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Dabrafenib plus trametinib in low-grade versus high-grade gliomas: a systematic review and meta-analysis

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Abstract

Background Dabrafenib plus trametinib is a novel targeted therapy for low-grade (LGG) and high-grade (HGG) gliomas. This systematic review and meta-analysis aimed to evaluate the safety and efficacy of dabrafenib plus trametinib in LGG and HGG gliomas.

Methods The electronic databases of PubMed/Medline, Scopus, Embase, and Web of Science were searched from inception to 5 September 2024. The meta-analyses, sensitivity analysis, publication bias, and meta-regression were performed through the R program.

Results Nine studies with 313 patients were included. Our data demonstrated that dual blockage resulted in a pooled complete response (CR) rate of 10% (95% CI: 5—18%), partial response rate (PR) rate of 39% (95% CI: 32-46%), stable disease (SD) rate of 36% (95% CI: 26-46%), and progressive disease (PD) rate of 17% (95% CI: 10- 29%). The PR was significantly higher in LGG ($P=0.03$), and the PD was substantially lower in LGG ($P<0.01$). Our results demonstrated a pooled overall objective response rate (ORR) of 47% (95% CI: 39—55%) without a significant difference in subgroups ($P=0.36$). The meta-regression demonstrated that lower age, BRAF V600 mutation, longer dual blockage treatment duration, and history of prior resection were associated with more favorable outcomes in HGGs. Our meta-analysis revealed a pooled discontinuation due to adverse events (AE) rate of 12% (95% CI: 4- 31%).

Conclusion Dabrafenib plus trametinib is associated with favorable outcomes in gliomas, especially among those with lower age, BRAF V600 mutation, longer dual blockage treatment duration, and history of prior resection. The co-administration of dabrafenib and trametinib was associated with more favorable outcomes among LGGs than HGGs.

Keywords Dabrafenib, Trametinib, Low-grade glioma, High-grade glioma, BRAF

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Introduction

Gliomas are the most frequent primary malignant lesion of the central nervous system, originating from glial cells [1]. The annual incidence rate of gliomas is approximately 6–8 cases per 100,000 individuals, comprising 25% of all primary intracranial lesions and 81% of all malignant brain lesions [2, 3]. The majority of cases occur in individuals without prior family history [3]. Regarding the World Health Organization (WHO) classification, gliomas are categorized into high-grade glioma (HGG) and low-grade glioma (LGG) [4]. Despite the recent advancements in the treatment of gliomas, the prognosis of these lesions has remained dismal, as the 5-year survival rate is about 7% in glioblastoma, which is the most aggressive subtype [1]. Considerable malignant behavior, high mortality rate, and significant likelihood of recurrence of the gliomas have turned these lesions into a challenging entity for neuro-oncologists and impose a considerable burden on society and families [3].

Surgical resection is the primary therapeutic option for managing glioma, and adjuvant treatment, including radiotherapy and chemotherapy, is generally considered in cases where complete surgical resection is not achievable [5]. Due to the significant side effects of chemotherapeutic agents and radiation adverse effects following irradiation, the establishment of novel therapeutic options with higher efficacy and lower complication rates was necessary. Recently, after investigation of the role of critical genes in the setting of malignancy, it was evident that B-Raf proto-oncogene serine/threonine-protein (BRAF) V600E mutation plays a significant role in various cancers, including 20% of LGG gliomas and acts through activation of mitogen-activated protein kinase (MAPK) signaling pathway [5]. Regarding this, researchers have extensively investigated the role of BRAF inhibitors and MAPK kinase (MEK) inhibitors in the setting of brain tumors, especially gliomas [5, 6].

Dabrafenib is a selective BRAF inhibitor that selectively targets the mutant BRAF kinase; however, resistance against the agent eventually occurs throughout administration [5]. Studies have demonstrated that adding trametinib, an MEK inhibitor, may diminish this resistance development [5]. Additionally, trametinib has been shown to possess anti-glioma effects regardless of monotherapy or combination therapy [5]. Several studies have demonstrated that a combination of dabrafenib and trametinib can block the MAPK pathway and inhibit BRAF V600 mutant cell proliferation and survival [5–16]. This systematic review and meta-analysis aimed to evaluate and compare the efficacy and safety of administering dual blockage by dabrafenib and trametinib in individuals with HGG and LGG.

Materials and methods

Objective

This study aimed to assess the effectiveness and safety of dual blockage with dabrafenib and trametinib in patients with HGG or LGG. It was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Search Strategy

A systematic literature search was conducted through four electronic databases: PubMed, Embase, Scopus, and Web of Science. On September 5th, 2024, the search was performed by utilizing the following keywords and their equivalents: "Dabrafenib", "Trametinib", and "glioma". The search syntax is available in Supplementary Table 1.

Eligibility criteria

The eligibility criteria were defined based on the following PICO:

- Population (P): Individuals who were diagnosed with HGG or LGG.
- Intervention (I): Administration of combination of dabrafenib and trametinib.
- Comparison (C): HGG versus LGG.
- Outcome (O): Progression-free survival (PFS), overall survival (OS), complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), objective response rate (ORR), clinical benefit response (CBR), adverse event (AE).

The inclusion criteria were (1) Retrospective and prospective randomized control trials, cohort studies, case-control studies, observation studies, and case series studies with ≥five patients, (2) Studies that have evaluated patients who were diagnosed with LGG or HGG regarding the WHO classification, (3) Studies that evaluated the clinical and radiological outcomes of the dual blockade by dabrafenib and trametinib, and (4) English studies. The exclusion criteria were (1) Case series with less than five individuals, case reposts, conference abstracts, preprints, commentaries, and editorials, (2) Lack of reporting the data, (3) Inability to separate the data of HGG or LGG from other lesions, (4) Overlap of participants with other studies.

Study selection process

Following the execution of the search strategy, the identified articles were imported into the Covidence systematic review software. Covidence determined the duplicates and resolved them automatically. Then, two independent reviewers (A.K. and M.S.A) evaluated the included studies through the title/abstract screening. Studies that met the inclusion criteria were included. A third reviewer

(B.H.) resolved the conflicts. Afterward, the two independent reviewers evaluated the included studies through full-text evaluation. A third reviewer (B.H.) resolved the conflicts.

Data extraction

Studies that met the inclusion criteria underwent the data extraction process. Two independent reviewers meticulously extracted data through a predesigned standardized Microsoft Excel data sheet.

The baseline characteristics were publication year, country, study design, number of males and females, age, and BRAF V600 mutations. The treatment characteristics were dose and duration of treatment. The outcomes included PFS, OS, CR, PR, SD, PD, ORR, CBR, and AEs. The diagnostic criteria among the studies were consistent, using WHO classification and molecular testing for critical mutations, such as BRAF V600. The radiological outcomes were evaluated through RANO criteria.

Risk of bias assessment

The risk of bias (ROB) in the included studies was evaluated by the Risk of Bias in Non-randomized Studies of Interventions – 1 (ROBINS-I) tool [18]. In addition, the ROB of the randomized control trials was assessed through the ROB-2 tool [19]. Two independent reviewers evaluated the ROB to judge the ROB of the included studies. This tool consists of seven domains, including bias due to confounding, bias in selection, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of the outcomes, and bias in the report.

Statistical analysis

All analyses were conducted using "meta" and "metafor" packages using the R language (R foundation of statistical computing V R-4.4.1). The random-effects model was employed for calculations when heterogeneity was evident in data, $I^2 > 50\%$, or Cochran's Q was significant ($p < 0.1$). Leave-one-out analysis was executed to evaluate the robustness of the calculated effect. Publication bias was judged using visual inspection of funnel plots for asymmetry and approved through Egger's regression test. A p-value < 0.05 was considered statistically significant.

Results

Study selection process

The screening process is demonstrated with PRISMA guidelines in Fig. 1. After searching the electronic databases, 946 studies were identified. Of these, 455 were detected as duplicates and resolved. After resolving the duplicates, 491 studies underwent title/abstract screening. Sixty-eight studies met the inclusion criteria and enrolled for the full-text screening. Eventually, nine studies were included in our study. A noteworthy fact is that a study by Wen et al. [16] was a subgroup of a more extensive study by Subbiah et al. [7]; therefore, the Subbiah et al. study was included, and the other study was excluded.

Risk of bias assessment

The overall risk of ROB in the non-randomized trials, assessed by the ROBINS-1 tool, indicated a moderate level (Table 1). Bias due to confounding, bias in selecting participants for the study, and bias due to missing data were the most potential sources of bias. Two studies were assessed through ROB-2 as randomized control trials; both had a low ROB.

Baseline characteristics

Nine studies with 313 patients were included in our study (Table 2). Table 2 demonstrates the baseline characteristics of the included studies. All of the studies were conducted after 2021. Five of the nine studies were conducted prospectively, and four were performed retrospectively. Of the nine studies, four mainly evaluated pediatrics, four assessed adults, and one comprised both adults and pediatrics. Among the patients, 44.2% were male and 55.8% were female. The median age ranged from 10 to 41.9 years old. Approximately 95.5% of the patients had BRAF V600 mutation. Dabrafenib was routinely administered at 150 mg twice daily, and trametinib was given at two mg once daily in most cases.

Clinical and radiological outcomes

Table 3 demonstrates the clinical and radiological outcomes. The median PFS ranged from 4.5 to 36.9 months. The 6-month, 1-year, and 2-year PFS ranged from 44 to 100%, 33–100%, and 11–100%, respectively. The Median OS ranged from 17.6 to 32.8 months. The 6-month, 1-year, and 2-year OS ranged from 91 to 100%, 76–100%, and 59–100%, respectively. The CR, PR, SD, and PD rates ranged from 0 to 25%, 11.1–60%, 17.5–66.6%, and 0–44.4%, respectively. The ORR and CBR rates ranged from 22.2 to 63.6% and 55.5–100%, respectively. The AE rate ranged from 40 to 100%, and the AE that led to discontinuation rate ranged from 4.1 to 22.2%.

Meta-analysis of the radiological outcomes

Nine studies were included in the meta-analysis of the CR rate (Fig. 2). The meta-analysis revealed a pooled total CR rate of 10% (95% CI: 5—18%). The pooled CR rate for the HGG was higher among HGG compared to LGG; however, the difference was not statistically significant (HGG: 14% [95% CI: 7- 27%] vs. LGG: 6% [95% CI: 3-13%], $P = 0.11$). The meta-regression demonstrated that lower age ($P = 0.0199$), presence of BRAF V600 mutation ($P = 0.0417$), and history of prior resection ($P = 0.0368$)

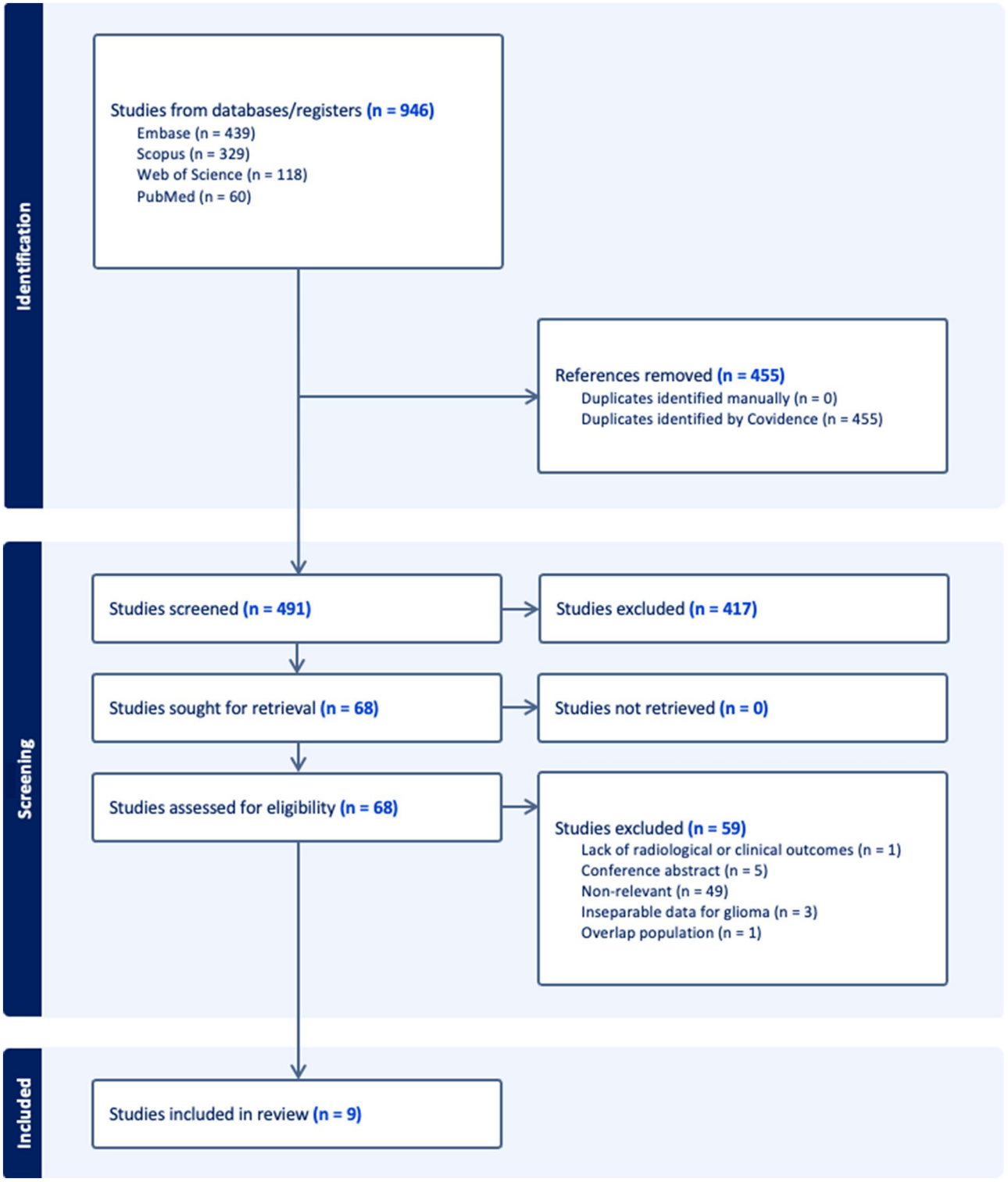

Fig. 1 Study selection process through PRISMA flow chart

were associated with a higher CR in HGGs (Table 4). On the other hand, meta-regression did not identify any possible source of heterogeneity for CR in LGG individuals (Table 5).

The meta-analysis of the PR demonstrated a pooled PR rate of 39% (95% CI: 32- 46%), and the pooled PR rate was significantly higher among individuals with LGG compared to the HGG (HGG: 32% [95% CI: 24- 41%] vs.

Table 1 Risk of bias assessment

ROBINS-1

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Rosenberg 2022	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Shimoi 2024	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Padovan 2023	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Lim-Fat 2021	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Subbiah 2023	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Bouffet 2022	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Berzero 2021	Serious	Moderate	Low	Low	Moderate	Low	Low	Serious

D1: Bias due to confounding, D2: Bias in selection of participants into the study, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias due to missing data, D6: Bias in measurement of outcomes, D7: Bias in selection of the reported result

ROB-2

Study	D1	D2	D3	D4	D5	Overall
Bouffet 2023	Low	Low	Low	Low	Low	Low
Hargrave 2023	Low	Low	Low	Low	Low	Low

D1: Bias due to confounding, D2: Bias in selection of participants into the study, D3: Bias in classification of interventions, D4: Bias due to deviations from intended interventions, D5: Bias in measurement of outcomes

LGG: 45% [95% CI: 37- 54%], $P=0.03$) (Fig. 3). The meta-regression did not identify any possible source of heterogeneity for PR in HGG and LGG individuals (Tables 4 and 5).

The meta-analysis of the SD rate resulted in a pooled SD rate of 36% (95% CI: 26-46%) and the pooled estimate was higher among LGG; however, the difference was not statistically significant (HGG: 34% [95% CI: 21- 51%] vs. LGG: 40% [95% CI: 32- 50%], $P=0.51$) (Fig. 4). The meta-regression did not identify any possible source of heterogeneity for SD in HGG and LGG individuals (Tables 4 and 5).

The meta-analysis of the PD demonstrated a pooled PD rate of 17% (95% CI: 10- 29%); however, the pooled PD rate was significantly lower among LGG patients (HGG: 26% [95% CI: 15- 40%] vs. LGG: 9% [95% CI: 5- 17%], $P<0.01$) (Fig. 5). The meta-regression demonstrated that higher age ($P=0.024$), normal BRAF V600 status ($P=0.005$), lower dual blockage treatment duration ($P=0.0101$) and no prior resection ($P=0.0123$) were associated with a higher PD in HGGs (Table 4). On the other hand, meta-regression did not identify any possible source of heterogeneity for PR in LGG individuals (Table 5).

The meta-analysis of ORR revealed a pooled ORR rate of 47% (95% CI: 39—55%); additionally, despite LGG's higher pooled ORR rate compared to HGG, the difference was not significant (HGG: 43% [95% CI: 30—56%] vs. LGG: 50% [95% CI: 41—59%], $P=0.36$) (Fig. 6). The meta-regression demonstrated that lower age ($P=0.0166$) and history of prior resection ($P=0.0119$) were associated with a higher ORR in HGGs (Table 4). On the other hand, meta-regression did not identify any possible source of heterogeneity for ORR in LGG individuals (Table 5). Eight studies were included in the ORR meta-analysis comparing adults and pediatrics (Fig. 7). Our meta-analysis revealed that despite a higher ORR rate among pediatrics, the pooled ORR rate was not statistically different (Pediatrics: 53% [95% CI: 44 −61%] vs. Adults: 39% [95% CI: 26 −54%], $P=0.11$).

The meta-analysis of CBR resulted in a pooled CBR rate of 82% (95% CI: 71- 90%) (Fig. 8). The pooled CBR was 75% (95% CI: 61- 85%) and 90% (95% CI: 78- 96%) in HGG and LGG, respectively; however, the difference was not significant ($P=0.05$). The meta-regression demonstrated that the presence of BRAF V600 mutation ($P=0.0094$), longer treatment duration ($P=0.0162$), and history of prior resection ($P=0.023$) were associated with a higher CBR in HGGs (Table 4). On the other hand, meta-regression did not identify any possible source of heterogeneity for CBR in LGG individuals (Table 5). Eight studies were included in the CBR meta-analysis, comparing adults and pediatrics (Fig. 9). Our meta-analysis revealed that despite a higher CBR rate among pediatrics, the pooled CBR rate was not statistically different (Pediatrics: 87% [95% CI: 72 −95%] vs. Adults: 73% [95% CI: 54 −86%], $P=0.16$).

Meta-analysis of clinical outcomes

Five studies were included in the meta-analysis of 6-month PFS (Supplementary Fig. S1). The meta-analysis revealed a pooled 6-month PFS rate of 74% (95% CI: 53- 88%) and the PFS-6 was significantly higher among LGG individuals compared to the HGG patients (HGG: 64% [95% CI: 51- 76%] vs. LGG: 88% [95% CI: 78- 94%], $P<0.01$) (Supplementary Fig. S1). Six studies were included in the meta-analysis of 1-year PFS (Supplementary Fig. S2). The meta-analysis revealed a pooled 1-year PFS rate of 63% (95% CI: 45- 79%) and the 1-year PFS was significantly higher among LGG individuals compared to the HGG patients (HGG: 46% [95% CI: 34- 60%] vs. LGG: 73% [95% CI: 58- 84%], $P=0.01$) (Supplementary Fig. S2).

Table 2 Baseline characteristics

Author	Year	Study Design	Country	Adult Vs. Pediatric	LGG Vs. HGG	Total pts	Gender	Age	BRAF V600 status	Dabrafenib dose	Trametinib dose	Duration	Prior surgery
Rosenberg et al.	2022	Retrospective	USA	Ped	HGG	11	NA	10.7	11	NA	NA	25	11
Bouffet et al.	2023	Prospective	Canada	Ped	LGG	73	M: 29, F: 44,	10	70	two equal doses per day (< 12 years of age: 5.25 mg/kg/d; ≥12 years of age: 4.5 mg/kg/d	< 6 years of age, 0.032 mg per kilogram; ≥ 6 years, 0.025 mg per kilogram	NA	None
Shimoi et al.	2024	Prospective	Japan	NA	HGG	12	NA	NA	12	150 mg twice daily	2 mg once daily	NA	NA
Lim-Fat et al.	2021	Retrospective	USA	Adult	HGG	5	NA	41	5	150 mg twice daily	2 mg once daily	NA	NA
Padovan et al.	2023	Retrospective	Italy	Adult	HGG	9	NA	NA	NA	NA	NA	NA	NA
Subbiah et al. - LGG	2023	Prospective	USA	Adult	LGG	13	M: 4, F: 9,	33.1	8	150 mg twice daily	2 mg once daily	12.5	12
Subbiah et al. - HGG	2023	Prospective	USA	Adult	HGG	45	M: 23, F: 22,	41.9	42	150 mg twice daily	2 mg once daily	12.5	42
Bouffet et al.	2022	Prospective	Canada	Ped	LGG	36	M: 18, F: 18,	10	36	age < 12 years, 5.25 mg/kg; age > 12 years, 4.5 mg/kg, capsule or oral suspension divided into two equal doses daily	(0.025 mg/kg once daily and 0.032 mg/kg once daily	24	30
Berzero 2021	2021	Retrospective	France	Adult	HGG	10	NA	NA	10	150 mg twice daily	2 mg once daily	NA	NA
Hargrave 2023	2023	Prospective	UK	Ped	HGG	41	M: 18, F: 23,	13	41	5.25 mg/kg/d for patients younger than 12 years; 4.5 mg/kg/d for patients age 12 years and older	0.032 mg/kg/d for patients younger than 6 years; 0.025 mg/kg/d for patients age 6 years and older	16.7	40

LGG: Low-grade glioma, HGG: High-grade glioma, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate, CBR: Clinical benefit rate, PFS: Progression-free survival, OS: Overall survival, AE: Adverse event

Table 3 Clinical and radiological outcomes

Author	Median PFS	PFS	Median OS	OS	Response	AE	AE leading to disc.
Rosenberg et al.	34.00	PFS-6: 100%, PFS-12:100%, PFS-24: 100%	28.00	OS-6: 91%, OS-12: 91%, OS-24: 82%	CR: 25%, PR: 38%, SD: 38%, PD: 0%, ORR: 63%, DC: 100%	56%	33%
Bouffet et al.	20.10	PFS-6: 88%, PFS-12: 67%, PFS-24: 40%	NA	OS-6: 100%, OS-12: 100%, OS-24: 100%	CR: 3%, PR: 44%, SD: 41%, PD: 11%, ORR: 47%, DC: 86%	100%	4%
Shimoi et al.	NA	NA	NA	NA	CR: 0%, PR: 33%, SD: 67%, PD: 0%, ORR: 33%, DC: 100%	NA	NA
Lim-Fat et al.	6.60	PFS-6: 80%, PFS-12: 80%, PFS-24: 80%	31.15	OS-6: 100%, OS-12: 100%, OS-24:100%	CR: 0%, PR: 60%, SD: 20%, PD: 20%, ORR: 60%, DC: 80%	40%	NA
Padovan et al.	5.23	PFS-6: 44%, PFS-12: 33%, PFS-24: 11%	NA	NA	CR: 11%, PR: 11%, SD: 44%, PD: 33%, ORR: 22%, DC: 78%	NA	NA
Subbiah et al. - LGG	9.20	NA	NA	NA	CR: 9%, PR: 55%, SD: 27%, PD: 9%, ORR: 64%, DC: 91%	92%	NA
Subbiah et al. - HGG	4.50	NA	17.60	NA	CR: 7%, PR: 27%, SD: 22%, PD: 44%, ORR: 33%, DC: 56%	93%	NA
Bouffet et al.	36.90	PFS-12: 81%, PFS-24: 81%	NA	NA	CR: 9%, PR: 46%, SD: 43%, PD: 3%, ORR: 54%, DC: 97%	100%	22%
Berzero 2021	NA	NA	NA	NA	SD: 50%, PD: 20%, ORR: 30%, DC: 80%	NA	NA
Hargrave 2023	9.00	PFS-6: 66%, PFS-12: 44%	32.80	OS-12: 76%, OS-24: 59%	CR: 25%, PR: 35%, SD: 18%, PD: 23%, ORR: 60%, DC: 75%	100%	5%

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate, CBR: Clinical benefit rate, PFS: Progression-free survival, OS: Overall survival, AE: Adverse event

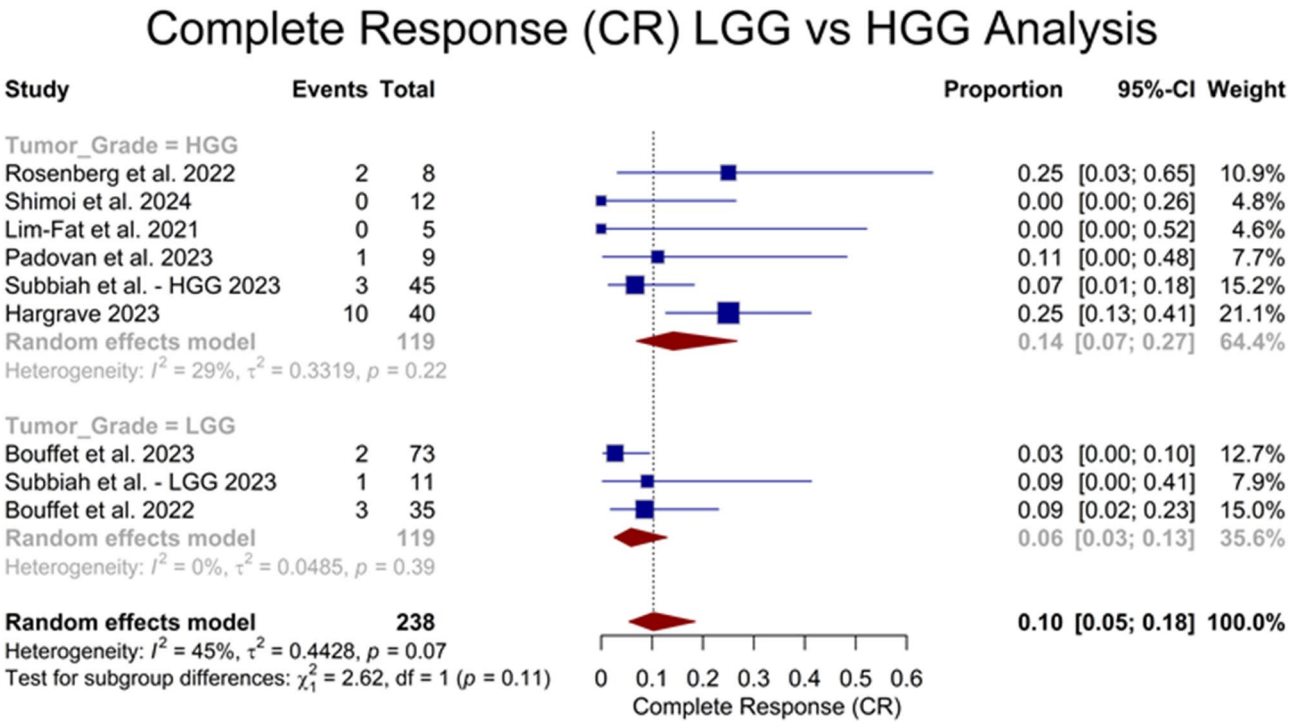

Fig. 2 Proportion meta-analysis of the complete response rate

Three studies were included in a meta-analysis of the six-month OS (Supplementary Fig. S3). The meta-analysis revealed a pooled 6-month OS rate of 95% (95% CI: 80- 99%), and despite a higher 6-month OS rate among LGG individuals, the difference was not statistically significant (HGG: 91% [95% CI: 64- 98%] vs. LGG: 100% [95% CI: 95- 100%], P=0.10). Four studies were included in a meta-analysis of the 1-year OS (Supplementary Fig. S4). The meta-analysis revealed a pooled 1-year OS rate of 91% (95% CI: 68- 98%), and despite a higher 1-year

Table 4 Meta-regression of dual blockage by dabrafenib and trametinib among HGG

Treatment Effect	Moderator	No. of Studies	Estimate	SE	*P* value	R2	I2	Tau2
CR	Age	4	-0.0515	0.0221	**0.0199**	100	0	0
CR	BRAF V600 Status	5	20.6695	10.1486	**0.0417**	100	0	0
CR	Treatment Duration	3	0.111	0.1096	0.3111	9.5142	65.0116	0.4378
CR	Prior Surgery	3	28.6035	13.6975	**0.0368**	100	0	0
PR	Age	4	-0.0086	0.015	0.5642	0	0.0001	0
PR	BRAF V600 Status	5	7.1363	6.3819	0.2635	0	0	0
PR	Treatment Duration	3	0.0485	0.0619	0.4329	0	0	0
PR	Prior Surgery	3	8.4943	9.3415	0.3632	0	0	0
SD	Age	4	-0.0003	0.0175	0.987	0	2.6978	0.0127
SD	BRAF V600 Status	6	10.9078	14.703	0.4582	0	60.4055	0.6176
SD	Treatment Duration	3	0.0459	0.0643	0.475	0	3.1028	0.006
SD	Prior Surgery	3	4.812	12.7815	0.7066	0	31.4209	0.1208
PD	Age	4	0.0364	0.0161	**0.024**	99.9995	0.0002	0
PD	BRAF V600 Status	6	-18.2044	6.4835	**0.005**	100	0	0
PD	Treatment Duration	3	-0.2257	0.0877	**0.0101**	100	0	0
PD	Prior Surgery	3	-26.6327	10.6444	**0.0123**	100	0	0
ORR	Age	4	-0.0344	0.0144	**0.0166**	100	0	0
ORR	BRAF V600 Status	6	10.6762	8.3711	0.2022	39.586	24.9625	0.1187
ORR	Treatment Duration	3	0.1027	0.0791	0.1946	48.3289	56.7265	0.1759
ORR	Prior Surgery	3	22.6261	8.9916	**0.0119**	100	0	0
CBR	Age	4	-0.0318	0.0183	0.0821	86.1455	4.7381	0.0413
CBR	BRAF V600 Status	6	16.6273	6.4017	**0.0094**	100	0	0
CBR	Treatment Duration	3	0.2086	0.0868	**0.0162**	100	0	0
CBR	Prior Surgery	3	23.7838	10.4615	**0.023**	100	0	0
Any AE	Age	4	-0.0238	0.0864	0.7832	0	87.5185	5.7666
Any AE	BRAF V600 Status	4	-21.5952	39.7629	0.5871	0	84.075	4.7449
Any AE	Treatment Duration	3	-0.2251	0.2027	0.2667	9.4594	66.7607	2.8856
Any AE	Prior Surgery	3	-28.6431	51.7421	0.5799	0	79.46	5.6741

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate, CBR: Clinical Befit rate, AE: Adverse event

OS rate among LGG individuals, the difference was not statistically significant (HGG: 80% [95% CI: 64- 89%] vs. LGG: 100% [95% CI: 95- 100%], $P=0.05$).

Meta-analysis of adverse event

Seven studies were included in the meta-analysis of any AE during the dual blockage treatment course (Fig. 10). The meta-analysis revealed a pooled any AE rate of 92% (95% CI: 71- 98%) and despite higher pooled any AE rate among LGG patients, the difference was not statistically significant (HGG: 83% [95% CI: 39- 97%] vs. LGG: 98% [95% CI: 89- 100%], $P=0.11$) (Fig. 8). The meta-regression did not identify any possible source for any AE in HGG individuals; however, determined that history of prior surgical resection was associated with a lower any AE among LGG patients ($P=0.0053$) (Tables 4 and 5).

Four studies were included in the meta-analysis of discontinuation of the dual blockage treatment to AE during the treatment course (Fig. 11). The meta-analysis revealed a pooled discontinuation of the dual blockage treatment to AE rate of 12% (95% CI: 4- 31%) and despite lower pooled discontinuation of the dual blockage treatment to AE rate among LGG patients, the difference was not statistically significant (HGG: 14% [95% CI: 2- 60%] vs. LGG: 10% [95% CI: 2- 43%], $P=0.83$) (Fig. 9).

Sensitivity analysis

The leave-one-out sensitivity analysis was performed to evaluate the robustness of the meta-analysis results. The leave-one-out sensitivity analyses were independently evaluated for HGG and LGG. Some sensitivity analyses were not feasible as only one study was included in one arm. The CR in the HGG sensitivity meta-analysis demonstrated a moderate robustness of the pooled estimate, as the mission of Hargrave et al. considerably impacted the results (Supplementary Fig. S5). The sensitivity meta-analysis for PR and SD in HGG demonstrated a highly robust result, while PD in HGG was moderately robust as Subbiah et study had a considerable impact on the results (Supplementary Figs. S6-S8). The sensitivity analysis of ORR and CBR in HGG was moderately robust, as the studies of Hargrave et al. and Subbiah et al. moderately influenced the results, respectively (Supplementary Figs. S9-S10). The sensitivity analysis of 6-month PFS and 6-month OS in HGG demonstrated high robustness concurrent with moderate robustness for 1-year PFS and

Table 5 Meta-regression of dual blockage by dabrafenib and trametinib among LGG

Treatment Effect	Moderator	No. of Studies	Estimate	SE	*P*-value	R2	I2	Tau2
CR	Age	3	0.0261	0.0571	0.6474	0	39.2257	0.2836
CR	BRAF V600 Status	3	-1.2179	3.6902	0.7414	0	44.101	0.3565
CR	Treatment Duration	3	-0.0094	0.0919	0.9184	0	0	0
CR	Female	3	-1.5405	7.6485	0.8404	0	40.7061	0.4145
CR	Male	3	1.5405	7.6485	0.8404	0	40.7061	0.4145
CR	Prior Surgery	3	-0.4931	6.9259	0.9432	0	0	0
PR	Age	3	0.0175	0.0275	0.5237	0	0	0
PR	BRAF V600 Status	3	-1.0451	1.754	0.5513	0	0	0
PR	Treatment Duration	3	-0.0007	0.0527	0.9894	0	1.2466	0.0025
PR	Female	3	0.7827	3.1739	0.8052	0	0	0
PR	Male	3	-0.7827	3.1739	0.8052	0	0	0
PR	Prior Surgery	3	3.864	3.8397	0.3143	0	0	0
SD	Age	3	-0.0279	0.0305	0.3604	0	0	0
SD	BRAF V600 Status	3	1.8038	1.9375	0.3519	0	0	0
SD	Treatment Duration	3	0.0123	0.0725	0.8647	0	46.5846	0.2116
SD	Female	3	-2.2165	3.3066	0.5027	0	0	0
SD	Male	3	2.2165	3.3066	0.5027	0	0	0
SD	Prior Surgery	3	-5.8511	4.2303	0.1666	100	0	0
PD	Age	3	0.0086	0.0605	0.8877	0	42.9075	0.4396
PD	BRAF V600 Status	3	-0.9554	3.8471	0.8039	0	42.4176	0.3966
PD	Treatment Duration	3	-0.0374	0.095	0.6939	0	0	0
PD	Female	3	7.0094	7.5572	0.3537	0	0	0
PD	Male	3	-7.0094	7.5572	0.3537	0	0	0
PD	Prior Surgery	3	6.5123	8.7064	0.4545	0	0	0
ORR	Age	3	0.0258	0.0284	0.3628	0	0	0
ORR	BRAF V600 Status	3	-1.3745	1.8079	0.4471	0	0	0
ORR	Treatment Duration	3	-0.0046	0.0544	0.933	0	0	0
ORR	Female	3	0.4082	3.7182	0.9126	0	27.8898	0.0495
ORR	Male	3	-0.4082	3.7182	0.9126	0	27.8898	0.0495
ORR	Prior Surgery	3	3.9054	3.9709	0.3254	0	0	0
CBR	Age	4	0.0065	0.0438	0.8821	0	28.828	0.3043
CBR	BRAF V600 Status	4	-0.0675	2.8805	0.9813	0	31.7779	0.3294
CBR	Treatment Duration	3	0.0374	0.095	0.6939	0	0	0
CBR	Female	4	-4.2628	7.0814	0.5472	0	29.7485	0.2312
CBR	Male	4	4.2628	7.0814	0.5472	0	29.7485	0.2312
CBR	Prior Surgery	3	-6.5123	8.7064	0.4545	0	0	0
Any AE	Age	3	-0.0934	0.0626	0.1361	100	0	0
Any AE	BRAF V600 Status	3	5.7745	3.962	0.145	100	0	0
Any AE	Treatment Duration	3	-0.0749	0.2299	0.7446	0	79.9604	5.4959
Any AE	Female	3	-10.5295	9.1164	0.2481	98.8026	0.2971	0.0055
Any AE	Male	3	10.5295	9.1164	0.2481	98.8026	0.2971	0.0055
Any AE	Prior Surgery	3	-23.6363	8.4701	**0.0053**	100	0	0

CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate, CBR: Clinical Befit rate, AE: Adverse event

1-year OS (Supplementary Figs. S11-S14). The sensitivity analysis of any AE in HGG was moderately robust, as the studies of Subbiah et al. moderately influenced the results (Supplementary Fig. S15).

The sensitivity analysis for CR in LGG was moderately robust, as the omission of the study by Subbiah et al. had a moderate impact on the results (Supplementary Fig. S16). The sensitivity analysis of the PR and SD in LGG demonstrated highly robust results, and the PD was moderately robust (Supplementary Fig. S17-S19). The ORR and CBR sensitivity analyses in LGG were highly and moderately robust, respectively (Supplementary Fig. S20-S21). The sensitivity analysis of the 1-year PFS in LGG was moderately robust (Supplementary Fig. S22). The sensitivity analysis of any AE and discontinuation due to AE demonstrate a moderate robustness of the results (Supplementary Figs. S23-S24).

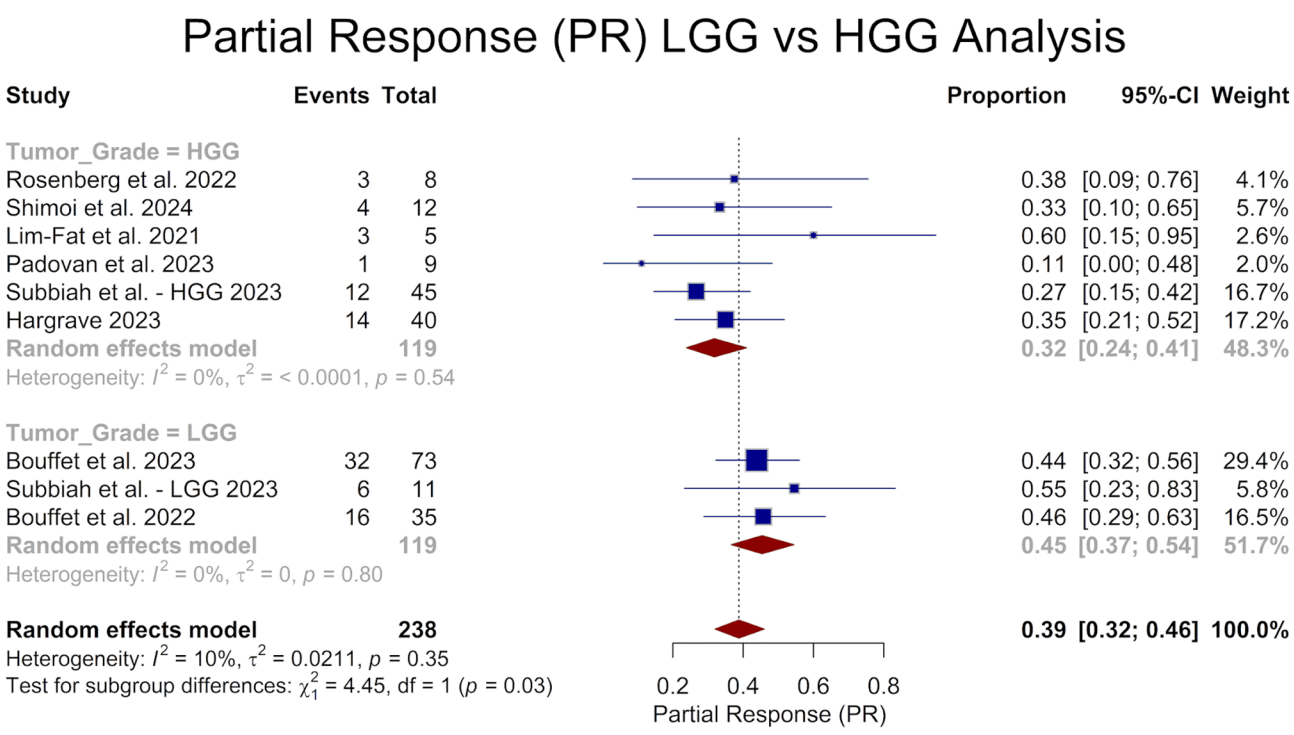

Fig. 3 Proportion meta-analysis of the partial response rate

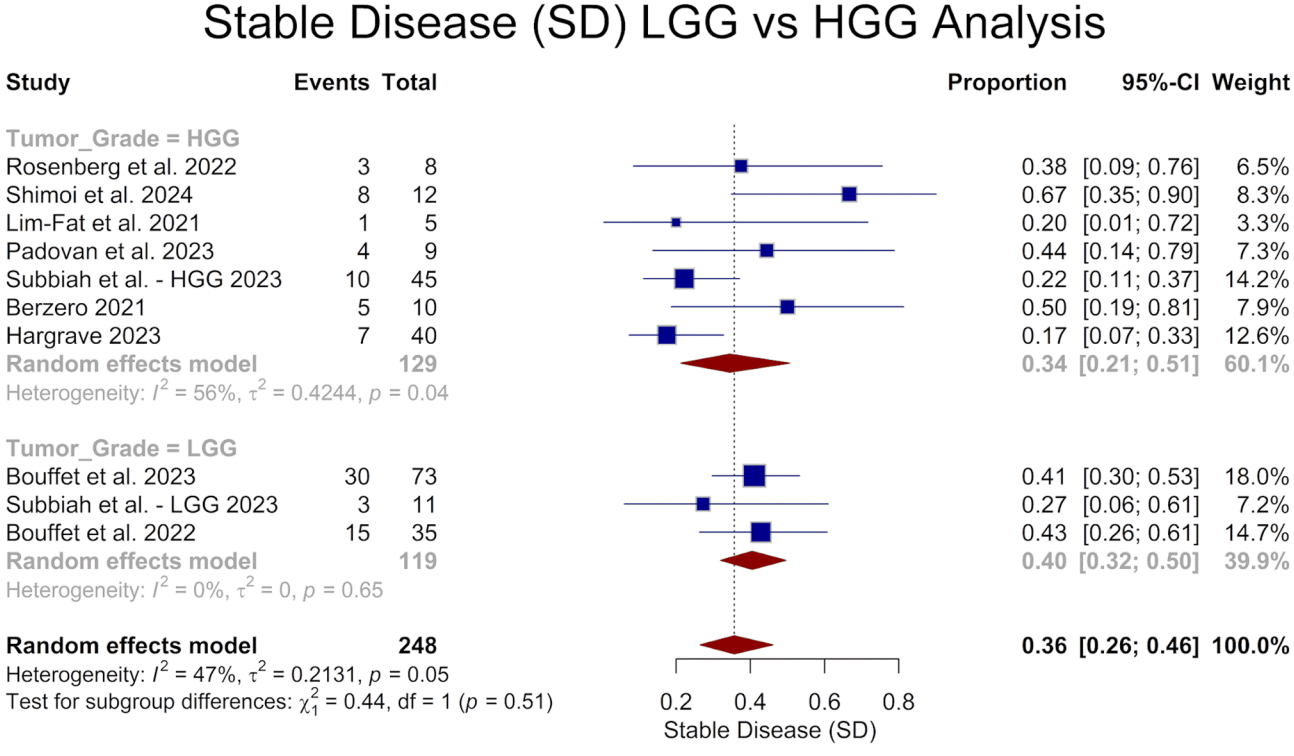

Fig. 4 Proportion meta-analysis of the stable disease rate

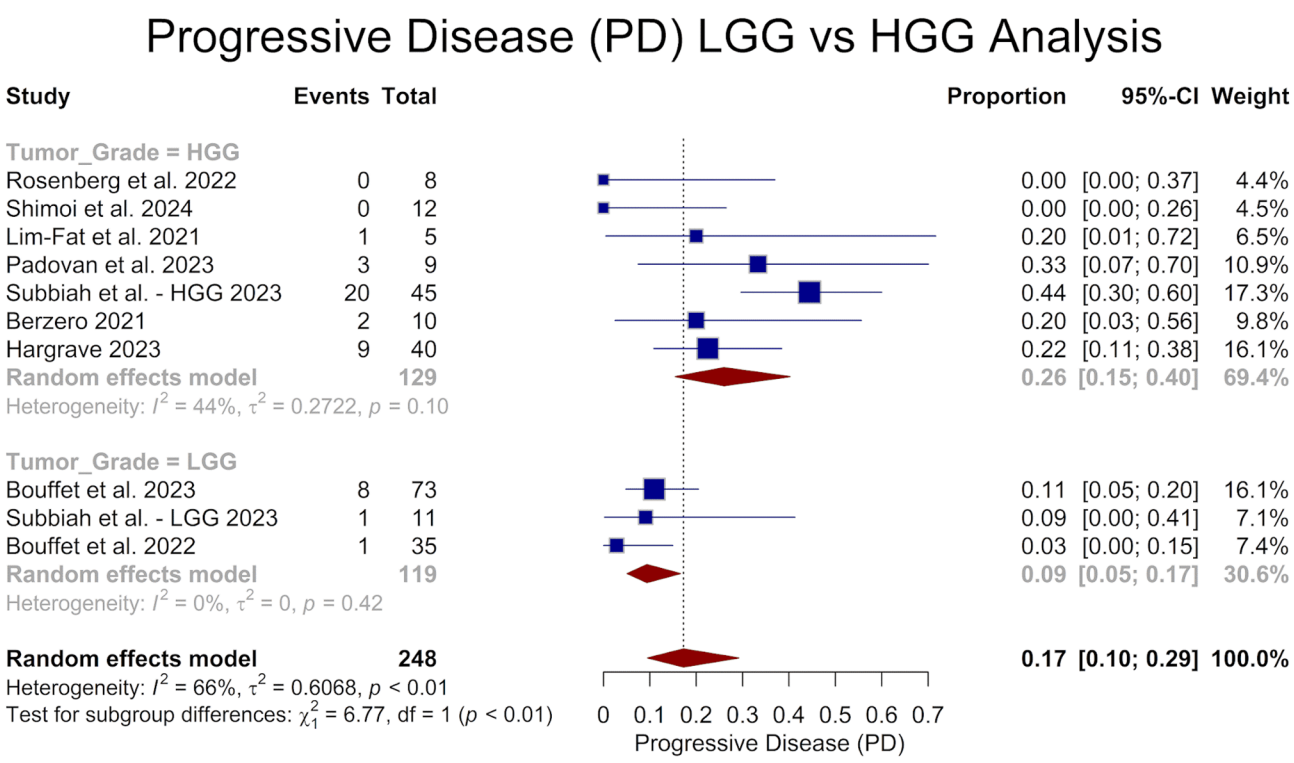

Fig. 5 Proportion meta-analysis of the progressive disease rate

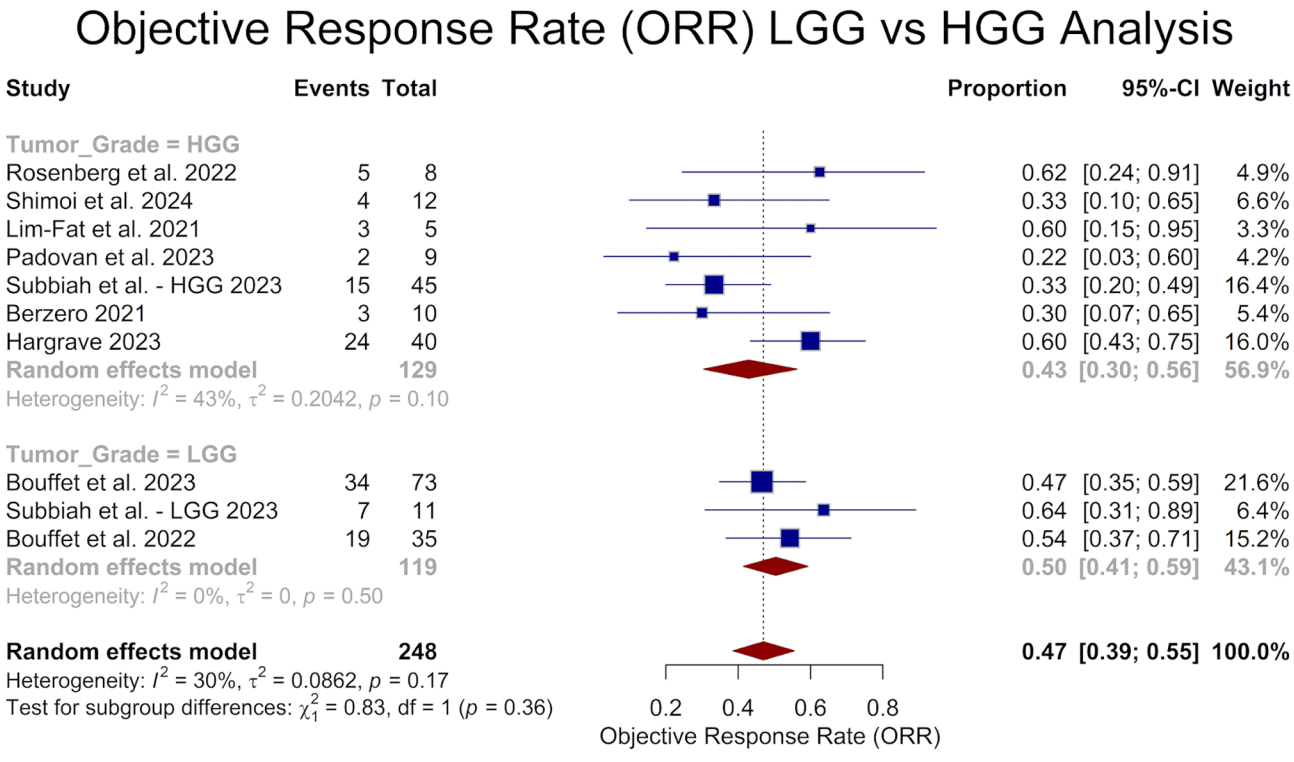

Fig. 6 Proportion meta-analysis of the objective response rate

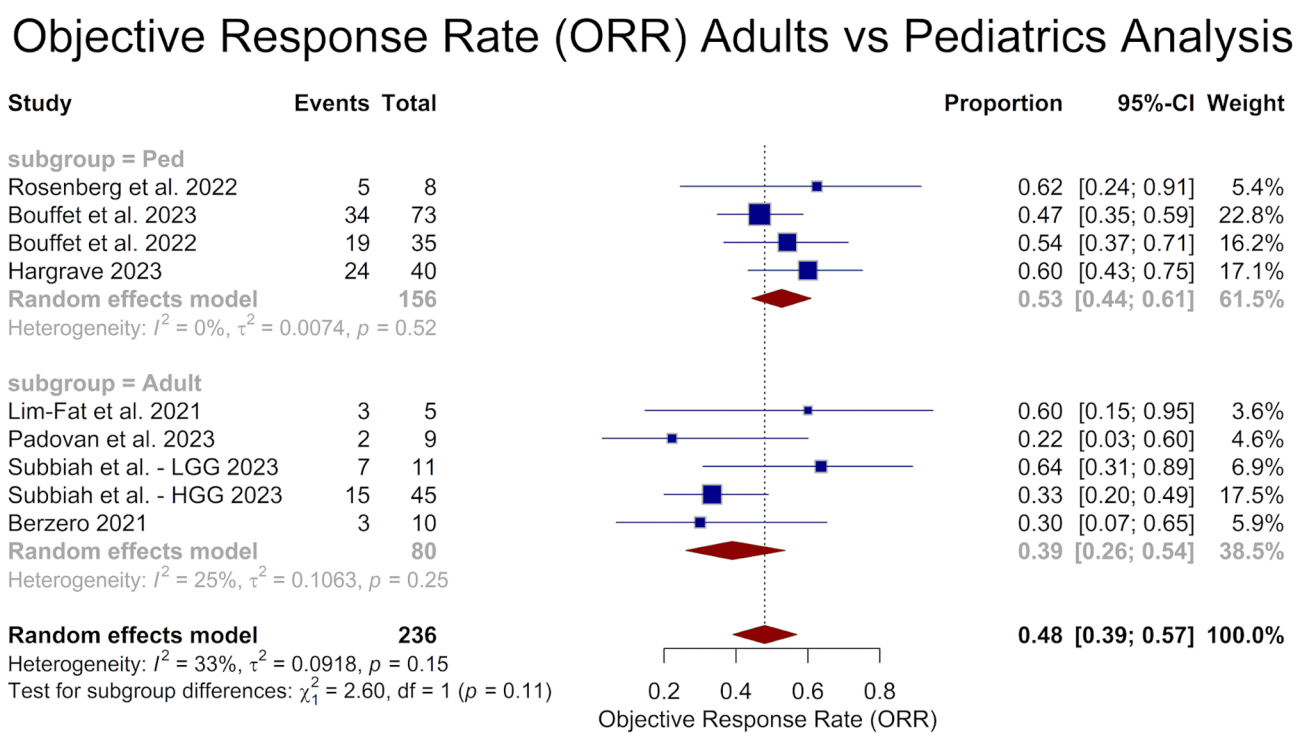

Fig. 7 Subgroup meta-analysis of the objective response rate following application of dabrafenib plus trametinib in pediatrics and adults with glioma

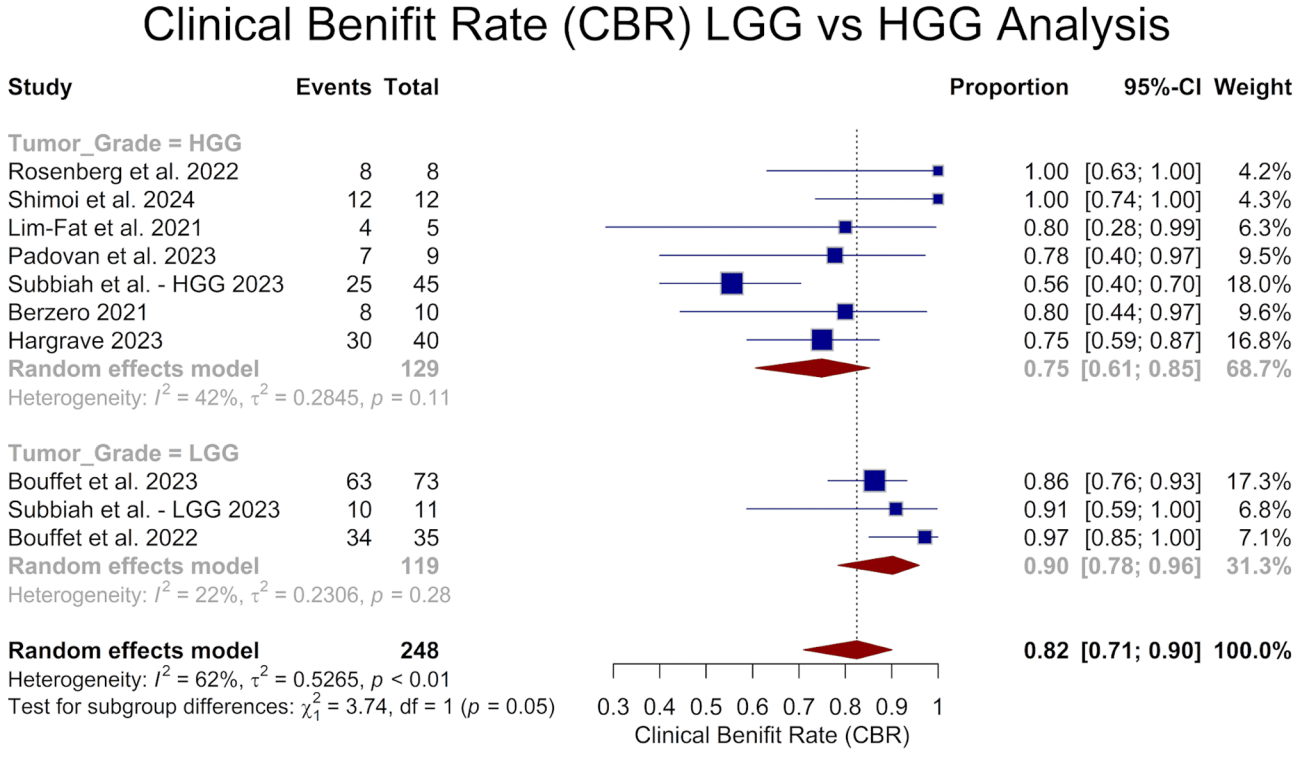

Fig. 8 Proportion meta-analysis of the objective response rate

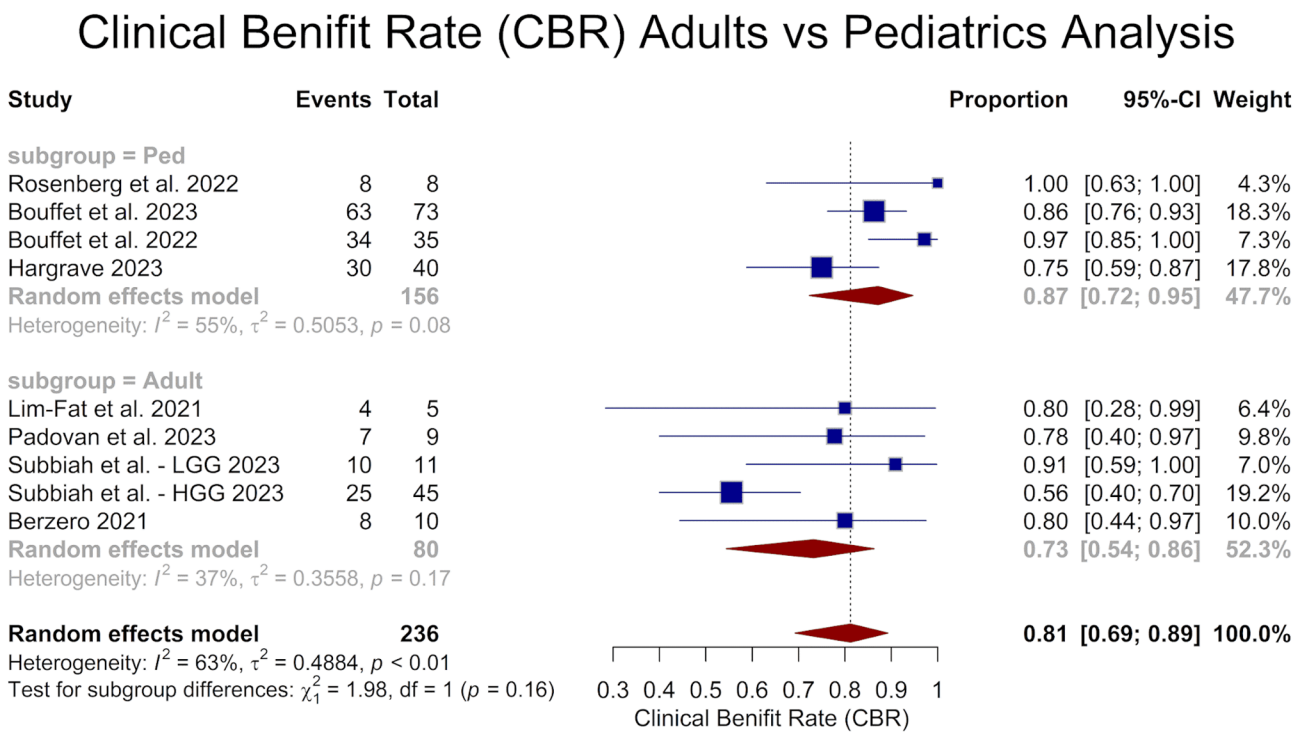

Fig. 9 Subgroup meta-analysis of the clinical benefit rate following application of dabrafenib plus trametinib in pediatrics and adults with glioma

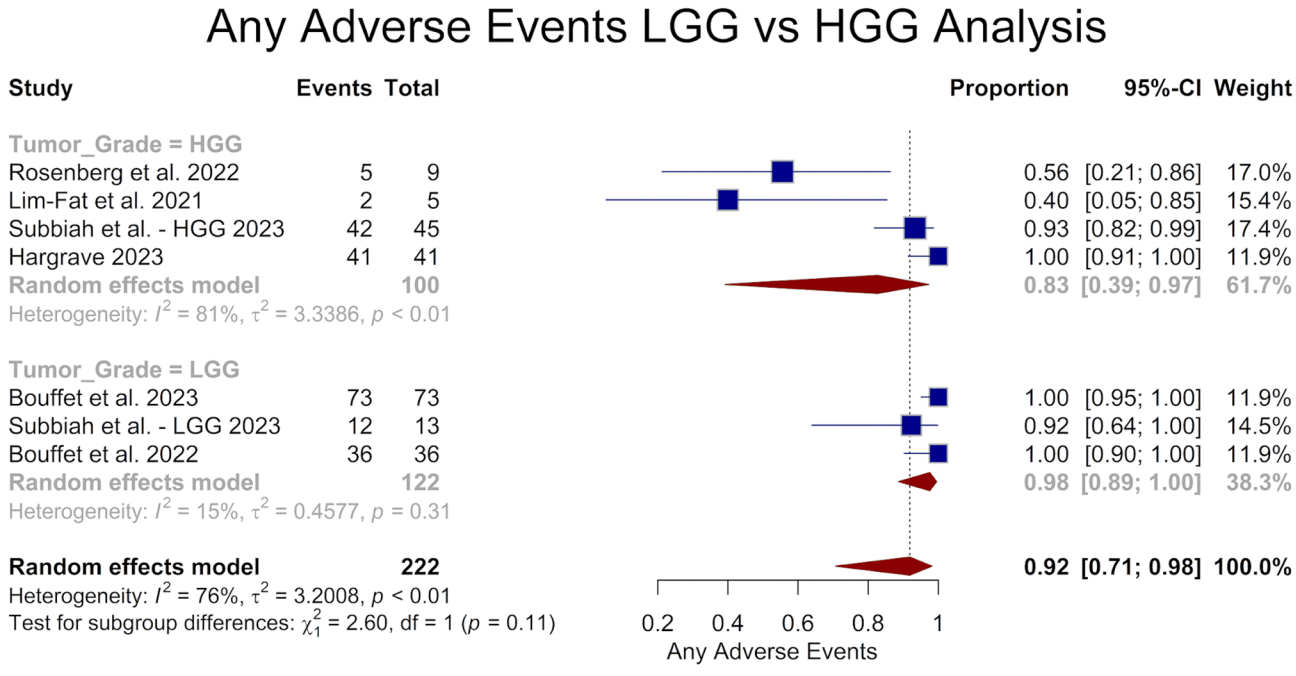

Fig. 10 Proportion meta-analysis of any adverse event

Publication Bias

The publication bias of the results was assessed through a combination of a funnel plot, Egger's test, and trim-and-fill analysis. Outcomes with more than two included studies were evaluated. Regarding the HGG, all of the results had a low likelihood and publication bias with a symmetrical distribution of the funnel plot concurrent with Egger's test was associated with $P>0.05$ except PD and CBR, which had an asymmetrical funnel plot pattern and Egger's test with a $P<0.05$; however, the trim-and-fill analysis was indicative of moderately robust results despite the publication bias for both (Supplementary

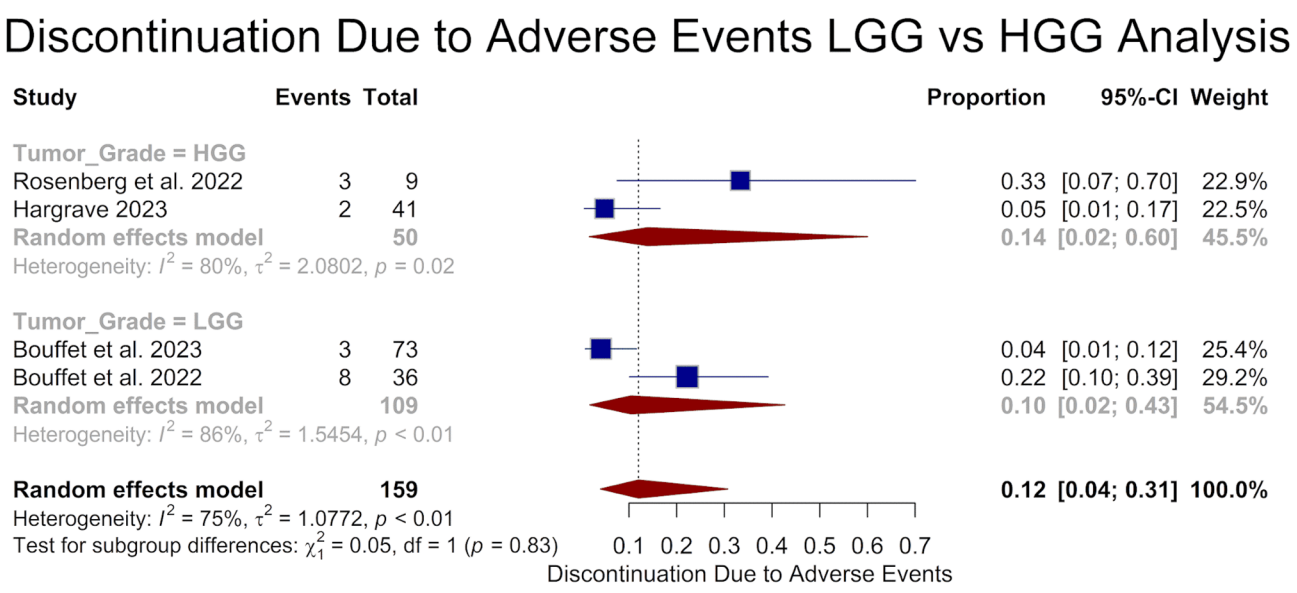

Fig. 11 Proportion meta-analysis of discontinuation of dual blockage therapy adverse event

Table 6 Summary of the meta-analysis findings

Outcome	Overall	LGG	HGG	*P*-value
CR	10% (95% CI: 5—18%)	6% (95% CI: 3- 13%)	14% (95% CI: 7- 27%)	0.11
PR	39% (95% CI: 32- 46%)	45% (95% CI: 37- 54%)	32% (95% CI: 24- 41%)	0.03
SD	36% (95% CI: 26-46%)	40% (95% CI: 32- 50%)	34% (95% CI: 21- 51%)	0.51
PD	17% (95% CI: 10- 29%)	9% (95% CI: 5- 17%)	26% (95% CI: 15- 40%)	< 0.01
ORR	47% (95% CI: 39- 55%)	50% (95% CI: 41- 59%)	43% (95% CI: 30- 56%)	0.36
CBR	82% (95% CI: 71- 90%)	90% (95% CI: 78- 96%)	75% (95% CI: 61- 85%)	0.05
6-month PFS	74% (95% CI: 53- 88%)	88% (95% CI: 78- 94%)	64% (95% CI: 51- 76%)	< 0.01
1-year PFS	63% (95% CI: 45- 79%)	73% (95% CI: 58- 84%)	46% (95% CI: 34- 60%)	0.01
6-month OS	95% (95% CI: 80- 99%)	100% (95% CI: 95- 100%)	91% (95% CI: 64- 98%)	0.10
1-year OS	of 91% (95% CI: 68- 98%)	80% (95% CI: 64- 89%)	100% (95% CI: 95- 100%)	0.05
Any AE	92% (95% CI: 71- 98%)	98% (95% CI: 89- 100%)	83% (95% CI: 39- 97%)	0.11
Discontinuation due to AE	12% (95% CI: 4- 31%)	10% (95% CI: 2- 43%)	14% (95% CI: 2- 60%)	0.83

LGG: Low-grade glioma, HGG: High-grade glioma, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Objective response rate, CBR: Clinical benefit rate, PFS: Progression-free survival, OS: Overall survival, AE: Adverse event

Figs. S25-S36). Regarding the LGG, all outcomes were associated with a symmetrical distribution of funnel plot and Egger's test with $P>0.05$ (Supplementary Figs. S37-S44).

Discussion

Our systematic review and meta-analysis demonstrated that dual blockage by dabrafenib and trametinib is associated with favorable clinical and radiological outcomes concurrent with low-rate discontinuation due to AE (Table 6). Our data showed that dual blockade in gliomas resulted in a pooled CR rate of 10%, PR rate of 39%, SD rate of 36%, and PD rate of 17%. Regarding the independent radiological outcomes in LGG and HGG, the PR was significantly higher in LGG ($P=0.03$), and PD was substantially lower in LGG ($P<0.01$). Notably, LGGs possess a lower invasive nature and slower progression than HGGs; therefore, therapeutic options like dual blockage are typically associated with better outcomes. In addition, the meta-regression demonstrated that lower age, BRAF V600 mutation, longer dual blockage treatment duration, and history of prior resection were associated with more favorable outcomes in HGGs.

Our results demonstrated a pooled ORR rate of 47%, and despite LGG's higher pooled ORR rate compared to HGG, the difference was insignificant ($P=0.36$). The meta-analysis showed a pooled CBR rate of 82% with an insignificant difference between LGG and HGG ($P=0.05$). The meta-regression demonstrated lower age, prior resection history, BRAF V600 mutation, and longer treatment duration were associated with higher ORR and CBR in HGGs.

Regarding the AE during the treatment course, our meta-analysis revealed a pooled AE rate of 92%, and the

difference was not statistically significant between LGG and HGG ($P=0.11$). In addition, our analysis demonstrated a pooled discontinuation of the dual blockage treatment to AEs rate of 12%.

Our result was consistent with prior systematic reviews and meta-analyses [5, 6]. Habibi et al. demonstrated a pooled ORR rate of 45%, a CR rate of 5%, a PR rate of 35%, an SD rate of 37%, and a PD rate of 18% [6]. Lei et al. demonstrated a pooled PFS of 6.10 months and a PFS rate of 79% with a CR rate of 18%, a PR rate of 30%, and an ORR rate of 39% [5].

The dual blockage treatment through a joint administration of Dabrafenib and Trametinib has emerged as a potential treatment option for gliomas, especially those with BRAF mutation [6]. This dual blockade treatment inhibits the atypical growth signals leading to cancer proliferation [6]. Recently, the dual blockage treatment has been extensively utilized in LGG and HGGs.

In the LGG setting, Bouffet et al. utilized dabrafenib and trametinib in pediatrics with BRAF V600-Mutant LGG [8]. They demonstrated that dual blockage therapy led to CR, PR, and SD rates of 9%, 46%, and 43%, respectively, and PD occurred in 3% of the patients [8]. They demonstrated that 100% of patients had experienced any AE; 61.1% were grade ≥ 3 [8]. AE led to dose reduction in 30.6%, dose interruption in 72.2%, and discontinuation in 22.2% of patients; however, none were associated with mortality [8]. Subbiah et al. administered dual blockage therapy, dabrafenib 150 mg twice daily and trametinib 2 mg once daily, in 13 adult patients with LGG [7]. They demonstrated a CR, PR, and SD rate of 9%, 55%, and 27% concurrent with a 9% PD rate [7]. They demonstrated that AE occurred in 92.3% of participants [7]. Bouffet et al., in a phase 2 randomized trial, administered dual blockage treatment in 73 pediatric individuals with BRAF V600 LGG [10]. They demonstrated that dabrafenib plus trametinib is associated with CR, PR, and SD rates of 3%, 44%, and 41%, respectively, while 11% experienced PD [10]. In their study, all individuals had experienced at least one AE that was higher than grade three in 47% of them [10]. The most common AE was pyrexia (68%), headache (47%), and vomiting (34%) [10].

The role of dual blockage therapy has been investigated extensively in HGGs. Rosenberg et al. in pediatric patients with BRAF-mutant HGGs [13]. They demonstrated that administration of dabrafenib, 5.25 mg/kg in < 12 years old and 4.5 mg/kg in ≥ 12 years old twice a day, and trametinib 0.032 mg/kg in < six years old and 0.025 mg/kg in ≥ six years old once daily, resulted in a CR, PR, and SD rates of 25%, 38%, 38% of individuals, respectively and PD was not observed in any of participants [13]. Shimoi et al. utilized dual blockage therapy in 47 individuals with solid tumors with or without BRAF V600 mutation, including 12 HGGs [11]. For HGGs, they demonstrated that co-administration of dabrafenib 150 mg twice daily and trametinib 2 mg once daily led to a CR, PR, and SD rate of 0%, 33%, and 67%, while none of the patients experienced PD [11]. Lim-Fat et al. evaluated the role of targeted therapies in 19 individuals with BRAF V600 mutant glioblastoma, where five received a combination therapy of dabrafenib and trametinib [14]. Of five patients, none experienced CR, 60% encountered PR, 20% had SD, and PD occurred in one patient [14]. Padovan et al. demonstrated a CR and PR rate of 11% concurrent with 44% SD and 33% PD in individuals with isocitrate dehydrogenase (IDH) wild-type glioblastoma [15]. Subbiah et al. evaluated the role of dual blockage in 45 individuals with HGG [7]. In their study, dabrafenib plus trametinib was associated with a CR rate of 7%, PR rate of 27%, SD rate of 22%, and PD rate of 44% [7]. Regarding AE, 93.3% of HGG patients experienced AE during treatment [7]. Hargrave et al., in a phase II trial, evaluated the efficacy and safety of dabrafenib plus trametinib in pediatrics with BRAF V600-mutant HGGs [12]. In their study, the dual blockage intervention resulted in an ORR rate of 60% and a CBR rate of 75% [8]. Berzero et al. demonstrated that dual blockage therapy was associated with ORR and CBR rates of 30% and 80%, respectively, while PD occurred in 20% of participants [9].

Study limitations

Our study has several noteworthy limitations. The relatively low number of included studies and patients may impact the power of the statistical analysis and its generalizability. The mixture of both retrospective and prospective studies could establish biases related to patient selection and outcome measurement that may affect the robustness of the results. In addition, some of the outcomes were associated with a moderate publication bias that can skew the outcomes toward favorable outcomes. Another limitation is that the differences in the clinical behavior of LGGs and HGGs may impact our findings, as the prognosis of the LGGs tends to be better than HGGs.

Conclusion

Our systematic review and meta-analysis highlighted the efficacy and safety of the dual blockade therapy through the co-administration of dabrafenib and trametinib in LGG and HGGs. Our results demonstrated that the dual blockage is associated with a favorable rate of CR, PR, SD, ORR, and CBR concurrent with a low rate of PD. The subgroup analysis revealed that individuals with LGG experience higher favorable radiological outcome rates, lower progression, and higher PFS and OS. Therefore, the co-administration of dabrafenib and trametinib is more efficient among LGGs than HGGs. We also demonstrated that dual blockage is associated with better outcomes among those with lower age, BRAF V600

mutation, longer dual blockage treatment duration, and history of prior resection in HGGs. Further randomized clinical trials with larger populations are required for more robust outcomes.

Abbreviations

LGG	Low-grade glioma
HGG	High-grade glioma
CR	Complete response
PR	Partial Response
SD	Stable disease
PD	Progressive disease
ORR	Overall response rate
CBR	Clinical benefit rate
WHO	World Health Organization
BRAF	B-Raf proto-oncogene serine/threonine-protein
MAPK	mitogen-activated protein kinase
MEK	MAPK kinase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PFS	Progression-free survival
OS	Overall survival
AE	Adverse event
ROB	Risk of bias
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions – 1
CI	Confidence interval
IDH	Isocitrate dehydrogenase

Supplementary Information

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Supplementary Material 1

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Author contributions
Conceptualization: B.H, S.M, Methodology: B.H, M.H, Software: B.H, A.Z, Validation: B.H, Formal Analysis: A.Z, Investigation: B.H, M.H, Resources: B.H, Data Curation: B.H, A.K, M.S.A, Writing – Original draft: B.H, A.H, M.Akh, R.T, Writing – Reviewing & Editing: B.H, M.H, S.M, Visualization: M.H.

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethical approval
The study is deemed exempt from receiving ethical approval.

Consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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