference in median OS, Panel A2) displays the HR for pooled OS, Panel B1) presents the mean difference in median PFS, and Panel B2) depicts the HR for pooled PFS.

revealed no significant differences (HR = 0.83, 95 % CI, 0.63–1.11, $p = 0.21$), with no evidence of publication bias (Begg's test $p = 0.71$) nor significant heterogeneity ($I^2 = 32$ %, $p = 0.22$).

The only PKI that induced a significant improvement in both OS and PFS was regorafenib [25].

3.4.3. PKI in combination with other treatments versus other treatments in recurrent GBM

The median OS analysis (Fig. 5 A1) did not reveal significant differences between the groups receiving PKI combined with other treatments and those receiving other treatments alone (-0.67 months, 95 % CI, −1.74–0.40, $p = 0.22$). There was no indication of publication bias (Begg's test $p = 0.68$) and no heterogeneity ($I^2 = 0$ %, $p = 0.66$). The analysis of median PFS (Fig. 5 B1) similarly showed no significant differences between the groups (0.37 months, 95 % CI, −0.78–1.51, $p = 0.53$) with no publication bias (Begg's test $p = 0.85$) but a high heterogeneity ($I^2 = 95$ %, $p < 0.01$).

The pooled OS HR (Fig. 5 A2) also did not show significant differences between the evaluated groups (HR = 0.96, 95 % CI, 0.77–1.19, $p = 0.69$). This analysis revealed no evidence of publication bias (Begg's test $p = 0.81$), and no heterogeneity ($I^2 = 34$ %, $p = 0.21$). Similarly, the pooled PFS HR (Fig. 5 B2) did not indicate significant differences

between the groups (HR = 0.91, 95 % CI, 0.81–1.01, $p = 0.11$), with no publication bias (Begg's test $p = 0.83$) and no heterogeneity ($I^2 = 0$ %, $p = 0.60$).

3.4.4. PKI in combination with other treatments versus PKI in recurrent GBM

The analysis of median OS (Fig. 6 A1) revealed no significant differences between the groups receiving PKI in combination with other treatments and those treated with PKI alone (0.27 months, 95 % CI, −1.51–2.05, $p = 0.77$). The analysis showed no evidence of publication bias (Begg's test $p = 0.8$) but indicated significant heterogeneity ($I^2 =$ 70 %, $p = 0.01$). Regarding median PFS (Fig. 6 B1), no significant differences were observed between the groups (-0.23 months, 95 % CI, −1.3–0.84, $p = 0.68$), with no publication bias (Begg's test $p = 0.82$) but high heterogeneity ($I^2 = 89$ %, $p < 0.001$).

The pooled OS (Fig. 6 A2) and PFS (Fig. 6 B2) analyses yielded consistent results. No significant differences were reported between the groups in the pooled OS (HR = 1.02, 95 % CI, 0.82–1.26, $p = 0.88$), with no publication bias (Begg's test $p = 0.84$) and no heterogeneity ($I^2 =$ 12 %, $p = 0.34$). Similarly, the pooled PFS analysis showed no significant differences (HR = 0.94, 95 % CI, 0.64–1.36, $p = 0.73$), with no evidence of publication bias (Begg's test $p = 0.82$) and no significant heterogeneity ($I^2 = 54$ %, $p = 0.07$).

4. Discussion

The results herein presented suggest that adding PKIs to standard chemo-radiotherapy may not lead to significant improvements in OS or PFS in patients with newly diagnosed or recurrent GBM. Across the various comparisons, including PKIs *versus* standard treatments and PKIs combined with other therapies, no meaningful differences were detected. The consistent lack of significant findings, coupled with low heterogeneity and minimal evidence of publication bias in most analyses, indicates that PKIs might not offer a substantial survival benefit in this setting. Results underscore the urgent need for further research to identify more effective treatment options for GBM.

GBM remains a particularly challenging malignancy, due to its marked infiltrative behavior, molecular, genetic, and phenotypic heterogeneity, presence of the BBB, and a high propensity for resistance development [61]. In recent years, for other solid tumors and hematological malignancies, the focus of cancer management has shifted towards targeted therapies, that offer durable antitumor effects and minimal toxicity, compared to traditional chemotherapy. Among these, PKIs have garnered attention due to their ability to target multiple pathways associated, also in the case of GBM, with disease progression and recurrence. Indeed, protein kinases, particularly RTKs, play essential roles in cell signaling pathways that regulate GBM cell growth, angiogenesis, and invasiveness [62].

Given the highly vascularized nature of GBM, VEGFRs, in addition to the ligand VEGF-A, have been recognized as RTKs with significant therapeutic potential. VEGFR-1, which is involved in pathological but not physiological angiogenesis, has been identified as an interesting target due to its expression in both GBM and GBM stem cells (GSCs) [63,64]. Inhibition of VEGFR-1 could disrupt the GBM microenvironment, particularly by affecting microglia/macrophages that regulate immune responses and facilitate tumor expansion by contributing to extracellular matrix degradation [65,66]. Regorafenib, a multi-kinase inhibitor that targets VEGFR1–3 isoforms and other proangiogenic and stromal kinases, has shown promising results. Preclinical studies demonstrated regorafenib ability to reduce tumor vascularization in GBM xenografts, and the REGOMA trial further supported its efficacy, leading to approval by the Italian regulatory agency (AIFA) for recurrent GBM [14,67]. However, although real-life observational studies have confirmed the REGOMA trial's findings in terms of OS and tolerability [68,69], the FDA and EMA have yet to grant similar approval.

Paradoxically, potential drawbacks of inhibiting RTKs and downstream signaling pathways involved in angiogenesis are related to the acquisition of an even more aggressive, infiltrative phenotype by GBM cells [70] and promotion of a more hypoxic environment [71]. The latter, in turn, may induce the expression of STAT3, which contributes to generate an immunosuppressive tumor microenvironment [71,72]. Moreover, in hypoxic conditions, GBM cells may coopt the host vasculature for the supply of nutrients and oxygen. Thus, vessel cooption represents an escape/resistance mechanism to antiangiogenic therapies and a strategy for further invading the brain tissue [73,74].

Other VEGFR inhibitors, such as axitinib and cediranib, have shown mixed results. Axitinib, while demonstrating antitumor activity and an acceptable safety profile in recurrent GBM patients, did not improve tumor response rates when combined with lomustine and increased hematological toxicity [47]. Similarly, cediranib initially showed promise in normalizing tumor blood vessels and reducing cerebral edema in preclinical [75] and clinical [76] models. However, a phase 3 randomized study failed to demonstrate PFS prolongation, either as monotherapy or in combination with lomustine [38]. Resistance to cediranib has been linked to EGFR upregulation, and its combination with EGFR inhibitors, like gefitinib, showed only a non-significant trend towards improved survival, suggesting that further exploration of this combination is necessary [42].

In addition to gefitinib, other EGFR-targeted PKIs have been tested due to the association of *EGFR* gene amplification or mutation with a poor prognosis in GBM patients [77]. Afatinib, a second-generation, irreversible EGFR inhibitor, has shown preclinical activity in reducing GBM and GSC proliferation and invasion, but clinical trials have reported limited efficacy of afatinib monotherapy in recurrent GBM and a higher incidence of adverse effects when combined with standard treatments [39]. Similarly, neratinib, an irreversible pan-EGFR inhibitor, demonstrated longer PFS in a phase 2 platform trial, although without significant improvement in OS [44]. These findings highlight the complexity of targeting the EGFR pathway in GBM and suggest that resistance mechanisms, such as General Control Non-derepressible 2 (GCN2) kinase pathway modulation, must be considered [78].

The search for effective treatments against newly diagnosed GBM has also led to explore combinations of standard therapies with various PKIs. Vandetanib, a multi-targeted PKI, was safe when administered in combination with radiotherapy and TMZ in phase 1 studies, but subsequent phase 2 trials failed to demonstrate a significant OS benefit [48]. Similarly, dasatinib, despite its multi-kinase inhibitory activity, showed limited clinical efficacy in recurrent GBM due to its suboptimal central nervous system (CNS) penetration and efficient efflux of the drug from the brain [43,79].

Inhibition of the TGFβR signaling pathway, another crucial player in GBM progression, has also been investigated with the PKI galunisertib. Although galunisertib was well tolerated in combination with lomustine or standard TMZ-based chemo-radiotherapy, two randomized controlled trials included in this meta-analysis showed that it did not provide a significant survival benefit [40,41]. Similarly, mTor inhibitors, such as everolimus and temsirolimus, despite their ability to cross the BBB in preclinical models, failed to demonstrate meaningful survival benefits in clinical trials, further highlighting the challenges in translating preclinical success into clinical efficacy [45,46,80,81].

Although the majority of GBMs have been shown to harbor alterations in RTK signaling pathways, the scarce success of PKIs-based targeted therapy for GBM can be attributed to the high intratumoral heterogeneity at clonal levels. Moreover, mutations present in the primary tumor might not be detected in the recurrent malignancy. Heterogeneity may also extend to cells of the tumor microenvironment, which functionally interact with cancer cells and contribute to GBM evolution [82]. Furthermore, not all RTK gene mutations confer sensitivity to PKIs. For instance, genetic alterations of EGFR, although common in GBM, mainly occur within the extracellular domain (e.g., the EGFRvIII), but for tumor response to EGFR inhibitors (like in the case of non-small cell lung cancer) certain sensitizing mutations must be present

at the level of the receptor kinase domain intracellularly [83]. Furthermore, compensatory overactivation of other RTKs within subclones of the same tumor might contribute to treatment failure, suggesting the importance of combinatorial treatments targeting different signaling pathways that, however, should consider the distribution of the RTK alterations on a single GBM patient-basis.

The limited success of PKIs in GBM can be also partly attributed to their poor BBB permeability. While some early studies indicated promising results regarding BBB penetration, further investigation revealed that many PKIs are actively effluxed from the brain by transporters like P-glycoprotein (P-gp/ABCB1) and Breast Cancer Resistance Protein (BCRP/ABCG2), significantly limiting their accumulation in the brain. This pattern is consistent across various PKIs, including gefitinib, cediranib, axitinib, galunisertib, afatinib, and dasatinib, all of which face challenges related to efficient efflux systems that prevent adequate CNS accumulation [84–89]. Strategies to overcome these barriers, such as co-administration with other agents that down-modulate drug efflux, have shown some promise. For example, combining vandetanib with everolimus has been shown to enhance BBB penetration [90]. However, this approach requires careful balancing of efficacy against the risk of increased systemic toxicity. Despite regorafenib's documented clinical efficacy, also its brain penetration is restricted by these efflux mechanisms [91], although low levels of the drug and its metabolites have been detected in the cerebrospinal fluid of glioma patients [92].

5. Conclusion

The meta-analysis findings highlight that PKIs do not significantly improve OS or PFS in newly diagnosed GBM, when combined with standard chemo-radiotherapy, compared to chemo-radiotherapy alone. In recurrent GBM, most PKIs also fail to demonstrate significant benefits in OS or PFS, except for the antiangiogenic VEGFRs inhibitor regorafenib, which shows a noteworthy improvement in both outcomes. The results obtained with regorafenib are more encouraging than those reported by other meta-analyses evaluating the efficacy of the anti-VEGF-A monoclonal antibody bevacizumab in the recurrent setting, showing benefits on PFS, but not on OS [27,93,94]. According to Lombardi et al., 2017, among different antiangiogenic agents, bevacizumab was the only drug capable to significantly improve PFS [27]. On the other hand, a recent meta-analysis, evaluating the efficacy of anti-VEGF-A combinatorial approaches in recurrent GBM, reported that combination therapies based on bevacizumab or different antiangiogenic agents (e.g., the PKI cediranib [38]; ofranergene obadenovec, a gene-based targeted approach, capable of specifically inducing Fas-mediated apoptosis of endothelial cells [95]; the recombinant peptide–Fc (IgG) fusion protein trebananib, binding angiopoietin 1 and 2 and blocking their interaction with the Tie2 RTK - a mechanism of angiogenesis alternative to the VEGF-A/VEGFR pathway [96]) did not offer any benefit in PFS, OS, or objective response ratio, and led to significant grade 3–5 adverse events, compared to the control group [97].

Another finding from our meta-analysis is that the combination of PKIs with other treatments does not yield superior results, compared to either other treatments or PKIs alone, suggesting a limited efficacy of PKIs in the general GBM population. These findings emphasize the need for further research to identify subgroups of patients or biomarkers that may respond better to these therapies.

Overall, while most of the studies analyzed in the present meta-analysis exhibit robust methodological designs, certain biases are present in a few, which should be acknowledged when interpreting the findings. These biases may encompass selection bias, variations in treatment regimens, and differences in patient populations, all of which could potentially impact the generalizability of the results. Nevertheless, this meta-analysis has notable strengths, such as the inclusion, in separate analyses of rigorously randomized studies, of both newly diagnosed and recurrent GBM patients, and a strong focus on clinically relevant endpoints like OS and PFS. These factors contribute to the reliability of the conclusions, even when considering the inherent limitations.

The findings from this meta-analysis highlight the ongoing challenges in developing effective PKI-based therapies for GBM. The poor BBB permeability of these agents, combined with their susceptibility to efflux by transporters, limits their efficacy in the CNS. Moreover, the high GBM heterogeneity, both related to cancer cells and cells of the tumor microenvironment, the occurrence of RTK genetic alterations not targetable with the available PKIs as well as activation of compensatory proliferative signaling pathways, might contribute to PKIs failure. While combinatorial approaches targeting multiple pathways or drug delivery systems able to enhance CNS penetration offer some promise, further studies are urgently needed. Research should focus on the deveopment of drug-delivery strategies to selectively target tumors located at the CNS site [98] as well as of more potent and specific agents with high BBB penetration, non-overlapping toxicities, and reduced risk of resistance due to the redundancy of protumoral signaling pathways. The ultimate goal remains to significantly improve survival outcomes for GBM patients, for whom current therapeutic options remain inadequate, especially in the recurrent setting.

CRediT authorship contribution statement

José Pinto-Fraga: Writing – original draft, Methodology, Formal analysis, Data curation. **Celia Garcia-Chico**: Writing – review & editing, Funding acquisition, Formal analysis, Data curation. **Simone Lista**: Writing – review & editing. **Pedro Miguel Lacal**: Writing – review & editing. **Giuseppe Carpenzano**: Writing – review & editing. **Maurizio Salvati**: Writing – review & editing. **Alejandro Santos-Lozano**: Writing – review & editing, Investigation, Formal analysis. **Grazia Graziani**: Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Claudia Ceci**: Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Grazia Graziani reports a relationship with Italian Ministry of University that includes: funding grants; Celia Garcia Chico reports a relationship with European University Miguel de Cervantes that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M. Price, K. Ryan, M.L. Shoaf, C. Neff, J.B. Iorgulescu, D.B. Landi, G. Cioffi, K. A. Waite, C. Kruchko, J.S. Barnholtz-Sloan, Q.T. Ostrom, Childhood, adolescent,

and adult primary brain and central nervous system tumor statistics for practicing healthcare providers in neuro-oncology, CBTRUS 2015–2019, Neurooncol. Pract. 11 (2024) 5–25, https://doi.org/10.1093/nop/npad061.
[2] S. Mohammed, M. Dinesan, T. Ajayakumar, Survival and quality of life analysis in glioblastoma multiforme with adjuvant chemoradiotherapy: a retrospective study, Rep. Pract. Oncol. Radiother. 27 (2022) 1026–1036, https://doi.org/10.5603/RPOR.a2022.0113.
[3] M. Tilak, J. Holborn, L.A. New, J. Lalonde, N. Jones, Receptor tyrosine kinase signaling and targeting in glioblastoma multiforme, 2021, Int. J. Mol. Sci. 22 (2021) 1–35, https://doi.org/10.3390/ijms22041831.
[4] G.S. Stoyanov, E. Lyutfi, R. Georgieva, R. Georgiev, D.L. Dzhenkov, L. Petkova, B. D. Ivanov, A. Kaprelyan, P. Ghenev, Reclassification of glioblastoma multiforme according to the 2021 world health organization classification of central nervous system tumors: a single institution report and practical significance, Cureus 14 (2022) 1–10, https://doi.org/10.7759/cureus.21822.
[5] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S. K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R. O. Mirimanoff, European organisation for research and treatment of cancer brain tumor and radiotherapy groups, national cancer institute of canada clinical trials group, radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. 352 (2005) 987–996, https://doi.org/10.1056/nejmoa043330.
[6] A.D. Norden, G.S. Young, K. Setayesh, A. Muzikansky, R. Klufas, G.L. Ross, A. S. Ciampa, L.G. Ebbeling, B. Levy, J. Drappatz, S. Kesari, P.Y. Wen, Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrencesymbol, Neurology 70 (2008) 779–787, https://doi.org/10.1212/01.wnl.0000304121.57857.38.
[7] M.D. Moen, Bevacizumab: In previously treated glioblastoma, Drugs 70 (2010) 181–189, https://doi.org/10.2165/11203890-000000000-00000.
[8] W. Wick, T. Gorlia, M. Bendszus, M. Taphoorn, F. Sahm, I. Harting, A.A. Brandes, W. Taal, J. Domont, A. Idbaih, M. Campone, P.M. Clement, R. Stupp, M. Fabbro, E. Le Rhun, F. Dubois, M. Weller, A. von Deimling, V. Golfinopoulos, J. C. Bromberg, M. Platten, M. Klein, M.J. van den Bent, Lomustine and Bevacizumab in Progressive Glioblastoma, N. Engl. J. Med. 377 (2017) 1954–1963, https://doi.org/10.1056/nejmoa1707358.
[9] O.L. Chinot, W. Wick, W. Mason, R. Henriksson, F. Saran, R. Nishikawa, A. F. Carpentier, K. Hoang-Xuan, P. Kavan, D. Cernea, A.A. Brandes, M. Hilton, L. Abrey, T. Cloughesy, Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (2014) 709–722, https://doi.org/10.1056/nejmoa1308345.
[10] M.R. Gilbert, J.J. Dignam, T.S. Armstrong, J.S. Wefel, D.T. Blumenthal, M. A. Vogelbaum, H. Colman, A. Chakravarti, S. Pugh, M. Won, R. Jeraj, P.D. Brown, K.A. Jaeckle, D. Schiff, V.W. Stieber, D.G. Brachman, M. Werner-Wasik, I. W. Tremont-Lukats, E.P. Sulman, K.D. Aldape, W.J.Jr Curran, M.P. Mehta, A randomized trial of bevacizumab for newly diagnosed glioblastoma, N. Engl. J. Med. 370 (2014) 699–708, https://doi.org/10.1056/nejmoa1308573.
[11] B. Carvalho, J.M. Lopes, R. Silva, J. Peixoto, D. Leitão, P. Soares, A.C. Fernandes, P. Linhares, R. Vaz, J. Lima, The role of c-Met and VEGFR2 in glioblastoma resistance to bevacizumab, Sci. Rep. 11 (2021) 1–8, https://doi.org/10.1038/s41598-021-85385-1.
[12] W.C. You, H.D. Lee, H.C. Pan, H.C. Chen, Re-irradiation combined with bevacizumab for recurrent glioblastoma beyond bevacizumab failure: survival outcomes and prognostic factors, Sci. Rep. 13 (2023) 1–9, htpps://doi.org/10.1038/s41598-023-36290-2.
[13] G. Kim, Y.T. Ko, Small molecule tyrosine kinase inhibitors in glioblastoma, Arch. Pharm. Res. 43 (2020) 385–394, 2020, doi: 10.1007/s12272-020-01232-3.
[14] J.R.D. Pearson, T. Regad, Targeting cellular pathways in glioblastoma multiforme, Signal Transduct. Target. Ther.. 2 (2017) 1–11, https://doi.org/10.1038/sigtrans.2017.40.
[15] A.B. Lassman, K.D. Aldape, P.J. Ansell, E. Bain, W.J. Curran, M. Eoli, P.J. French, M. Kinoshita, J. Looman, M. Mehta, Y. Muragaki, Y. Narita, C. Ocampo, L. Roberts-Rapp, M. Song, M.A. Vogelbaum, A.M.E. Walenkamp, T.J.C. Wang, P. Zhang, M. J. van den Bent, Epidermal growth factor receptor (EGFR) amplification rates observed in screening patients for randomized trials in glioblastoma, J. Neurooncol. 144 (2019) 205–210, https://doi.org/10.1007/s11060-019-03222-y.
[16] G. Peng, Y. Wang, P. Ge, C. Bailey, P. Zhang, D. Zhang, Z. Meng, C. Qi, Q. Chen, J. Chen, J. Niu, P. Zheng, Y. Liu, Y. Liu, The HIF1α-PDGFD-PDGFRα axis controls glioblastoma growth at normoxia/mild-hypoxia and confers sensitivity to targeted therapy by echinomycin, J. Exp. Clin. Cancer Res. 40 (2021) 1–16, https://doi.org/10.1186/s13046-021-02082-7.
[17] Y. Gao, W.R. Vallentgoed, P.J. French, Finding the right way to target EGFR in glioblastomas; lessons from lung adenocarcinomas, Cancers 10 (2018) 1–11, https://doi.org/10.3390/cancers10120489.
[18] N. Higa, T. Akahane, S. Yokoyama, H. Yonezawa, H. Uchida, T. Takajo, R. Otsuji, T. Hamada, K. Matsuo, M. Kirishima, N. Hata, R. Hanaya, A. Tanimoto, R. Yoshimoto, Prognostic impact of *PDGFRA* gain/amplification and *MGMT* promoter methylation status in patients with *IDH* wild-type glioblastoma, Neurooncol. Adv. 4 (2022) 1–9, https://doi.org/10.1093/noajnl/vdac097.
[19] R.G. Verhaak, K.A. Hoadley, E. Purdom, V. Wang, Y. Qi, M.D. Wilkerson, C. R. Miller, L. Ding, T. Golub, J.P. Mesirov, G. Alexe, M. Lawrence, M. O'Kelly, P. Tamayo, B.A. Weir, S. Gabriel, W. Winckler, S. Gupta, L. Jakkula, H.S. Feiler, J. G. Hodgson, C.D. James, J.N. Sarkaria, C. Brennan, A. Kahn, P.T. Spellman, R. K. Wilson, T.P. Speed, J.W. Gray, M. Meyerson, G. Getz, C.M. Perou, D.N. Hayes, Cancer genome atlas research network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1, Cancer Cell 17 (2010) 98–110, https://doi.org/10.1016/j.ccr.2009.12.020.
[20] A. Lasorella, M. Sanson, A. Iavarone, FGFR-TACC gene fusions in human glioma, Neuro Oncol. 19 (2017) 475–483, https://doi.org/10.1093/neuonc/now240.
[21] S.A. Forbes, D. Beare, H. Boutselakis, S. Bamford, N. Bindal, J. Tate, C.G. Cole, S. Ward, E. Dawson, L. Ponting, R. Stefancsik, B. Harsha, C.Y. Kok, M. Jia, H. Jubb, Z. Sondka, S. Thompson, T. De, P.J. Campbell, COSMIC: somatic cancer genetics at high-resolution, Nucleic Acids Res 45 (2017) D777–D783, https://doi.org/10.1093/nar/gkw1121.
[22] D. Frumento, G. Grossi, M. Falesiedi, F. Musumeci, A. Carbone, S. Schenone, Small molecule tyrosine kinase inhibitors (TKIs) for glioblastoma treatment, Int. J. Mol. Sci. 25 (2024) 1–32, https://doi.org/10.3390/ijms25031398.
[23] R. Roskoski, Properties of FDA-approved small molecule protein kinase inhibitors: A 2023 update, Pharmacol. Res. 187 (2022) 106552, https://doi.org/10.1016/j.phrs.2022.106552.
[24] R. Roskoski, Properties of FDA-approved small molecule protein kinase inhibitors: A 2024 update, Pharmacol. Res. 200 (2024) 107059, https://doi.org/10.1016/j.phrs.2024.107059.
[25] G. Lombardi, G.L. De Salvo, A.A. Brandes, M. Eoli, R. Rudà, M. Faedi, I. Lolli, A. Pace, B. Daniele, F. Pasqualetti, S. Rizzato, L. Bellu, A. Pambuku, M. Farina, G. Magni, S. Indraccolo, M.P. Gardiman, R. Soffietti, V. Zagonel, Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial, Lancet Oncol. 20 (2019) 110–119, https://doi.org/10.1016/S1470-2045(18)30675-2.
[26] A. Scherm, F.M. Ippen, P. Hau, H. Baurecht, W. Wick, J. Gempt, H. Knüttel, M. F. Leitzmann, C. Seliger, Targeted therapies in patients with newly diagnosed glioblastoma—a systematic meta-analysis of randomized clinical trials, Int. J. Cancer 152 (2023) 2373–2382, https://doi.org/10.1002/ijc.34433.
[27] G. Lombardi, A. Pambuku, L. Bellu, M. Farina, A. Della Puppa, L. Denaro, V. Zagonel, Effectiveness of antiangiogenic drugs in glioblastoma patients: a systematic review and meta-analysis of randomized clinical trials, Crit. Rev. Oncol. Hematol. 111 (2017) 94–102, https://doi.org/10.1016/j.critrevonc.2017.01.018.
[28] M.A. Habibi, N. Shad, M.S. Mirjnani, S. Fasihi, S. Sadeghi, S. Karami, M. H. Ahmadvand, P. Delbari, A.H. Zare, A.H. Zare, S.A.N. Alavi, Is add-on Bevacizumab therapy to Temozolomide and radiotherapy associated with clinical utility for newly diagnosed Glioblastoma? A systematic review and meta-analysis, Neurosurg. Rev. 47 (2024) 445, https://doi.org/10.1007/s10143-024-02667-8.
[29] M. Ameratunga, N. Pavlakis, H. Wheeler, R. Grant, J. Simes, M. Khasraw, Anti-angiogenic therapy for high-grade glioma, Cochrane Database Syst. Rev. 11 (2018) 1–52, https://doi.org/10.1002/14651858.CD008218.pub4.
[30] Q. Xiao, S. Yang, G. Ding, M. Luo, Anti-vascular endothelial growth factor in glioblastoma: a systematic review and meta-analysis, Neurol. Sci. 39 (2018) 2021–2031, https://doi.org/10.1007/s10072-018-3568-y.
[31] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 372 (2021) 1–9, https://doi.org/10.1136/bmj.n71.
[32] C. Schardt, M.B. Adams, T. Owens, S. Keitz, P. Fontelo, Utilization of the PICO framework to improve searching PubMed for clinical questions, BMC Med. Inform. Decis. Mak. 7 (2007) 1–6, https://doi.org/10.1186/1472-6947-7-16.
[33] E. Hariton, J.J. Locascio, Randomised controlled trials - the gold standard for effectiveness research: study design: randomised controlled trials, BJOG 13 (2018) 1716, https://doi.org/10.1111/1471-0528.15199.
[34] J.A.C. Sterne, J. Savović, M.J. Page, R.G. Elbers, N.S. Blencowe, I. Boutron, C. J. Cates, H.Y. Cheng, M.S. Corbett, S.M. Eldridge, J.R. Emberson, M.A. Hernán, S. Hopewell, A. Hróbjartsson, D.R. Junqueira, P. Jüni, J.J. Kirkham, T. Lasserson, T. Li, A. McAleenan, B.C. Reeves, S. Shepperd, I. Shrier, L.A. Stewart, K. Tilling, I. R. White, P.F. Whiting, J.P.T. Higgins, RoB 2: a revised tool for assessing risk of bias in randomised trials, BMJ 366 (2019) l–8, https://doi.org/10.1136/bmj.l4898.
[35] M.K.B. Parmar, V. Torri, L. Stewart, Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints, Stat. Med. 17 (1998) 2815–2834, https://doi.org/10.1002/(sici)1097-0258(19981230)17:24< 2815::aid-sim110> 3.0.co;2-8. Erratum in: Stat Med. 2004 Jun 15;23(11):1817. PMID: 9921604.
[36] M. Borenstein, L.V. Hedges, J.P.T. Higgins, H.R. Rothstein, A basic introduction to fixed-effect and random-effects models for meta-analysis, Res. Synth. Methods 1 (2010) 97–111, https://doi.org/10.1002/jrsm.12.
[37] H.C. Bucher, G.H. Guyatt, L.E. Griffith, S.D. Walter, The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials, J. Clin. Epidemiol. 50 (1997) 683–691, https://doi.org/10.1016/S0895-4356(97)00049-8.
[38] T.T. Batchelor, P. Mulholland, B. Neyns, L.B. Nabors, M. Campone, A. Wick, W. Mason, T. Mikkelsen, S. Phuphanich, L.S. Ashby, J. Degroot, R. Gattamaneni, L. Cher, M. Rosenthal, F. Payer, J.M. Jürgensmeier, R.K. Jain, A.G. Sorensen, J. Xu, Q. Liu, M. van den Bent, Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma, J. Clin. Oncol. 31 (2013) 3212–3218, https://doi.org/10.1200/JCO.2012.47.2464.
[39] D.A. Reardon, L.B. Nabors, W.P. Mason, J.R. Perry, W. Shapiro, P. Kavan, D. Mathieu, S. Phuphanich, A. Cseh, Y. Fu, J. Cong, S. Wind, D.D. Eisenstat, BI 1200 36 Trial group and the canadian brain tumour consortium, phase i/

randomized phase II study of afatinib, an irreversible ErbB family blocker, with or without protracted temozolomide in adults with recurrent glioblastoma, Neuro. Oncol. 17 (2015) 430–439, https://doi.org/10.1093/neuonc/nou160.
[40] A. Wick, A. Desjardins, C. Suarez, P. Forsyth, I. Gueorguieva, T. Burkholder, A. L. Cleverly, S.T. Estrem, S. Wang, M.M. Lahn, S.C. Guba, D. Capper, J. Rodon, Phase 1b/2a study of galunisertib, a small molecule inhibitor of transforming growth factor-beta receptor I, in combination with standard temozolomide-based radiochemotherapy in patients with newly diagnosed malignant glioma, Invest. N. Drugs 38 (2020) 1570–1579, https://doi.org/10.1007/s10637-020-00910-9.
[41] A.A. Brandes, A.F. Carpentier, S. Kesari, J.M. Sepulveda-Sanchez, H.R. Wheeler, O. Chinot, L. Cher, J.P. Steinbach, D. Capper, P. Specenier, J. Rodon, A. Cleverly, C. Smith, I. Gueorguieva, C. Miles, S.C. Guba, D. Desaiah, M.M. Lahn, W. Wick, A Phase II randomized study of galunisertib monotherapy or galunisertib plus lomustine compared with lomustine monotherapy in patients with recurrent glioblastoma, Neuro. Oncol. 18 (2016) 1146–1156, https://doi.org/10.1093/neuonc/now009.
[42] N. Brown, C. McBain, S. Nash, K. Hopkins, P. Sanghera, F. Saran, M. Phillips, F. Dungey, L. Clifton-Hadley, K. Wanek, D. Krell, S. Jeffries, I. Khan, P. Smith, P. Mulholland, Multi-center randomized phase II study comparing cediranib plus gefitinib with cediranib plus placebo in subjects with recurrent/progressive glioblastoma, PLoS One 11 (2016) 1–15, https://doi.org/10.1371/journal.pone.0156369.
[43] E. Galanis, S.K. Anderson, E.L. Twohy, X.W. Carrero, J.G. Dixon, D.D. Tran, S. A. Jeyapalan, D.M. Anderson, T.J. Kaufmann, R.W. Feathers, C. Giannini, J. C. Buckner, P.Z. Anastasiadis, D. Schiff, A phase 1 and randomized, placebo-controlled phase 2 trial of bevacizumab plus dasatinib in patients with recurrent glioblastoma: alliance/north central cancer treatment group N0872, Cancer 125 (2019) 3790–3800, https://doi.org/10.1002/cncr.32340.
[44] R. Rahman, L. Trippa, E.Q. Lee, I. Arrillaga-Romany, G. Fell, M. Touat, C. McCluskey, J. Wiley, S. Gaffey, J. Drappatz, M.R. Welch, E. Galanis, M. S. Ahluwalia, H. Colman, L.B. Nabors, J. Hepel, H. Elinzano, D. Schiff, U. N. Chukwueke, R. Beroukhim, L. Nayak, J.R. McFaline-Figueroa, T.T. Batchelor, M. L. Rinne, T.J. Kaley, C. Lu-Emerson, I.K. Mellinghoff, W.L. Bi, O. Arnaout, P. P. Peruzzi, D. Haas-Kogan, S. Tanguturi, D. Cagney, A. Aizer, L. Doherty, M. Lavallee, B. Fisher-Longden, S. Dowling, J. Geduldig, F. Watkinson, W. Pisano, S. Malinowski, S. Ramkissoon, S. Santagata, D.M. Meredith, E.A. Chiocca, D. A. Reardon, B.M. Alexander, K.L. Ligon, P.Y. Wen, Inaugural results of the individualized screening trial of innovative glioblastoma therapy: a phase ii platform trial for newly diagnosed glioblastoma using bayesian adaptive randomization, J. Clin. Oncol. 41 (2023) 5524–5535, https://doi.org/10.1200/JCO.23.00493.
[45] P. Chinnaiyan, M. Won, P.Y. Wen, A.M. Rojiani, M. Werner-Wasik, H.A. Shih, L. S. Ashby, H.H. Michael Yu, V.W. Stieber, S.C. Malone, J.B. Fiveash, N.A. Mohile, M. S. Ahluwalia, M.M. Wendland, P.J. Stella, A.Y. Kee, M.P. Mehta, A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: results of NRG oncology RTOG 0913, Neuro. Oncol. 20 (2018) 666–673, https://doi.org/10.1093/neuonc/nox209.
[46] W. Wick, T. Gorlia, P. Bady, M. Platten, M.J. van den Bent, M.J. Taphoorn, J. Steuve, A.A. Brandes, M.F. Hamou, A. Wick, M. Kosch, M. Weller, R. Stupp, P. Roth, V. Golfinopoulos, J.S. Frenel, M. Campone, D. Ricard, C. Marosi, S. Villa, A. Weyerbrock, K. Hopkins, K. Homicsko, B. Lhermitte, G. Pesce, M.E. Hegi, 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. 22 (2016) 4797–4806, https://doi.org/10.1158/1078-0432.CCR-15-3153.
[47] J. Duerinck, S. Du Four, F. Bouttens, C. Andre, V. Verschaeve, F. Van Fraeyenhove, C. Chaskis, N. D'Haene, M. Le Mercier, A. Rogiers, A. Michotte, I. Salmon, B. Neyns, Randomized phase II trial comparing axitinib with the combination of axitinib and lomustine in patients with recurrent glioblastoma, J. Neurooncol. 136 (2018) 115–125, https://doi.org/10.1007/s11060-017-2629-z.
[48] E.Q. Lee, T.J. Kaley, D.G. Duda, D. Schiff, A.B. Lassman, E.T. Wong, T. Mikkelsen, B.W. Purow, A. Muzikansky, M. Ancukiewicz, J.T. Huse, S. Ramkissoon, J. Drappatz, A.D. Norden, R. Beroukhim, S.E. Weiss, B.M. Alexander, C. S. McCluskey, M. Gerard, K.H. Smith, R.K. Jain, T.T. Batchelor, K.L. Ligon, P. Y. Wen, A multicenter, phase II, randomized, noncomparative clinical trial of radiation and temozolomide with or without vandetanib in newly diagnosed glioblastoma patients, Clin. Cancer Res. 21 (2015) 3610–3618, https://doi.org/10.1158/1078-0432.CCR-14-3220.
[49] M. Sahade, F. Caparelli, P.M. Hoff, Cediranib: A VEGF receptor tyrosine kinase inhibitor, Futur. Oncol. 8 (2012) 775–781, https://doi.org/10.2217/fon.12.73.
[50] S. Herbertz, J.S. Sawyer, A.J. Stauber, I. Gueorguieva, K.E. Driscoll, S.T. Estrem, A. L. Cleverly, D. Desaiah, S.C. Guba, K.A. Benhadji, C.A. Slapak, M.M. Lahn, Clinical development of galunisertib (Ly2157299 monohydrate), a small molecule inhibitor of transforming growth factor-beta signaling pathway, Drug Des. Devel. Ther. 9 (2015) 4479–4499, https://doi.org/10.2147/DDDT.S86621.
[51] S. Singh, S. Sadhukhan, A. Sonawane, 20 years since the approval of first EGFR-TKI, gefitinib: Insight and foresight, Biochim. Biophys. Acta Rev. Cancer 1878 (2023) 1–22, https://doi.org/10.1016/j.bbcan.2023.188967.
[52] M. Gross-Goupil, L. François, A. Quivy, A. Ravaud, Axitinib: A review of its safety and efficacy in the treatment of adults with advanced renal cell carcinoma, Clin. Med. Insights Oncol.. 7 (2013) 269–277, https://doi.org/10.4137/CMO.S10594.
[53] Z. Nekoukar, M. Moghimi, E. Salehifar, A narrative review on adverse effects of dasatinib with a focus on pharmacotherapy of dasatinib-induced pulmonary toxicities, Blood Res. 56 (2021) 229–242, https://doi.org/10.5045/BR.2021.2021117.
[54] A. Grothey, J.Y. Blay, N. Pavlakis, T. Yoshino, J. Bruix, Evolving role of regorafenib for the treatment of advanced cancers, Cancer Treat. Rev. 86 (2019) 101993, https://doi.org/10.1016/j.ctrv.2020.101993.
[55] G. Sartori, L. Belluomini, F. Lombardo, A. Avancini, I. Trestini, E. Vita, D. Tregnago, J. Menis, E. Bria, M. Milella, S. Pilotto, Efficacy and safety of afatinib for non-small-cell lung cancer: state-of-the-art and future perspectives, Expert Rev. Anticancer Ther. 20 (2020) 531–542, https://doi.org/10.1080/14737140.2020.1776119.
[56] H.E. Ramos, F. Hecht, A. Berdelou, I. Borget, S. Leboulleux, E. Baudin, M. Schlumberger, Long-term follow-up and safety of vandetanib for advanced medullary thyroid cancer, Endocrine 71 (2021) 434–442, https://doi.org/10.1007/s12020-020-02426-x.
[57] S.R. Tiwari, P. Mishra, J. Abraham, Neratinib, A novel HER2-targeted tyrosine kinase inhibitor, Clin. Breast Cancer 16 (2016) 344–348, https://doi.org/10.1016/j.clbc.2016.05.016.
[58] C. Moreau-Bachelard, M. Robert, C. Gourmelon, E. Bourbouloux, A. Patsouris, J. S. Frenel, M. Campone, Evaluating everolimus for the treatment of breast cancer, Expert Opin. Pharmacother. 24 (2023) 1105–1111, https://doi.org/10.1080/14656566.2023.2214677.
[59] R.M. Bukowski, Temsirolimus: a safety and efficacy review, Expert Opin. Drug Saf. 5 (2012) 861–879, https://doi.org/10.1517/14740338.2012.713344.
[60] R. Roskoski, Classification of small molecule protein kinase inhibitors based upon the structures of their drug-enzyme complexes, Pharmacol. Res. 103 (2016) 26–48, https://doi.org/10.1016/j.phrs.2015.10.021.
[61] W. Wu, J.L. Klockow, M. Zhang, F. Lafortune, E. Chang, L. Jin, Y. Wu, H. E. Daldrup-Link, Glioblastoma multiforme (GBM): an overview of current therapies and mechanisms of resistance, Pharm. Res 171 (2021) 1–26, https://doi.org/10.1016/j.phrs.2021.105780.
[62] B. Foroughi-Nia, J. Barar, M.Y. Memar, A. Aghanejad, S. Davaran, Progresses in polymeric nanoparticles for delivery of tyrosine kinase inhibitors, Life Sci. 278 (2021) 1–11, https://doi.org/10.1016/j.lfs.2021.119642.
[63] M.G. Atzori, L. Tentori, F. Ruffini, C. Ceci, E. Bonanno, M. Scimeca, P.M. Lacal, G. Graziani, The anti-vascular endothelial growth factor receptor-1 monoclonal antibody D16F7 inhibits glioma growth and angiogenesis in vivo, J. Pharmacol. Exp. Ther. 364 (2018) 77–86, https://doi.org/10.1124/jpet.117.244434.
[64] M.G. Atzori, L. Tentori, F. Ruffini, C. Ceci, L. Lisi, E. Bonanno, M. Scimeca, E. Eskilsson, T. Daubon, H. Miletic, L. Ricci Vitiani, R. Pallini, P. Navarra, R. Bjerkvig, S. D'Atri, P.M. Lacal, G. Graziani, The anti-vascular endothelial growth factor receptor-1 monoclonal antibody D16F7 inhibits invasiveness of human glioblastoma and glioblastoma stem cells, J. Exp. Clin. Cancer Res. 36 (2017) 1–15, https://doi.org/10.1186/s13046-017-0577-2.
[65] L. Lisi, G.M. Pia Ciotti, M. Chiavari, F. Ruffini, P.M. Lacal, G. Graziani, P. Navarra, Vascular endothelial growth factor receptor 1 in glioblastoma-associated microglia/macrophages, Oncol. Rep. 43 (2020) 2083–2092, https://doi.org/10.3892/or.2020.7553.
[66] C. Russo, L. Lisi, L. Tentori, P. Navarra, G. Graziani, C. Combs, Exploiting microglial functions for the treatment of glioblastoma, Curr. Cancer Drug Targets 17 (2016) 267–281, https://doi.org/10.2174/1568009616666160813191240.
[67] M.P. Mongiardi, R. Pallini, Q.G.D. Alessandris, A. Levi, M.L. Falchetti, Regorafenib and glioblastoma: a literature review of preclinical studies, molecular mechanisms and clinical effectiveness, Expert Rev. Mol. Med. 26 (2024) 1–7, https://doi.org/10.1017/erm.2024.8.
[68] R. Rudà, F. Bruno, A. Pellerino, E. Pronello, R. Palmiero, L. Bertero, S. Crasto, V. Polo, R. Vitaliani, E. Trincia, V. Internò, C. Porta, R. Soffietti, Observational real-life study on regorafenib in recurrent glioblastoma: does dose reduction reduce toxicity while maintaining the efficacy? J. Neurooncol. 160 (2022) 389–402, https://doi.org/10.1007/s11060-022-04155-9.
[69] M. Caccese, I. Desideri, V. Villani, M. Simonelli, M. Buglione, S. Chiesa, E. Franceschi, P. Gaviani, I. Stasi, C. Caserta, S. Brugnara, I. Lolli, E. Bennicelli, P. Bini, A.S. Cuccu, S. Scoccianti, M. Padovan, S. Gori, A. Bonetti, P. Giordano, A. Pellerino, F. Gregucci, N. Riva, S. Cinieri, V. Internò, M. Santoni, G. Pernice, C. Dealis, L. Stievano, F. Paiar, G. Magni, G.L. De Salvo, V. Zagonel, G. Lombardi, REGOMA-OSS: a large, Italian, multicenter, prospective, observational study evaluating the efficacy and safety of regorafenib in patients with recurrent glioblastoma, ESMO Open 9 (2024) 1–7, https://doi.org/10.1016/j.esmoop.2024.102943.
[70] A.K. Lucio-Eterovic, Y. Piao, J.F. de Groot, Mediators of glioblastoma resistance and invasion during antivascular endothelial growth factor therapy, Clin. Cancer Res. 15 (2009) 4589–4599, https://doi.org/10.1158/1078-0432.CCR-09-0575.
[71] J. de Groot, J. Liang, L.Y. Kong, J. Wei, Y. Piao, G. Fuller, W. Qiao, A. B. Heimberger, Modulating antiangiogenic resistance by inhibiting the signal transducer and activator of transcription 3 pathway in glioblastoma, Oncotarget 3 (2012) 1036–1048, https://doi.org/10.18632/oncotarget.663.
[72] M. Ott, C. Kassab, A. Marisetty, Y. Hashimoto, J. Wei, D. Zamler, J.S. Leu, K. H. Tomaszowski, A. Sabbagh, D. Fang, P. Gupta, W. Priebe, R.J. Zielinski, J. K. Burks, J.P. Long, L.Y. Kong, G.N. Fuller, J. DeGroot, E.P. Sulman, A. B. Heimberger, Radiation with STAT3 blockade triggers dendritic cell-T cell interactions in the glioma microenvironment and therapeutic efficacy, Clin. Cancer Res. 26 (2020) 4983–4994, https://doi.org/10.1158/1078-0432.CCR-19-4092.
[73] J.L. Rubenstein, J. Kim, T. Ozawa, M. Zhang, M. Westphal, D.F. Deen, M. A. Shuman, Anti-VEGF antibody treatment of glioblastoma prolongs survival but results in increased vascular cooption, Neoplasia 2 (2000) 306–314, https://doi.org/10.1038/sj.neo.7900102.
[74] G. Seano G, R.K. Jain, Vessel co-option in glioblastoma: emerging insights and opportunities, Angiogenesis 23 (2020) 9–16, https://doi.org/10.1007/s10456-019-09691-z.

[75] W.S. Kamoun, C.D. Ley, C.T. Farrar, A.M. Duyverman, J. Lahdenranta, D. A. Lacorre, T.T. Batchelor, E. di Tomaso, D.G. Duda, L.L. Munn, D. Fukumura, A. G. Sorensen, R.K. Jain, Edema control by cediranib, a vascular endothelial growth factor receptor - Targeted kinase inhibitor, prolongs survival despite persistent brain tumor growth in mice, J. Clin. Oncol. 27 (2009) 2542–2552, https://doi.org/10.1200/JCO.2008.19.9356.

[76] A.G. Sorensen, K.E. Emblem, P. Polaskova, D. Jennings, H. Kim, M. Ancukiewicz, M. Wang, P.Y. Wen, P. Ivy, T.T. Batchelor, R.K. Jain, Increased survival of glioblastoma patients who respond to antiangiogenic therapy with elevated blood perfusion, Cancer Res 72 (2012) 402–407, https://doi.org/10.1158/0008-5472.CAN-11-2464.

[77] L. Orellana, Convergence of EGFR glioblastoma mutations: evolution and allostery rationalizing targeted therapy, Mol. Cell. Oncol. 6 (2019) 1–3, https://doi.org/10.1080/23723556.2019.1630798.

[78] C.P. Tang, O. Clark, J.R. Ferrarone, C. Campos, A.S. Lalani, J.D. Chodera, A. M. Intlekofer, O. Elemento, I.K. Mellinghoff, GCN2 kinase activation by ATP-competitive kinase inhibitors, Nat. Chem. Biol. 18 (2022) 207–215, https://doi.org/10.1038/s41589-021-00947-8.

[79] D. Schiff, J. Sarkaria, Dasatinib in recurrent glioblastoma: failure as a teacher, Neuro. Oncol.. 17 (2015) 910–911, https://doi.org/10.1093/neuonc/nov086.

[80] J.N. Sarkaria, E. Galanis, W. Wu, P.J. Peller, C. Giannini, P.D. Brown, J.H. Uhm, S. McGraw, K.A. Jaeckle, J.C. Buckner, North central cancer treatment group Phase i trial N057K of everolimus (RAD001) and temozolomide in combination with radiation therapy in patients with newly diagnosed glioblastoma multiforme, Int. J. Radiat. Oncol. Biol. Phys. 81 (2011) 468–475, https://doi.org/10.1016/j.ijrobp.2010.05.064.

[81] J.N. Sarkaria, E. Galanis, W. Wu, A.B. Dietz, T.J. Kaufmann, M.P. Gustafson, P. D. Brown, J.H. Uhm, R.D. Rao, L. Doyle, C. Giannini, H.A. Jaeckle, J.C. Buckner, Combination of temsirolimus (CCI-779) with chemoradiation in newly diagnosed glioblastoma multiforme (GBM) (NCCTG trial N027D) is associated with increased infectious risks, Clin. Cancer Res. 16 (2010) 5573–5580, https://doi.org/10.1158/1078-0432.CCR-10-1453.

[82] R. Mathur, Q. Wang, P.G. Schupp, A. Nikolic, S. Hilz, C. Hong, N.R. Grishanina, D. Kwok, N.O. Stevers, Q. Jin, M.W. Youngblood, L.A. Stasiak, Y. Hou, J. Wang, T. N. Yamaguchi, M. Lafontaine, A. Shai, I.V. Smirnov, D.A. Solomon, S.M. Chang, S. L. Hervey-Jumper, M.S. Berger, J.M. Lupo, H. Okada, J.J. Phillips, P.C. Boutros, M. Gallo, M.C. Oldham, F. Yue, J.F. Costello, Glioblastoma evolution and heterogeneity from a 3D whole-tumor perspective, Cell 187 (2024) 446–463, https://doi.org/10.1016/j.cell.2023.12.013.

[83] E. Eskilsson, G.V. Røsland, G. Solecki, Q. Wang, P.N. Harter, G. Graziani, R.G. W. Verhaak, F. Winkler, R. Bjerkvig, H. Miletic, EGFR heterogeneity and implications for therapeutic intervention in glioblastoma, Neuro Oncol. 20 (2018) 743–752, https://doi.org/10.1093/neuonc/nox191.

[84] S. Agarwal, R. Sane, J.L. Gallardo, J.R. Ohlfest, W.F. Elmquist, Distribution of gefitinib to the brain is limited by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2)-mediated active efflux, J. Pharmacol. Exp. Ther. 334 (2010) 147–155, https://doi.org/10.1124/jpet.110.167601.

[85] W. Tang, A. McCormick, J. Li, E. Masson, Clinical pharmacokinetics and pharmacodynamics of cediranib, Clin. Pharmacokinet. 56 (2017) 689–702, https://doi.org/10.1007/s40262-016-0488-y.

[86] B. Poller, D. Iusuf, R.W. Sparidans, E. Wagenaar, J.H. Beijnen, A.H. Schinkel, Differential impact of P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) on axitinib brain accumulation and oral plasma pharmacokinetics, Drug Metab. Dispos. 39 (2011) 729–735, https://doi.org/10.1124/dmd.110.037317.

[87] W. Li, M. Tibben, Y. Wang, M.C. Lebre, H. Rosing, J.H. Beijnen, A.H. Schinkel, P-glycoprotein (MDR1/ABCB1) controls brain accumulation and intestinal disposition of the novel TGF-β signaling pathway inhibitor galunisertib, Int. J. Cancer 146 (2020) 1631–1642, https://doi.org/10.1002/ijc.32568.

[88] S. van Hoppe, R.W. Sparidans, E. Wagenaar, J.H. Beijnen, A.H. Schinkel, Breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-gp/ABCB1) transport afatinib and restrict its oral availability and brain accumulation, Pharmacol. Res. 120 (2017) 43–50, https://doi.org/10.1016/j.phrs.2017.01.035.

[89] S. Agarwal, R.K. Mittapalli, D.M. Zellmer, J.L. Gallardo, R. Donelson, C. Seiler, S. A. Decker, K.S. Santacruz, J.L. Pokorny, J.N. Sarkaria, W.F. Elmquist, J.R. Ohlfest, Active efflux of dasatinib from the brain limits efficacy against murine glioblastoma: broad implications for the clinical use of molecularly targeted agents, Mol. Cancer Ther. 11 (2012) 2183–2192, https://doi.org/10.1158/1535-7163.MCT-12-0552.

[90] M. Minocha, V. Khurana, B. Qin, D. Pal, A.K. Mitra, Co-administration strategy to enhance brain accumulation of vandetanib by modulating P-glycoprotein (P-gp/Abcb1) and breast cancer resistance protein (Bcrp1/Abcg2) mediated efflux with m-TOR inhibitors, Int. J. Pharm. 434 (2012) 306–314, https://do.org/10.1016/j.ijpharm.2012.05.028.

[91] A. Kort, S. Durmus, R.W. Sparidans, E. Wagenaar, J.H. Beijnen, A.H. Schinkel, Brain and testis accumulation of regorafenib is restricted by breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1), Pharm. Res. 32 (2015) 2205–2216, https://doi.org/10.1007/s11095-014-1609-7.

[92] P.S. Zeiner, M. Kinzig, I. Divé, G.D. Maurer, K. Filipski, P.N. Harter, C. Senft, O. Bähr, E. Hattingen, J.P. Steinbach, F. Sörgel, M. Voss, E. Steidl, M. W. Ronellenfitsch, Regorafenib csf penetration, efficacy, and mri patterns in recurrent malignant glioma patients, J. Clin. Med. 8 (2019) 1–14, https://doi.org/10.3390/jcm8122031.

[93] T. Zhang, Q. Xin, J.M. Kang, Bevacizumab for recurrent glioblastoma: a systematic review and meta-analysis, Eur. Rev. Med. Pharmacol. Sci. 25 (2021) 6480–6491, https://doi.org/10.26355/eurrev_202111_27092.

[94] Y. Wang, D. Xing, M. Zhao, J. Wang, Y. Yang, The role of a single angiogenesis inhibitor in the treatment of recurrent glioblastoma multiforme: a meta-analysis and systematic review, PLoS One 11 (2016) 11–13, https://doi.org/10.1371/journal.pone.0152170.

[95] T.F. Cloughesy, A. Brenner, J.F. de Groot, N.A. Butowski, L. Zach, J.L. Campian, B. M. Ellingson, L.S. Freedman, Y.C. Cohen, N. Lowenton-Spier, T. Rachmilewitz Minei, S. Fain Shmueli, GLOBE, Study Investigators, P.Y. Wen, A randomized controlled phase III study of VB-111 combined with bevacizumab vs bevacizumab monotherapy in patients with recurrent glioblastoma (GLOBE), Neuro Oncol. 22 (2020) 705–717, https://doi.org/10.1093/neuonc/noz232.

[96] E.Q. Lee, P. Zhang, P.Y. Wen, E.R. Gerstner, D.A. Reardon, K.D. Aldape, J. F. deGroot, E. Pan, J.J. Raizer, L.J. Kim, S.J. Chmura, H.I. Robins, J.M. Connelly, J. D. Battiste, J.L. Villano, N. Wagle, R.T. Merrell, M.M. Wendland, M.P. Mehta, NRG/RTOG 1122: A phase 2, double-blinded, placebo-controlled study of bevacizumab with and without trebananib in patients with recurrent glioblastoma or gliosarcoma, Cancer 126 (2020) 2821–2828, https://doi.org/10.1002/cncr.32811.

[97] V. Solipuram, R. Soltani, B.P. Venkatesulu, S. Annam, F. Alavian, S. Ghasemi, Efficacy of anti-VEGF drugs based combination therapies in recurrent glioblastoma: systematic review and meta-analysis, Curr. Rev. Clin. Exp. Pharmacol. 19 (2024) 173–183, https://doi.org/10.2174/2772432817666220517163609.

[98] H.K. Brar, J. Jose, Z. Wu, M. Sharma, Tyrosine kinase inhibitors for glioblastoma multiforme: challenges and opportunities for drug delivery, Pharmaceutics 15 (2022) 1–28, https://doi.org/10.3390/pharmaceutics15010059.