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The safety and efficacy of encorafenib plus binimetinib for brain metastases: a systematic review and meta-analysis

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Abstract

Purpose Brain metastases (BMs) present a significant therapeutic challenge due to limited blood-brain barrier permeability, which restricts the efficacy of systemic treatments. To address this, we systematically evaluated the effectiveness and safety of encorafenib plus binimetinib in patients with BMs.

Methods We conducted a systematic literature search from inception to January 2025 to assess the intracranial efficacy of encorafenib in combination with binimetinib. Studies reporting related outcomes were included.

Results Four studies, encompassing 1,789 patients with 472 BMs, were included. The pooled intracranial overall response rate (ORR) was approximately 48% with substantial variability across studies. Additionally, about 29% of patients achieved stable disease (SD). Meta-regression suggested that sex, performance status, number of brain lesions, and prior treatments may influence treatment response.

Conclusion Encorafenib plus binimetinib has demonstrated promising outcomes in the setting of BMs. Given the limitations of the available data, further prospective and controlled studies are required to validate our findings and identify the optimal patient population.

Keywords Brain metastases, Encorafenib, Binimetinib, BRAF mutation, Meta-analysis

1 Introduction

Brain metastases (BMs) are a challenging entity in the management of cancer patients, which occurs in approximately 10%–20% of adults with cancer [1]. Although lung, breast, and melanoma malignancies are the most frequent origins of BMs, any cancer type can metastasize to the brain parenchyma [2]. Despite advances in therapeutic options for brain metastases, they are still associated with a dismal prognosis, as management remains challenging due to the limited effectiveness of systemic therapies, variations in primary tumor types, and the restrictive nature of the blood-brain barrier [3, 4]. The primary objective of medical interventions for BMs is to prevent tumor growth

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and alleviate neurological symptoms, ultimately enhancing both quality of life and overall survival (OS) [5].

Targeted therapies combining a B-Raf proto-oncogene serine/threonine kinase (BRAF) inhibitor and a mitogen-activated protein kinase (MEK) inhibitor have demonstrated effectiveness against BRAF V600-mutant cancers, including metastatic melanoma [6–10]. The BRAF V600E mutation causes continuous activation of the BRAF protein, which persistently stimulates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway. This promotes uncontrolled cell growth and survival, driving cancer development. Although BRAF inhibitors can block this pathway, using them alone often leads to resistance, as the MAPK pathway may be reactivated through alternative mechanisms [11–13]. Combining BRAF and MEK1/MEK2 inhibitors delays the development of resistance and reduces the incidence of secondary malignancies. BRAF inhibitors specifically block the active BRAF V600 mutant, while MEK inhibitors stop downstream ERK signaling. Encorafenib plus Binimetinib, in particular, offers a favorable safety profile and potent pathway inhibition compared with other BRAF/MEK combinations, making it an attractive option for clinical evaluation. This dual pathway suppression reduces adaptive resistance, improves the durability of the treatment response, and lowers the risk of secondary tumors seen with BRAF monotherapy [14].

Several studies have investigated the efficacy and safety of the combination therapy of Encorafenib plus Binimetinib in the management of BMs [15, 16]. While the systemic benefits of Encorafenib plus Binimetinib are well-established, their effectiveness in BMs is under investigation. This study aims to evaluate the efficacy and safety of Encorafenib plus Binimetinib in metastatic brain tumors, focusing on tumor control, neurological outcomes, and overall survival (OS).

2 Methods

2.1 Objective

This systematic review and meta-analysis were designed to investigate the therapeutic effectiveness and safety profile of encorafenib plus binimetinib combination therapy in patients with metastatic brain tumors. The study design adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure standardized reporting [17].

2.2 Search strategy

On January 1, 2025, a systematic search was conducted across PubMed, Embase, Scopus, and Web of Science. The search utilized syntax independently prepared for each database, featuring the keywords “Encorafenib” AND “Binimetinib” AND “metastatic brain tumors” and their related terms (Supplementary Table S1). No additional filters were applied for the search.

2.3 Eligibility criteria

The inclusion criteria were as follows:

1. Patients with BMs who received combined encorafenib plus binimetinib.

2. Studies reported the radiological outcomes, such as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), or clinical outcomes in at least five patients.

The exclusion criteria were as follows:

1. Inability to separate the outcomes of BMs from other entities.
2. Inability to separate the outcomes related to encorafenib plus binimetinib from other modalities.
3. Case reports, case series < 5 patients, review articles, book chapter, conference abstract, letter to the editor.
4. Studies in languages other than English.
5. Studies with overlapping populations.

2.4 Study selection process

The search results were imported into the Covidence Software to conduct the screening process. Covidence automatically identified and omitted duplicates. Two independent reviewers screened the studies, evaluating both the titles and abstracts, as well as the full-text content. A third reviewer resolved any conflicts. Studies that met the inclusion criteria were selected for data extraction.

2.5 Data extraction

Two independent reviewers conducted data extraction with precision, using a standardized Microsoft Excel data sheet prepared by one of the authors. The extracted data included general study information, patient demographics, tumor characteristics, and prior treatments.

2.6 Risk of bias assessment

The risk of bias for each included study was assessed using the appropriate Cochrane tools, based on the study design. The Cochrane Risk of Bias 2 (RoB 2) tool was applied to randomized controlled trials (RCTs), evaluating five key domains: randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported result [18]. For non-randomized studies, the ROBINS-I tool was used, which assesses risk across seven domains, including confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and reporting bias [19]. Each study's design and methodology were reviewed, and risk levels were judged accordingly using the standardized domains of each tool (Supplementary Table S3).

2.7 Statistical analysis

The appropriate effect size was selected according to the Cochrane Handbook [20]. Clinical and radiological outcomes were pooled and reported as incidence rates. Heterogeneity among studies was assessed using the Chi-square P-value and the I^2 statistic. A Chi-square P-value of less than 0.05 indicated significant heterogeneity, while the I^2 value was used to quantify its extent [20]. A sensitivity analysis employing a leave-one-out method was conducted to evaluate the robustness of the results. Subgroup analyses and meta-regression were performed based on sex, Eastern Cooperative Oncology

Group (ECOG) performance status, number of lesions, prior treatments, and age to assess the influence of these variables and explore potential sources of heterogeneity (Supplementary Table S2). Publication bias across studies was assessed using Egger's regression test. All statistical analyses were conducted using STATA version 17.

3 Results

3.1 Study selection process

Our systematic search yielded 434 relevant studies across four electronic databases. After excluding 200 duplicates, 234 studies remained. During the title and abstract screening, 227 studies were excluded and deemed ineligible at the screening and eligibility assessment steps. We then obtained and evaluated seven full-text papers, excluding three studies due to the lack of full-text availability. Ultimately, four studies were deemed eligible and included in the review and meta-analysis (Fig. 1).

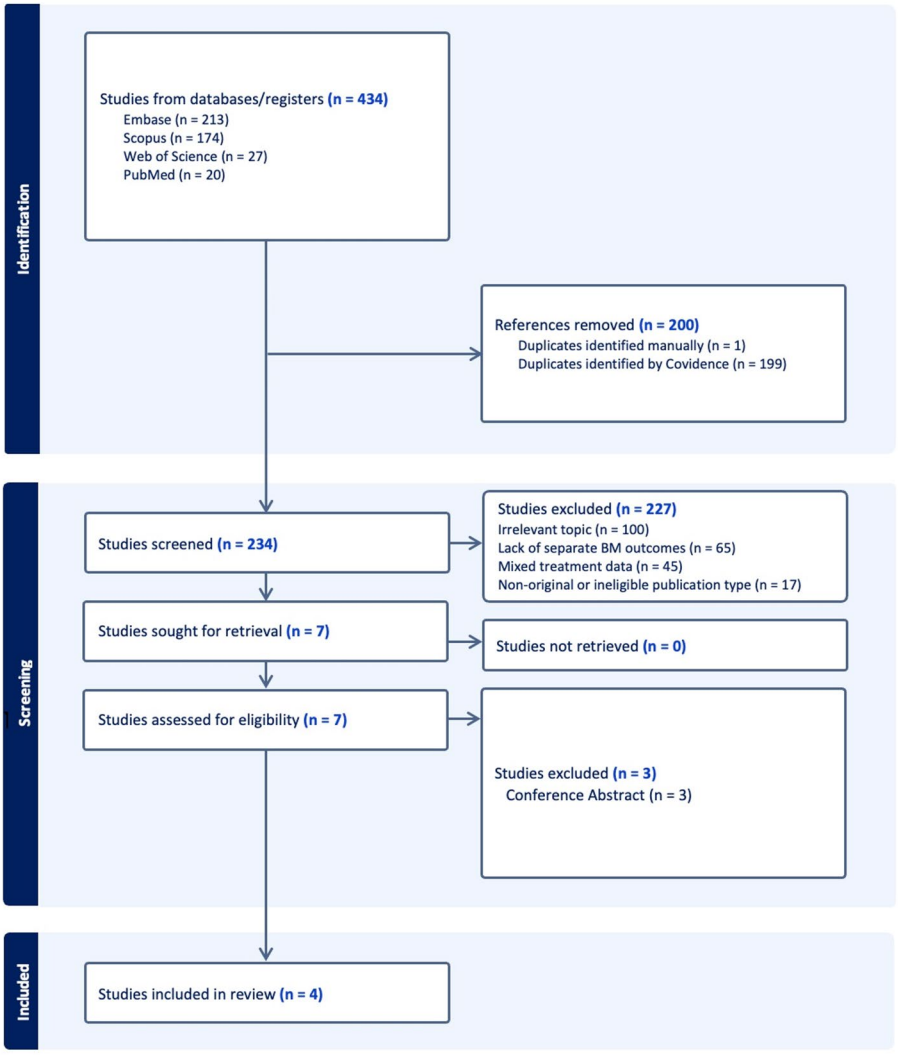


Fig. 1 PRISMA flow diagram depicting the screening process

3.2 Baseline characteristics and clinical outcomes

We extracted data from four eligible studies, which included 1,789 patients, among whom 472 had BMs. Across the included studies, 1106 were male, and 686 were female. The median age of the patients ranged from 52.5 to 56 years. Prior therapies included surgery, radiotherapy, chemotherapy, and immunotherapy. These studies were conducted in Germany [21], the United States [22], Spain [23], and one study was Multinational, involving Australia, the United States, and Italy [24]. These studies were conducted from 2019 to 2024 (Table 1). Radiological outcomes (CR, PR, SD, PD) and clinical outcomes were reported across the included studies (Table 2).

3.3 Complete response

Four studies reported CR. Encorafenib plus Binimetinib therapy yielded an overall CR rate of 12% (95% CI: 9%–15%), with low heterogeneity (Fig. 2). Meta-regression analyses indicated that sex was associated with CR (Supplementary Table S2).

3.4 Partial response

Four studies reported PR. The pooled PR rate was 36% (95% CI: 14%–58%), with high heterogeneity (Fig. 3). Meta-regression analyses identified ECOG status and number of lesions as significant predictors of PR (Supplementary Table S2).

3.5 Overall response rate

Four studies reported ORR. The pooled ORR was 48% (95% CI: 27%–68%), with high heterogeneity (Fig. 4). Meta-regression analyses suggested that sex, age, number of lesions, and ECOG status were associated with ORR (Supplementary Table S2).

3.6 Stable disease

Four studies reported SD. The SD rate was 29% (95% CI: 13%–44%), with substantial heterogeneity (Fig. 5). Male sex, younger age, ECOG-1, and prior immunotherapy were significantly associated with SD in meta-regression analyses (Supplementary Table S2).

3.7 Progressive disease

Three studies reported PD. The pooled PD rate was 18% (95% CI: −2%–38%), with very high heterogeneity (Fig. 6). Meta-regression analyses did not identify any significant predictors of PD (Supplementary Table S2).

3.8 Safety and adverse events

Quantitative meta-analysis of safety outcomes was not feasible due to limited reporting and heterogeneity. Safety outcomes were reported in three studies. In the case series by Holbrook et al. [22], fatigue occurred in 17% of patients and myalgia in 13%, with rare events including retinal detachment, iritis, pancytopenia, and neuropathy [22]. In the E-BRAIN/GEM1802 study [23], diarrhea was reported in 27%, fatigue in 25%, nausea in 22.9%, ALT increase in 18.8%, and AST increase in 16.7% of patients; Grade 3–4 toxicities occurred in 25% [23]. In the POLARIS trial [24], 92% of patients experienced treatment-related adverse events, including diarrhea (54%), ALT increase (46%), fatigue (38%), nausea (38%), and AST increase (31%); Grade 3–4 events occurred in a subset

Table 1 Baseline characteristics of included studies

Study	Country	Year	No. of patients with BM	Age (median)	Sex (M/F)	ECOG	LDH	No. of lesions	Prior RT/IT/CT	BRAF mutation type
Franklin, 2023 [21]	Germany	2023	387	≤ 65: 45.8%, > 65: 54.2%	1055/649 (total study)	0: 46.4% 1: 12.6% Unknown: 37.4%	52.2% elevated; 28.9% >2x ULN	NR	RT: NR / IT: 4% / CT: 0.4%	NR
Holbrook, 2019 [22]	USA	2019	24	52.5 (25–75)	14/10	0: 42% 1: 42% 2: 13% 3: 4%	Median 190 U/L (82–774)	< 3:13% 4–10: 42%, > 10: 46%	RT: 58% / IT: 46% / CT: 21%	NR
Márquez-Rodas, 2024 [23]	Spain	2024	48	54 (18–88)	24/24	0: 54.2%, 1: 41.7%, 2: 4.2%	≤ULN: 54.2%, >ULN: 43.8%	1: 44%, 2: 31%, 3: 25%	RT: Not allowed / IT: 33% / CT: 0%	V600E: 87%, V600K: 23%, V600R: 12.5%
Menzies, 2024 [24]	Multi	2024	13	56.0 (39–83)	10/3	0: 61.5%, 1: 38.5%	Median 3.5×ULN (2.5–56.8)	1–2: 54%, ≥ 3: 46%	RT: 7.7% / IT: 69.2% / CT: 0%	V600E: 69%, V600K: 23%

BM brain metastases, *ECOG* Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *IT* immunotherapy, *RT* radiotherapy, *CT* chemotherapy. "NR" indicates that the corresponding data point was not available in the original publication or was not explicitly stated by the author

of patients, including one Grade 4 ALT increase [24]. Dose interruptions or reductions were reported in some patients, and no treatment-related deaths occurred.

3.9 Sensitivity analysis

Sensitivity analysis revealed that the ORR, CR, PR, and SD were robust, and the omission of each study did not significantly influence the pooled estimate. This suggests that these response rates are highly sensitive to study selection, indicating potential heterogeneity across the dataset (Supplementary Figs. S6-S10).

3.10 Quality assessment

The studies included in the review demonstrate generally acceptable quality. Most of the studies show low to moderate risk of bias, indicating solid methodology and reliable results. Even those with moderate to high risk of bias still provide valuable insights, contributing positively to the overall findings.

3.11 Publication bias

Publication bias was evaluated through the use of Egger's test and funnel plots [25]. The funnel plots and Egger's test revealed no significant publication bias for all parameters including, ORR (t = 0.61, P = 0.6051), PR (t = 0.90, p = 0.4645), CR (t = -0.34, p = 0.7673), PD (t = -0.01, p = 0.9959), and SD (t = 4.014, p = 0.0537) (Supplementary Figures S1-S5).

4 Discussion

This systematic review and meta-analysis indicated that encorafenib plus binimetinib in BM patients was associated with promising clinical and radiological outcomes. Our findings suggest a pooled ORR rate of 48% (95% CI: 27%-68%), indicating encouraging therapeutic efficacy. Our data showed that treatment with encorafenib plus binimetinib in patients with metastatic brain tumors resulted in a pooled CR rate of 12% (95% CI: 9% – 15%), PR rate of 36% (95% CI: 14%–58%), SD rate of 29% (95% CI: 13% – 44%), and PD rate of 18% (95% CI: -2% to 38%). These findings highlighted the potential role of encorafenib plus binimetinib in patients with BM.

Comparatively, various BRAF-targeted therapies have been evaluated in patients with BMs. Dabrafenib plus trametinib, a dual BRAF/MEK combination, demonstrated intracranial ORRs of 58% (CR 1%, PR 57%, SD 21%, PD 18%) in a multi-cohort phase 2 trial [26] and 41.5% in another study of stage III & IV BRAF V600-mutant melanoma with BMs [27]. Triplet regimens including atezolizumab, cobimetinib, and vemurafenib reported ORRs of 52% (CR 0%, PR 52%, SD 34%, PD 9%) [28] and 48.4% (CR 3.2%, PR 45.2%, SD 16.1%, PD 35.5%) in the ISABELLA study cohort [29]. Vemurafenib monotherapy generally showed lower intracranial responses, with reported ORRs of 18% (CR 2%, PR 16%, SD 29%) [30], 42% PR and 38% SD in a pilot study [31], and 50% ORR with median PFS of 4.6 months [32].

The intracranial CR rate observed with encorafenib plus binimetinib was higher than that reported in prior dual, triplet, or monotherapy studies, while intracranial ORR and PR were generally comparable, and SD fell within previously reported ranges. These results highlight the potential of encorafenib plus binimetinib to provide meaningful intracranial tumor shrinkage and improved complete responses in patients with BRAF

Table 2 Summary of outcomes reported in included studies

Study	Median OS (month)	6 Month OS	1 Year OS	Median PFS (month)	ORR (%)	CR (%)	PR (%)	SD (%)	PD (%)
Franklin, 2023 [21]	36.9	NR	NR	6.7	29.7	12.4	17.3	12.6	35.3
Holbrook, 2019 [22]	NR	NR	NR	NR	33	13	20.8	45.8	16.6
Márquez-Rodas, 2024 [23]	15.9	91.6	59.2	intracranial: 8.5 extracranial: 7.7	70.8	10.4	60.4	27	2
Menzies, 2024 [24]	NR	NR	NR	NR	60	10	50	40	0

NR Not reported, *OS* Overall survival, *PFS* Progression-free survival, *ORR* Objective response rate, *CR* Complete response, *PR* Partial response, *SD* Stable disease, *PD* Progressive disease

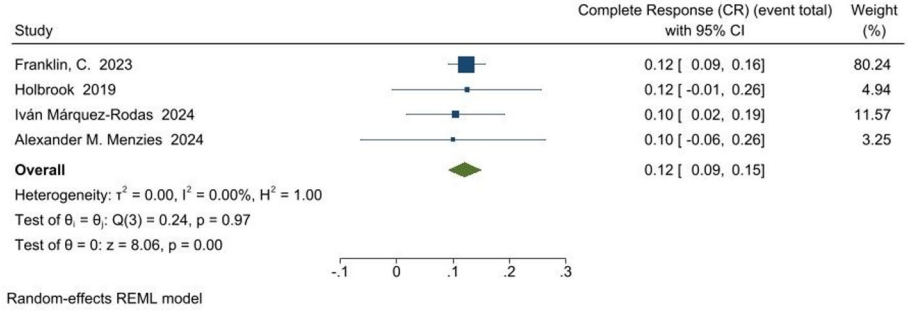


Fig. 2 Complete response rate

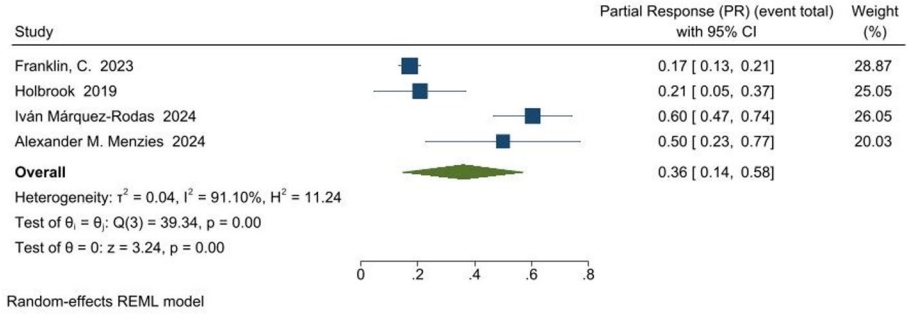


Fig. 3 Partial response rate

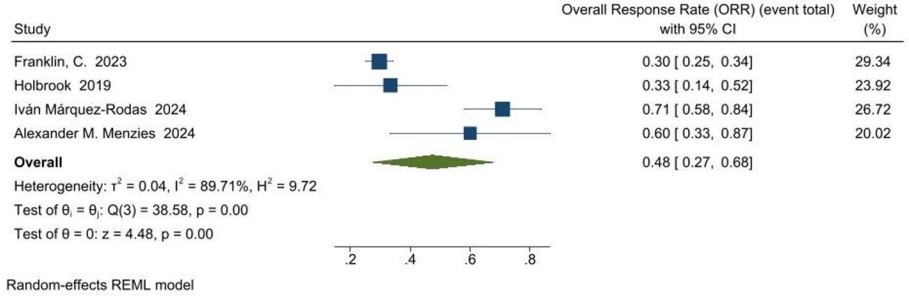


Fig. 4 Overall response rate

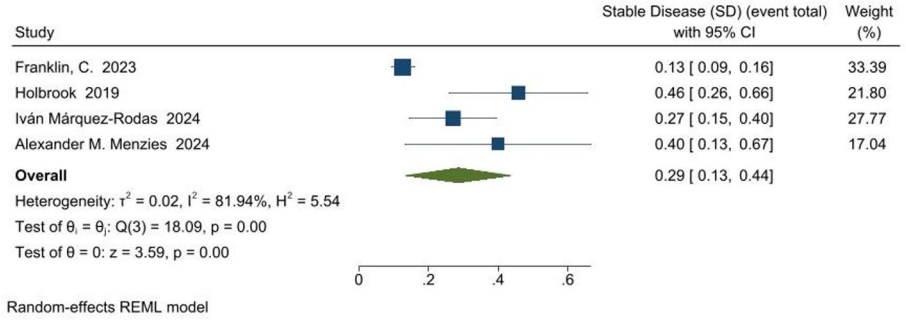


Fig. 5 Stable disease rate

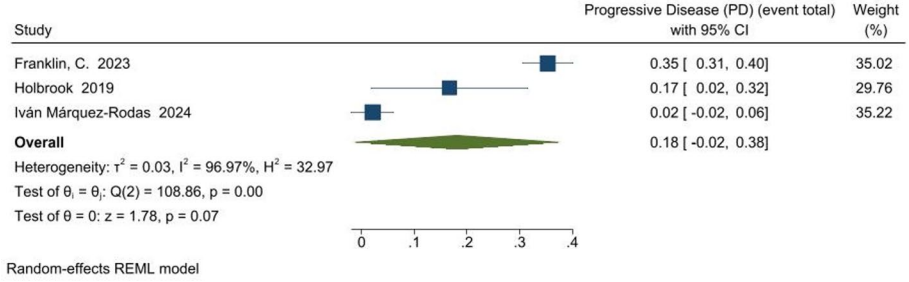


Fig. 6 Progressive disease rate

V600-mutant melanoma with brain metastases, although the considerable heterogeneity across included studies suggests that these findings should be interpreted with caution.

Similarly, several epidermal growth factor receptor (EGFR)-targeting tyrosine kinase inhibitors (TKIs) have shown remarkable intracranial activity in patients with EGFR-mutant non–small cell lung cancer (NSCLC) and brain metastases. Among them, osimertinib demonstrated notably high intracranial response rates, underscoring the efficacy of third-generation TKIs in achieving durable control of brain lesions [33–37]. Although these findings represent exceptional intracranial outcomes, the results from our analysis, 12% CR, 36% PR, and 29% SD, remain clinically meaningful, particularly given the broader and more heterogeneous population of patients with BRAF-mutant melanoma included in our pooled cohort.

Beyond targeted therapies, immune checkpoint inhibitors (ICIs) have also demonstrated therapeutic potential in brain metastases. Trials assessing pembrolizumab and nivolumab have reported intracranial clinical benefit rates (iCBR = CR + PR + SD) around 40%–50%, which are generally lower than our observed iCBR of 77% with encorafenib plus binimetinib [38]. Notably, combination strategies, such as ICIs administered with brain radiotherapy (BRT), have been associated with higher partial response rates, approximately 60% in some series, suggesting enhanced tumor shrinkage compared with ICI monotherapy [39]. Nevertheless, the CR rate achieved with encorafenib plus binimetinib (12%) was comparable to that of combined ICI–BRT regimens (13%–14%), indicating a similar ability to induce complete intracranial responses.

Collectively, these comparisons emphasize the therapeutic relevance of BRAF/MEK inhibition in the intracranial setting. While ICIs and EGFR-TKIs achieve high response rates in selected molecular subgroups, encorafenib plus binimetinib appears to provide a favorable balance between tumor shrinkage, disease stabilization, and treatment

tolerability in patients with BRAF-mutant melanoma and brain metastases. Given the considerable heterogeneity among included studies, these findings should be interpreted with caution; however, they support the consideration of encorafenib plus binimetinib as a clinically meaningful option, particularly for patients in whom immunotherapy is unsuitable or has failed.

The results of this systematic review and meta-analysis suggest that the combination of encorafenib plus binimetinib offers a favorable safety profile and promising efficacy in patients with BMs, particularly those with BRAF V600-mutant melanoma. These findings support the potential use of this targeted regimen as a viable treatment option in clinical practice, especially for patients who may not be candidates for immunotherapy or who have progressed on prior treatments. Given the intracranial activity observed, clinicians may consider incorporating this combination into treatment strategies where control of central nervous system disease is critical.

Compared with other available BRAF/MEK combinations, encorafenib plus binimetinib may offer a more favorable safety profile and sustained intracranial control, making it a reasonable treatment option in patients with BRAF-mutant melanoma and brain metastases. Nevertheless, given the lack of direct head-to-head data, this regimen should not yet be considered superior to other BRAF/MEK inhibitors. At present, its use may be most appropriate in patients who are not eligible for, or who have progressed following, immunotherapy and broader clinical implementation should be approached with caution due to the limited number of high-quality trials and the need for more robust, prospective data specifically addressing long-term intracranial outcomes and quality of life in this population.

The observed heterogeneity in our analysis likely reflects variations across studies in several key areas, including tumor-related factors (e.g., number, size, and location of BMs), baseline patient characteristics (such as performance status, age, and extracranial disease burden), and differences in prior treatments, including systemic therapies, radiotherapy, and surgical interventions. Additionally, inconsistencies in response assessment criteria and follow-up durations may have further contributed to variability in reported outcomes.

While current evidence supports the clinical potential of encorafenib plus binimetinib for patients with BMs, particularly in BRAF-mutant melanoma, future research should prioritize prospective, randomized trials focused specifically on intracranial efficacy and long-term neurological outcomes. Comparative studies with immune checkpoint inhibitors, stereotactic radiosurgery, and other targeted agents are also needed to better define this combination's place in the treatment landscape. Moreover, efforts to identify biomarkers predicting response or resistance, as well as studies evaluating sequencing strategies (e.g., targeted therapy followed by immunotherapy), could further optimize patient selection and improve outcomes. Investigations into patient-reported outcomes, cognitive function, and quality of life are also critical to guide holistic care in this vulnerable population.

The relatively small number of included studies, particularly retrospective studies, along with the limited sample size of enrolled patients, may compromise the statistical power of this meta-analysis and reduce the reliability of pooled estimates. High heterogeneity observed for key outcomes such as ORR, PR, and SD (I^2 consistently > 80%) further limits the generalizability of these results, whereas the CR rate, characterized by low

heterogeneity, appears more robust. The observed high heterogeneity was investigated using meta-regression. However, the small number of studies limited the possibility of performing subgroup analyses. Several clinically important variables, including time to treatment failure (TTF), OS, PFS, and detailed adverse event profiles, were either underreported or entirely omitted, restricting the depth of analysis. Additionally, short follow-up periods in some studies constrained the evaluation of long-term treatment efficacy and safety. Collectively, these factors underscore the need for cautious interpretation of the findings.

5 Conclusion

In this study, we highlight the potential of encorafenib plus binimetinib as a treatment option for metastatic brain tumors. The combination shows moderate but clinically meaningful intracranial activity, making it a viable targeted option. Nevertheless, larger prospective studies are required to confirm these findings and optimize clinical use.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-04265-6.

Supplementary material 1.

Supplementary material 2.

Supplementary material 3.

Supplementary material 4.

Acknowledgements
None.

AI usage
AI-based tools were used to assist with language editing, search strategy drafting, and code generation. All content was verified by the authors, who take full responsibility for the work. This manuscript complies with all instructions to authors. All authors meet authorship criteria and have approved the final manuscript. This manuscript has not been published and is not under consideration elsewhere. A PRISMA checklist was used and is included with the submission.

Author contributions
Conceptualization: B.H., M.H.; Methodology: B.H., A.B., M.H.; Literature Search: A.B., A.D.B., M.B., M.D.; Data Extraction: A.B., A.D.B., M.B., M.D.; Risk of Bias Assessment: A.B., A.D.B., M.B., M.D.; Statistical Analysis: B.H.; Writing – Original Draft: B.H., A.B., M.H., B.H., I.M.; Writing – Review & Editing: M.A.H., R.H., B.H.; Supervision: B.H.; Project Administration: B.H., Revision: M.Sh.

Funding
The authors declare that no funding source was used.

Data availability
The data supporting this study's findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study is deemed exempt from receiving ethical approval.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 20 August 2025 / Accepted: 8 December 2025

Published online: 10 December 2025

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