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REVIEW

New emerging treatment options for metastatic melanoma: a systematic review and meta-analysis of skin cancer therapies

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Abstract

Skin cancer, notably melanoma, poses a significant global health burden, with rising incidence and mortality rates. While therapeutic advancements have improved outcomes, metastatic melanoma remains challenging to treat. This study aims to systematically review systemic treatment options for advanced melanoma, focusing on efficacy and safety in the first-line setting. Through a comprehensive search and meta-analysis of randomized controlled trials conducted from 2013 to 2023, 11 studies encompassing 2816 participants were analyzed. Treatment options included BRAF inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), and immune checkpoint inhibitors (ipilimumab). Combined therapy with vemurafenib, cobimetinib, and ipilimumab demonstrated superior overall survival (OS) and progression-free survival (PFS) compared to monotherapy, with a significant odds ratio (OR) of 6.95 (95% CI: 4.25–9.64, $p < 0.00001$) for OS and 2.49 (95% CI: 1.42–3.56, $p < 0.00001$) for PFS. Additionally, dabrafenib and trametinib combination therapy showed improved outcomes with favorable tolerability, including a significant reduction in adverse event (AE) risk, with an OR of 2.20 (95% CI: 1.72–2.81). Furthermore, our analysis highlighted vemurafenib-associated dermatological toxicities, emphasizing the need for effective management strategies. The study underscores the evolving treatment landscape in melanoma management, with a potential shift towards immune checkpoint inhibitors in the adjuvant setting, particularly for BRAF-mutated disease. However, limitations in meta-analysis methodologies and the need for long-term investigations into treatment implications on survival and quality of life underscore the importance of continued research.

Keywords Melanoma · Chemotherapy · Immunotherapy · Immune checkpoint inhibitor · Cytokines

Introduction

The global health landscape faces a formidable challenge posed by skin cancer, notably melanoma, whose incidence has shown a concerning upward trend in recent times [1]. Annually, approximately 200,000 new cases of melanoma emerge worldwide, accompanied by a staggering 65,000 deaths [2]. Despite strides in therapeutic innovations, metastatic melanoma has historically carried a bleak outlook, with mean survival rates spanning from 15–60%

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[3]. Nonetheless, the treatment paradigm has undergone a transformative shift with the emergence of novel anticancer therapies targeting diverse kinases implicated in cancer progression [4].

The introduction of targeted therapies, notably BRAF inhibitors, signifies a crucial juncture in melanoma treatment strategies [5]. Mutations activating the BRAF (V600E) kinase are prevalent in approximately 60% of melanomas and are closely associated with disease progression [6]. Vemurafenib, an oral synthetic BRAF inhibitor, has demonstrated remarkable selectivity and efficacy in clinical settings, notably extending survival among patients with metastatic melanoma [7]. However, these therapeutic advancements are not immune to challenges, as evidenced by the prominence of cutaneous adverse events among reported complications linked to vemurafenib administration [8].

In addition to BRAF inhibitors, immune checkpoint inhibitors like ipilimumab have emerged as pivotal components in melanoma treatment [9]. By targeting cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), ipilimumab enhances T-cell activation and tumor lysis, leading to improved OS rate in patients with advanced melanoma [10]. However, the efficacy of these treatments must be balanced against their associated adverse effects, highlighting the need for comprehensive evaluation and management strategies [11].

Furthermore, chemotherapy agents like dacarbazine, once a mainstay in melanoma treatment, have faced scrutiny regarding their efficacy compared to newer therapies like immune checkpoint inhibitors [12]. The emergence of targeted therapies and immunotherapies has fundamentally transformed the melanoma treatment landscape, particularly for patients harboring BRAF mutations [13]. However, challenges such as the development of resistance and adverse events persist, underscoring the need for alternative treatment approaches and comprehensive evaluation of existing therapies [14]. In this context, a systematic review and meta-analysis play a crucial role in synthesizing existing evidence, evaluating treatment efficacy, and delineating the strength of recommendation and level of evidence for each treatment modality.

Hence, our study aims to systematically assess the effectiveness and safety profiles of diverse systemic treatment modalities for advanced melanoma, with a primary focus on first-line interventions. Specifically, we intend to scrutinize the comparative impacts of ipilimumab, dacarbazine, vemurafenib, cobimetinib, dabrafenib, and trametinib. Employing a meta-analysis methodology, our objective is to amalgamate both direct evidence from head-to-head trials and indirect evidence gleaned from a shared comparator. This comprehensive approach aims to establish a sturdy comparative framework, facilitating the evaluation of treatment efficacy and guiding evidence-based clinical decision-making in the realm of advanced melanoma management.

Materials and methods

PICO question and eligibility criteria

Our research question was guided by the Population, Intervention, Comparison, and Outcome (PICO) framework. We sought to assess the effectiveness and safety of both mono- and combined therapy options, namely ipilimumab, dacarbazine, vemurafenib, cobimetinib, dabrafenib, and trametinib, in treating advanced melanoma within the timeframe of the last decade (2013–2023). Eligible studies included randomized controlled trials (RCTs) conducted during this period, focusing on treatment-naive adult patients diagnosed with metastatic melanoma as shown in Table 1. The interventions under scrutiny encompassed targeted therapies (BRAF or MEK inhibitors) or immune checkpoint inhibitors (CTLA-4 or PD-1 inhibitors). Key outcomes of interest included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and serious adverse events (SAEs).

Search strategy

Our search approach involved a methodical examination of prominent databases such as MEDLINE, EMBASE, and Cochrane, spanning from their inception to 2023. We utilized controlled vocabulary terms (MeSH and EMTREE) in diverse combinations, coupled with pertinent keywords like "melanoma," "targeted therapy," and "immunotherapy." Additionally, we conducted manual searches of reference lists in relevant articles, meta-analyses, and systematic reviews to ensure thorough coverage of the literature.

Table 1 Inclusion and exclusion criteria for the study

Inclusion criteria:	Exclusion criteria:
Randomized controlled trials (RCTs) conducted between 2013 and 2023.	Non-randomized studies. Studies conducted before 2013.
Studies involving treatment-naive adult patients with metastatic melanoma.	Studies involving patients with other types of cancer.
Interventions including mono- or combined therapy options of ipilimumab, dacarbazine, vemurafenib, cobimetinib, dabrafenib, and trametinib.	Studies involving interventions other than the specified mono- or combined therapy options.

Study selection

Two reviewers autonomously evaluated the suitability of titles and abstracts, procured full-text articles of potentially qualifying studies, and established final eligibility through a comprehensive assessment of the full text. Any disparities were resolved through consensus or with the involvement of a third adjudicator. The concurrence between reviewers was gauged using the Cohen κ coefficient.

Data extraction

Two reviewers independently collected data using a standardized template. The extracted information encompassed study characteristics, demographic data of the population, intervention specifics, and relevant outcomes such as OS, PFS, ORR, and SAEs. The data included trial design particulars, patient demographics, gender distribution, treatment modalities, dosages, follow-up duration, mean OS and PFS rates, reported adverse events, and significant findings. Any discrepancies were resolved through deliberations involving a third author.

Main outcomes and quality assessment

The primary outcomes were analyzed, presenting risk ratios (RR) with corresponding 95% confidence intervals (CI) for categorical results regarding overall survival and progression-free survival. Adverse events (AEs) such as rash, photosensitivity, purpura, pyrexia, and diarrhea were considered. The severity of all adverse events was graded on a scale ranging from 1 to 5. Individual studies' potential biases were evaluated independently using the Cochrane Collaboration risk-of-bias assessment tool, with any discrepancies resolved through consensus (Figs. 1, 2 and 3). In addition the Joanna Briggs Institute (JBI) was used to determine the risk bias assessments.

Meta-analysis

Utilizing a random-effects model, pooled estimates were generated to accommodate anticipated heterogeneity in the data. Data analysis was executed using Review Manager version 5.3, with continuous outcomes presented as mean differences (MD) alongside corresponding 95% confidence intervals (CI), while dichotomous outcomes were articulated as risk ratios (RR) with 95% CI. Statistical heterogeneity was evaluated using the Cochran Q statistic and I^2 statistic, with statistical significance set at $P < 0.10$. Mean OS, PFS, and ORR values reported in each study were determined using a fixed-effect model for dichotomous heterogeneity. Forest plots and funnel plots were employed to gauge the heterogeneity of the results.

Results

Characteristics of the studies

The systematic review initially identified 522 records from various databases, primarily Embase ($n = 242$), followed by PubMed ($n = 171$), Cochrane ($n = 78$), and Scopus ($n = 31$), with an additional record from alternative sources, totaling 523. After eliminating duplicates ($n = 93$), 430 records underwent screening based on title and abstract, resulting in the exclusion of 234 articles. Subsequently, 196 full-text articles were evaluated, leading to the exclusion of 185, including literature reviews or editorials ($n = 72$), non-cancer studies ($n = 51$), and those not reporting OS and PFS outcomes ($n = 7$), among others. Finally, 11 full-text articles met the eligibility criteria and were included in the review and meta-analysis as selected studies for analysis (Fig. 4).

Study participants and baseline characteristics

The review encompassed 2816 participants across diverse studies investigating metastatic melanoma treatments. Gender distribution varied, with majority included male (89%). Participant ages ranged from 49.0 to 55.0 years. Underlying conditions included unresectable/metastatic melanoma with BRAFV600 mutations and treatment-naive metastatic melanoma. Studies utilized varied designs (phases I-III, multicenter), assessing BRAF inhibitors (vemurafenib, dabrafenib), alone or with MEK inhibitors (trametinib, cobimetinib), and immunotherapy (ipilimumab). Follow-up spanned 5 years to 28.0 months. Median overall survival ranged from 6.8 to 443.0 days; progression-free survival, 1.6 to 416.0 days. Common adverse events included pyrexia, nausea, arthralgia, rash, and gastrointestinal symptoms (Table 2).

Comparative analysis of adverse events: vemurafenib monotherapy vs. combined therapy with vemurafenib, cobimetinib, and ipilimumab in melanoma treatment

The study compared AE outcomes between vemurafenib monotherapy and combined therapy with vemurafenib, cobimetinib, and ipilimumab. Among patients with ECOG PS 1, the odds ratio (OR) favored combination therapy at 1.27 (95% CI: 1.02–1.60). Notably, patients with LDH levels below 2 times ULN showed significantly lower AE risk with combination therapy 1.43 (95% CI: 0.99–2.05).

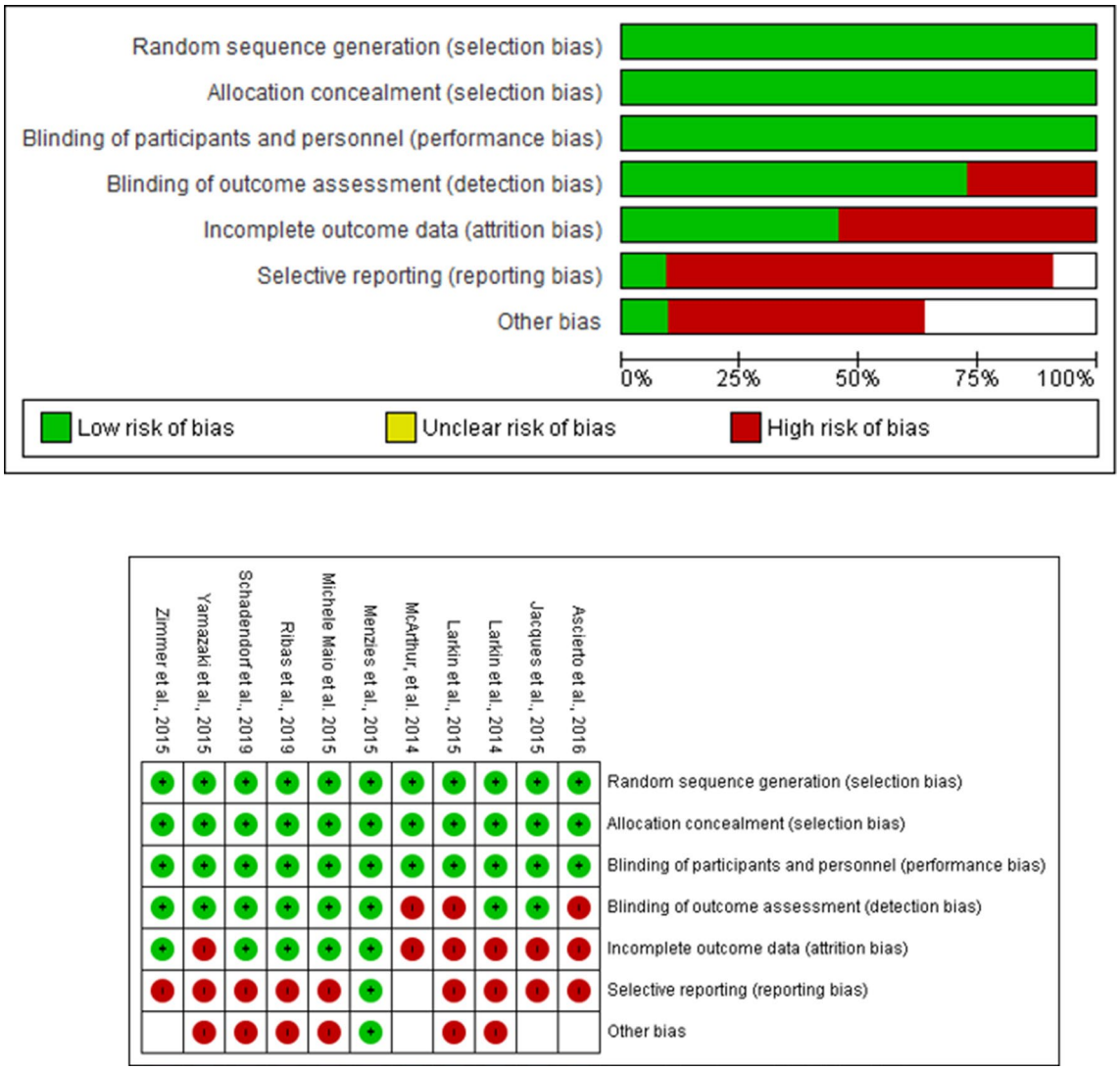

Fig. 1 Cochrane risk of bias assessment for the selected studies

Rash risk was also lower with combination therapy 2.09 (95% CI: 1.64–2.67). Other AEs like photosensitivity and pyrexia, showed moderate significant differences 2.18 (95% CI: 1.71–2.78) and 1.09 (95% CI: 0.79–1.51) respectively. These findings suggest that while combination therapy may elevate certain AE risks, particularly in ECOG PS 1 and LDH levels below 2 times ULN, it may reduce rash risk compared to vemurafenib monotherapy (Maio et al., 2015) as shown in Fig. 5.

In studies comparing adverse events (AEs) and therapy discontinuation between vemurafenib monotherapy and combination therapies, discontinuation rates due to AEs were reported in both cases. For combination therapy with vemurafenib, cobimetinib, and ipilimumab, therapy discontinuation was commonly linked to severe adverse events such as rash, photosensitivity, and pyrexia. In one study, the discontinuation rate for combination therapy due to toxicity was around 13–23%, depending on the severity of the AEs reported. In monotherapy with vemurafenib, discontinuation due to AEs was lower, around 10–12%, but severe cases of cutaneous toxicity were still a leading cause of discontinuation.

Superior clinical outcomes with combined therapy vs. vemurafenib monotherapy

Our analysis compared clinical outcomes between vemurafenib monotherapy and combined therapy with vemurafenib, cobimetinib, and ipilimumab. Patients receiving combined therapy demonstrated significantly improved OS compared to vemurafenib monotherapy, with an OR of 6.95 (95% CI: 4.25–9.64, $p < 0.00001$). Similarly, PFS was markedly superior in the combined therapy group, with an OR of 2.49 (95% CI: 1.42–3.56, $p < 0.00001$). Although

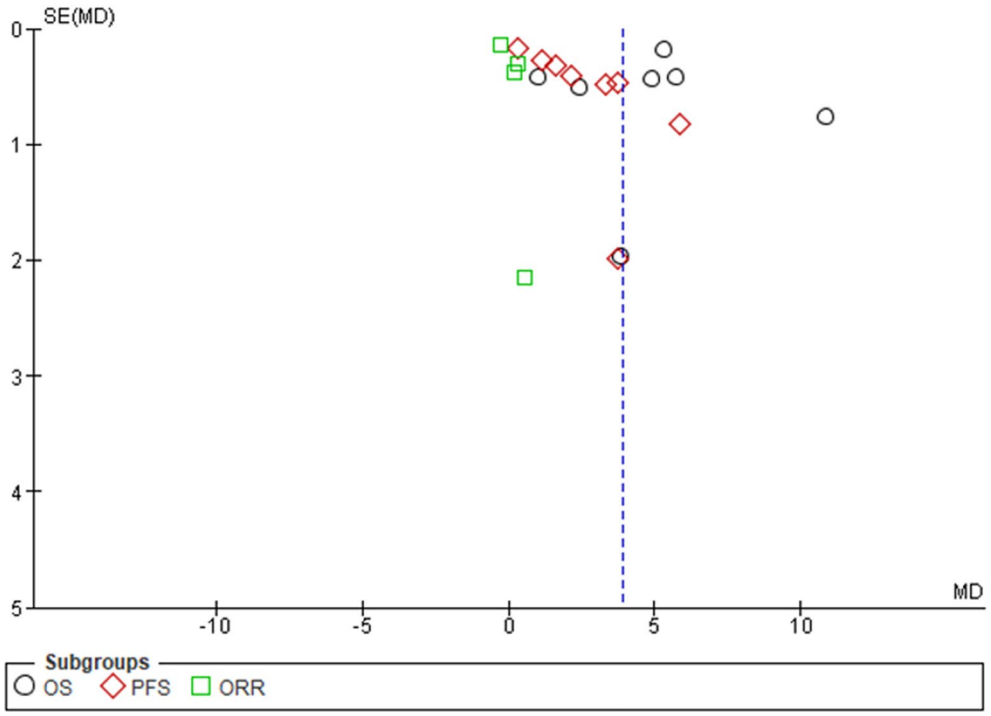

Fig. 2 Funnel plot of Vemurafenib Monotherapy vs. Combined Therapy with Vemurafenib, Cobimetinib, and Ipilimumab in Melanoma Treatment

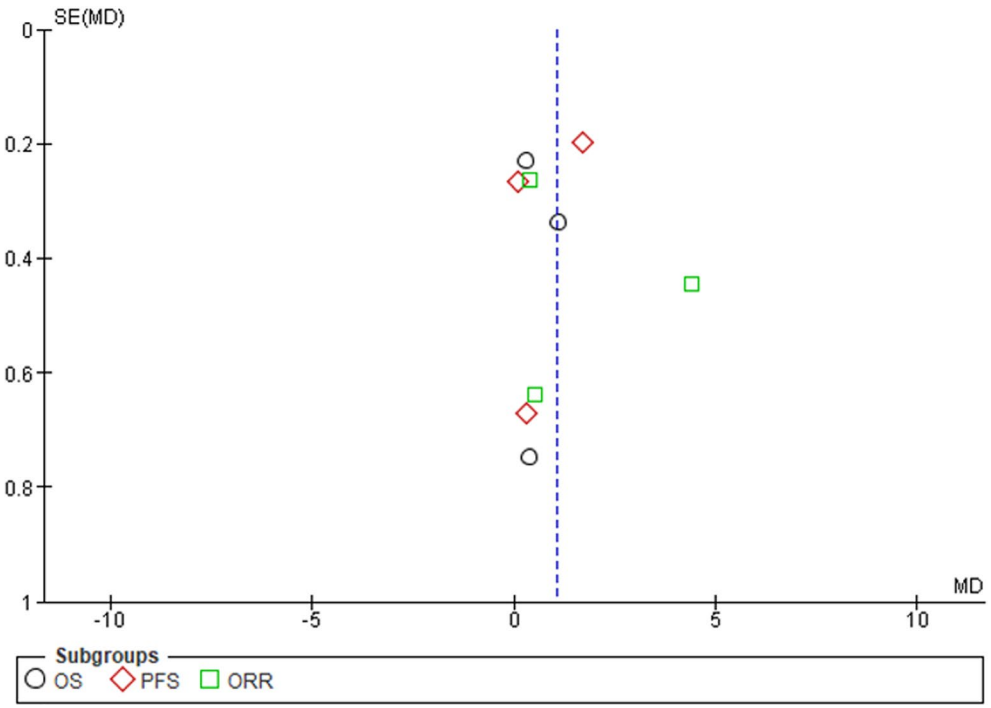

Fig. 3 Funnel plot of Dabrafenib + Trametinib Combined Therapy vs. Dabrafenib Monotherap

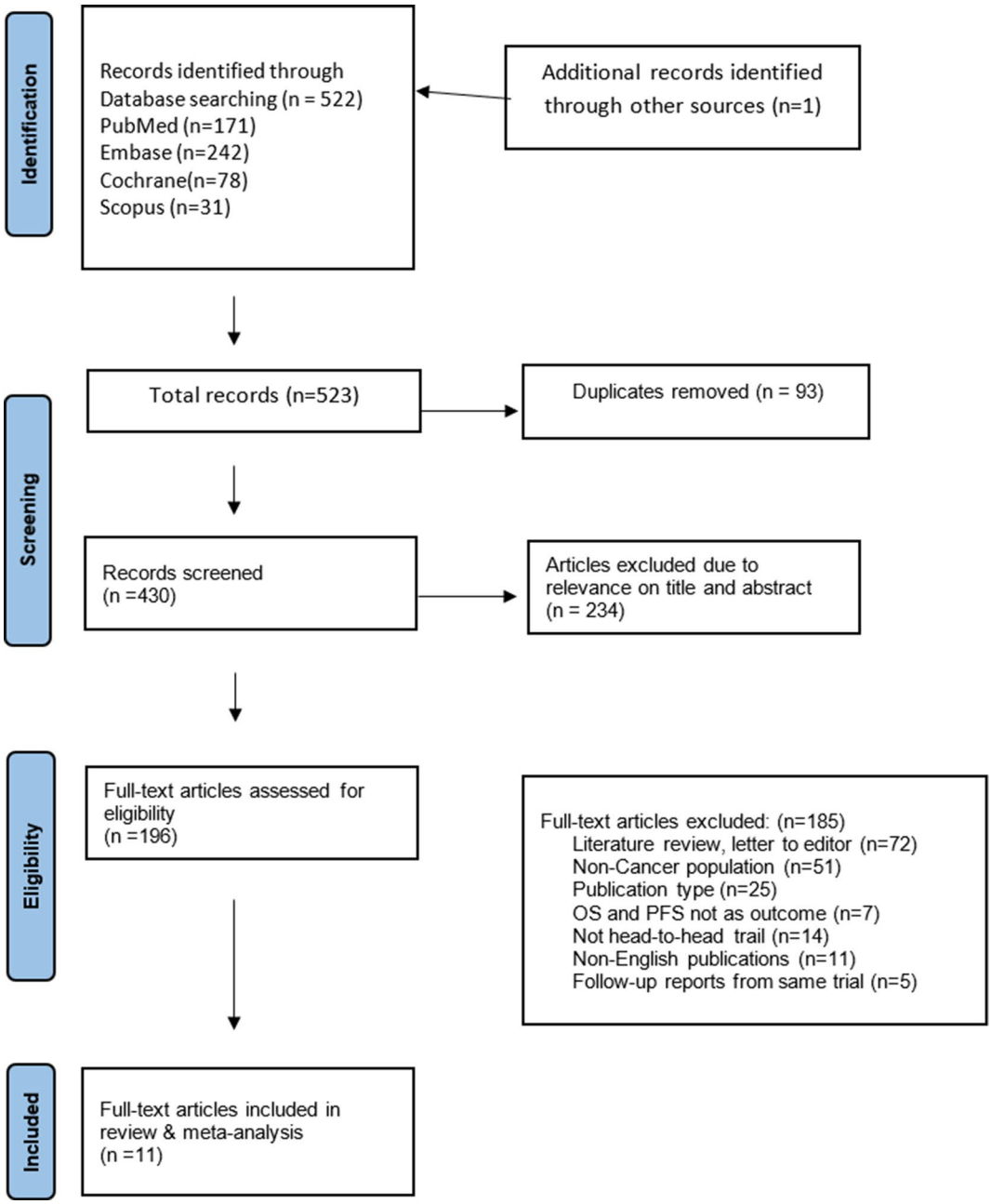

Fig. 4 PRISMA study

the ORR favored combined therapy, it was not statistically significant (OR: -0.05, 95% CI: -0.41-0.32, $p = 0.80$). These findings underscore the significant clinical benefits of combined therapy in enhancing survival outcomes and delaying disease progression compared to vemurafenib monotherapy [15] as shown in Fig. 6.

Enhanced clinical outcomes with dabrafenib + trametinib combined therapy vs. dabrafenib monotherapy

Our study aimed to compare dabrafenib monotherapy versus combination therapy with dabrafenib and trametinib across various AEs and clinical parameters. Patients on combined therapy showed significantly improved outcomes in ECOG Performance Status (PS), the overall effect size was 1.26 (95% CI: 0.91–1.74) and Lactate Dehydrogenase (LDH) levels showed a substantial effect size of 2.20 (95%

Table 2 Data extraction sheet of selected eleven studies for systematic review

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Michele Maio et al. 2015	Phase III, Multicenter	Treatment-naive patients with unresectable stage IIIc, N3 (AJCC TNM) or stage IV melanoma; ECOG performance status 0 or 1	Ipilimumab (10 mg/kg) + Dacarbazine (850 mg/m2) vs. Placebo + Dacarbazine (850 mg/m2)	Minimum follow-up of 5 years	Phase III	18.2% (Ipilimumab group) vs. 8.8% (Placebo group) at 5 years	Median PFS was 7.2 months (95% CI: 5.2–6.2 months)	Skin-related immune-related adverse events (irAEs) observed, exclusively grade 3 or 4	Ipilimumab plus dacarbazine group had significantly higher 5-year survival rate compared to placebo group ($P = 0.002$); plateau in survival curve observed around year 3; ipilimumab treatment associated with durable long-term survival benefit; higher proportion of long-term survival observed with ipilimumab treatment.
Yamazaki et al., 2015	Open-label multicenter phase I/II study conducted in Japan	Eleven patients; 3 male, 8 females; Median age: 49.0 years (range: 23–68 years) Underlying Disease: BRAFV600 mutation-positive unresectable or recurrent melanoma	Vemurafenib 960 mg orally twice daily for 28-day treatment cycles	Data cutoff date: June 6, 2014	Phase I/II	Median OS: 443.0 days (95% CI, 116.0 days–not reached)	Median PFS: 416.0 days (95% CI, 84.0–443.0)	Arthralgia, myalgia, alopecia, rash, maculopapular rash, decreased appetite	Overall response rate: 75.0% (95% CI, 34.9–96.8) Median response duration: 240.0 days (95% CI, 56.0–388.0) Disease control rate: 87.5% (95% CI, 47.3–99.7) No treatment-related deaths reported Vemurafenib demonstrated manageable toxicities and significant efficacy in Japanese patients with metastatic melanoma with BRAFV600 mutations

Table 2 (continued)

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Larkin et al., 2015	Open-label, multicentre study conducted in 44 countries	Total patients enrolled: 3226; Male: 57%; Median age: 55.0 years; Majority with ECOG PS 0–1 (89%); 71% with stage M1c disease; Previous systemic therapy received by half of the patients including dacarbazine, temozolomide, interferon, ipilimumab, and fotemustine	Oral vemurafenib 960 mg twice a day until disease progression, unacceptable toxicity, withdrawal of consent, or death; Dose interruption and reduction allowed for intolerable toxicity	Follow-up lasted until 24 months after the last patient was enrolled or until death, withdrawal of consent, or loss to follow-up	Phase III	Median overall survival: 12.0 months; Kaplan-Meier estimates at 6, 12, and 18 months: 75%, 52%, and 36%, respectively	Median progression-free survival: 5.6 months; Kaplan-Meier estimates at 6, 12, and 18 months: 47%, 19%, and 8%, respectively	rash, arthralgia, fatigue, photosensitivity reaction, alopecia, and nausea; Grade 3 or 4 adverse events reported in 46% of patients, including cutaneous squamous cell carcinoma, rash, liver function abnormalities, arthralgia, and fatigue	Vemurafenib safety consistent with pivotal trials; High incidence of adverse events, including cutaneous squamous cell carcinoma and keratoacanthoma; Elderly patients and those with ECOG PS 2 or greater had increased serious adverse events; Majority of deaths unrelated to vemurafenib; Median overall survival and progression-free survival rates reported.
McArthur, et al. 2014	Multicenter; Patients recruited from 104 centres in 12 countries worldwide	Patients with treatment-naive metastatic melanoma, positive for BRAFV600 mutations, age $\geq$ 18, ECOG 0 or 1, adequate hematological, hepatic, and renal function. Exclusions: history of cancer within 5 years (except skin or cervical carcinoma.	Vemurafenib (960 mg orally twice daily) vs. Dacarbazine (1000 mg/m^2 intravenously every 3 weeks)	Median: 12.5 months for Vemurafenib, 9.5 months for Dacarbazine	Phase 3	Vemurafenib: 13.6 months (95% CI 12.0–15.2) vs. Dacarbazine: 9.7 months (7.9–12.8); HR 0.70 (95% CI 0.57–0.87); $p = 0.0008$	Vemurafenib: 6.9 months (95% CI 6.1–7.0) vs. Dacarbazine: 1.6 months (1.6–2.1); HR 0.38 (95% CI 0.32–0.46); $p < 0.0001$	Vemurafenib: Cutaneous squamous-cell carcinoma, rash, keratoacanthomas, abnormal liver function tests. Dacarbazine: Neutropenia.	Vemurafenib demonstrated significantly longer OS and PFS compared to Dacarbazine in treatment-naive metastatic melanoma patients with BRAFV600 mutations. Subgroup analyses showed similar benefits in BRAFV600E and BRAFV600K mutation-positive patients.

Table 2 (continued)

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Larkin et al., 2014	Randomized phase 3 study conducted in multiple locations	Patients with previously untreated unresectable locally advanced or metastatic BRAF V600 mutation–positive melanoma. Age ≥ 18 years, ECOG performance-status score of 0 or 1.	Vemurafenib (960 mg twice daily) + Cobimetinib (60 mg once daily for 21 days, followed by 7 days off) vs. Vemurafenib (960 mg twice daily) + Placebo.	Median follow-up: 7.3 months (range, 0.5 to 16.5).	Phase 3	Interim analysis of overall survival showed 9-month survival rates of 81% in combination group vs. 73% in control group.	Combination therapy: median progression-free survival 9.9 months vs. 6.2 months in control group (HR 0.51; 95% CI, 0.39 to 0.68; $P < 0.001$).	Higher incidence of adverse events of grade 3 or higher with combination therapy (65% vs. 59%), including central serous retinopathy, gastrointestinal events, photosensitivity, elevated aminotransferase levels, and increased creatine kinase level.	Addition of cobimetinib to vemurafenib associated with significant improvement in progression-free survival among patients with BRAF V600–mutated metastatic melanoma, with some increase in toxicity.
Ascierto et al., 2016	Randomised, double-blind, placebo-controlled, phase 3 trial; 135 clinical sites in 19 countries	- Total patients: 495 - Age: ≥18 years - Histologically confirmed BRAFV600 mutation-positive unresectable stage IIIC or stage IV melanoma	Cobimetinib (60 mg once daily for 21 days followed by a 7-day rest period in each 28-day cycle) + Vemurafenib (960 mg twice daily)	Median follow-up: 14.2 months (IQR 8.5–17.3)	Phase 3	Cobimetinib + Vemurafenib: 22.3 months (95% CI 20.3–not estimable) Placebo + Vemurafenib: 17.4 months (95% CI 15.0–19.8)	Cobimetinib + Vemurafenib: 12.3 months (95% CI 9.5–13.4) Placebo + Vemurafenib: 7.2 months (95% CI 5.6–7.5)	Most common grade 3–4 adverse events in Cobimetinib + Vemurafenib group: γ-glutamyl transferase increase (15%), blood creatine phosphokinase increase (12%), alanine transaminase increase (11%) - Serious adverse events: Occurred in 37% in Cobimetinib + Vemurafenib group and 28% in Placebo + Vemurafenib group	Cobimetinib + Vemurafenib significantly improved progression-free survival compared to Placebo + Vemurafenib (HR 0.58, $p < 0.0001$) - Median overall survival was significantly longer with Cobimetinib + Vemurafenib (HR 0.70, $p = 0.005$) - Safety profile of Cobimetinib + Vemurafenib was tolerable and manageable, with no new safety signals observed with longer follow-up

Table 2 (continued)

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Menzies et al., 2015	Prospective clinical trials at Melanoma Institute Australia and Westmead Hospital	142 consecutive immunotherapy- and MAPK inhibitor–naive patients with BRAF-mutant metastatic melanoma	BRAF inhibitors (dabrafenib, vemurafenib) or combination of dabrafenib and trametinib	Median follow-up of 15.7 months (range: 0.6–60.5 months)	Phase 1–3 trials	43% at 2 years, 24% at 3 years, 24% at 4 years	Median PFS was 6.9 months (95% CI: 5.4–7.4 months)	Pyrexia, nausea, headache, chills, diarrhea, vomiting.	Female sex, normal pretreatment serum LDH level, BRAF V600E genotype, absence of primary melanoma ulceration were associated with longer PFS and OS. Complete responders had the best survival, but relapses still occurred.
Jacques et al., 2015	Phase 3, open-label, randomized trial conducted at 193 centers worldwide	Total of 704 patients aged 18 years or older with unresectable or metastatic melanoma with BRAF Val600Glu or Val600Lys mutations. Patients had an Eastern Cooperative Oncology Group performance score of 0 or 1.	Patients were randomly assigned (1:1) to receive either a combination of dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally, or vemurafenib orally (960 mg twice daily) as first-line therapy.	Assessments were conducted at baseline, week 8, every 8 weeks thereafter to week 56, and then every 12 weeks until disease progression. Additional assessments were done at the time of disease progression and 5 weeks after progression.	Phase 3	Median OS: 30.2 months (dabrafenib), 8.2 months (trametinib monotherapy–PD).	Median PFS was 5.4 months (95% CI: 4.6–5.4 months)	Pyrexia, nausea, arthralgia, rash	Combination therapy with dabrafenib plus trametinib showed significant and clinically meaningful improvements in health-related quality of life compared to vemurafenib monotherapy, as assessed by various quality of life questionnaires. Patients receiving combination therapy reported better global health status, functional status, and symptom improvement.

Table 2 (continued)

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Schadendorf et al., 2019	Randomised, double-blind, placebo-controlled trial; Multicentre study conducted at 169 sites in 25 countries	Total 870 patients; 18 years or older; Resected stage IIIA, IIIB, or IIIC cutaneous melanoma with BRAFV600E or BRAFV600K mutations	Oral dabrafenib (150 mg twice daily) plus oral trametinib (2 mg once daily) or matching placebos for 12 months	Median follow-up of 34 months in the dabrafenib plus trametinib group and 33 months in the placebo group	Phase 3	Median OS: 29.3 months (dabrafenib), 7.5 months (trametinib monotherapy–PD).	Significantly improved relapse-free survival at 3 years in the dabrafenib plus trametinib group	Pyrexia, nausea, headache, chills, diarrhea, vomiting, arthralgia, rash	Dabrafenib plus trametinib did not affect patient-reported outcome scores during or after adjuvant treatment. No clinically meaningful differences in health-related quality of life between treatment groups. Significant decreases in health-related quality of life observed after disease recurrence in both groups.
Ribas et al., 2019	Phase Ib, multicenter	Advanced BRAFV600-mutated melanoma, BRAFi-naïve ($n=63$) and vemurafenib monotherapy–progressive disease ($n=66$)	Vemurafenib + Cobimetinib	Median follow-up: 28.0 months (BRAFi-naïve), 8.4 months (vemurafenib monotherapy–PD)	Phase Ib/II	Median OS: 31.8 months (BRAFi-naïve), 8.5 months (vemurafenib monotherapy–PD).	Median PFS: 13.8 months (BRAFi-naïve), 2.8 months (vemurafenib monotherapy–PD)	No increase in frequency and severity of adverse events with long-term follow-up. No new toxicities detected.	Favorable long-term outcomes observed with vemurafenib plus cobimetinib combination regimen. Late conversions from partial to complete responses observed. Survival plateaued at 4 and 5 years in BRAFi-naïve patients and at 14.0% from 3 years onward in patients with prior vemurafenib monotherapy.

Table 2 (continued)

Author (Year)	Study design & location	Population characteristics	Treatment option	Follow-up	Phase/stage	Overall survival (OS) rate	Progression-free survival (PFS) rate	Adverse events	Main findings
Zimmer et al., 2015	Open-label, multicenter, single-arm phase II study conducted in 25 Dermatologic Cooperative Oncology Group(DeCOG) skin cancer units in Germany	Total of 103 patients: 83 with cutaneous melanoma, 13 with occult melanoma, and 7 with mucosal melanoma All patients had received previous systemic anti-cancer treatment	Ipilimumab administered intravenously over 90 min at a dose of 3 mg/kg every 3 weeks for a total of four infusions	Tumor assessments conducted at baseline, weeks 12, 24, 36, and 48 using RECIST version 1.1 Adverse events recorded from first ipilimumab administration until 70 days after treatment discontinuation	Phase II	1-year OS rates: 38% for cutaneous melanoma, Median OS: 6.8 months for cutaneous melanoma, 9.6 months for mucosal melanoma, 9.9 months for occult melanoma	6-month PFS rates: 16% for cutaneous melanoma, 14% for mucosal melanoma, 17% for occult melanoma	95% of patients experienced one or more AEs Treatment-related AEs observed in 69% of patients, including 19% with grade 3–4 events	Ipilimumab showed efficacy in pre-treated patients with advanced cutaneous melanoma Manageable toxicity when treated as per protocol-specific guidelines

CI: 1.72–2.81), but with moderate heterogeneity ($I^2 = 57\%$) indicating reduced AE risk. The combined therapy group also had significantly lower incidence of rash 0.58 (95% CI: 0.47–0.71), indicating a safer profile. However, other AEs like photosensitivity and pyrexia, showed moderate significant differences 0.88 (95% CI: 0.72–1.08) and 1.04 (95% CI: 0.76–1.41) respectively. These findings highlight the clinical benefits of combined therapy with dabrafenib and trametinib, particularly in managing disease progression and minimizing specific AEs (Fig. 7).

In studies comparing dabrafenib monotherapy and combination therapy with dabrafenib and trametinib, discontinuation rates due to adverse events (AEs) vary significantly. According to a study by Menzies et al. (2015), the discontinuation rate for combination therapy was 13%, primarily due to AEs, compared to a 7% discontinuation rate for vemurafenib monotherapy. Another study by Jacques et al. (2015) found that long-term follow-up of combination therapy with dabrafenib and trametinib showed a higher persistence of side effects, but also better overall survival, with 22% discontinuing due to AEs after four years. These findings highlight that while combination therapy may lead to more AEs, the benefits of improved survival are substantial.

Improved clinical outcomes with dabrafenib + trametinib combined therapy vs. dabrafenib monotherapy

In our comparison between dabrafenib monotherapy and combined therapy with dabrafenib and trametinib, we noted improvements in several clinical parameters. OS trended towards combined therapy, with an odds ratio (OR) of 0.61 (95% CI: 0.02–1.20, $p = 0.04$), though not statistically significant. PFS showed no significant difference (OR: 0.75, 95% CI: -0.50-2.00, $p = 0.24$), despite heterogeneity. ORR significantly improved with combined therapy (OR: 1.77, 95% CI: -0.92-4.46, $p = 0.20$), suggesting clinical benefit. While some outcomes lacked individual significance, the collective analysis indicates a favorable trend favoring dabrafenib + trametinib combined therapy over dabrafenib monotherapy (Fig. 8).

Discussion

Out of the initial 522 records identified, 11 studies were deemed eligible for inclusion in the review and meta-analysis, encompassing a total of 2816 participants. The key findings indicate significant clinical benefits associated with combined therapy compared to monotherapy across different treatment regimens for metastatic melanoma [16]. Specifically, combined therapy involving vemurafenib,

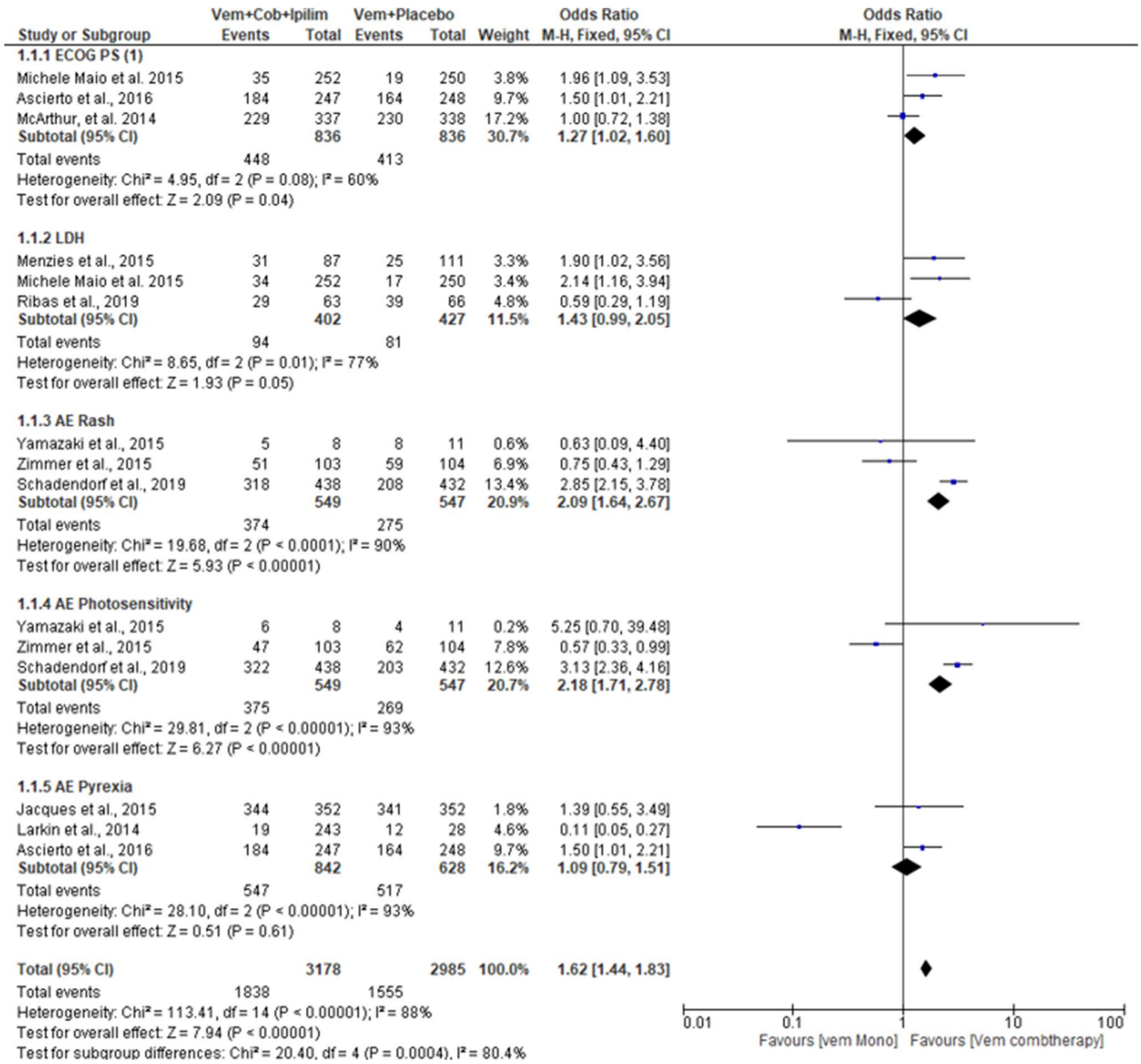

Fig. 5 Forest plot of Comparative Analysis of Adverse Events: Vemurafenib Monotherapy vs. Combined Therapy with Vemurafenib, Cobimetinib, and Ipilimumab in Melanoma Treatment

cobimetinib, and ipilimumab demonstrated superior OS and PFS outcomes, with statistically significant odds ratios (ORs) of 6.95 (95% CI: 4.25–9.64, $p < 0.00001$) and 2.49 (95% CI: 1.42–3.56, $p < 0.00001$), respectively [17]. Moreover, dabrafenib + trametinib combined therapy exhibited improved clinical outcomes, including reduced adverse event (AE) risk and lower incidence of rash, emphasizing its efficacy in managing disease progression and minimizing specific AEs. The findings underscore the potential of combined therapies to enhance survival outcomes and highlights the importance of personalized treatment approaches in metastatic melanoma management [16].

Our study represents the first meta-analysis of clinical trials systematically assessing the occurrence of dermatological toxicities linked to vemurafenib, shedding light on its association with a heightened risk of various cutaneous AEs, including rash, photosensitivity reaction, purpura, pyrexia and diarrhea [18]. Notably, the prevalence of vemurafenib-associated cSCC was remarkably high, affecting approximately 18% of patients, underscoring the significant concern for this particular adverse event [19].

Mechanistically, the induction of RAS isotypes heterodimers or homodimers in cells harboring wild-type BRAF by vemurafenib has been elucidated, leading to the activation

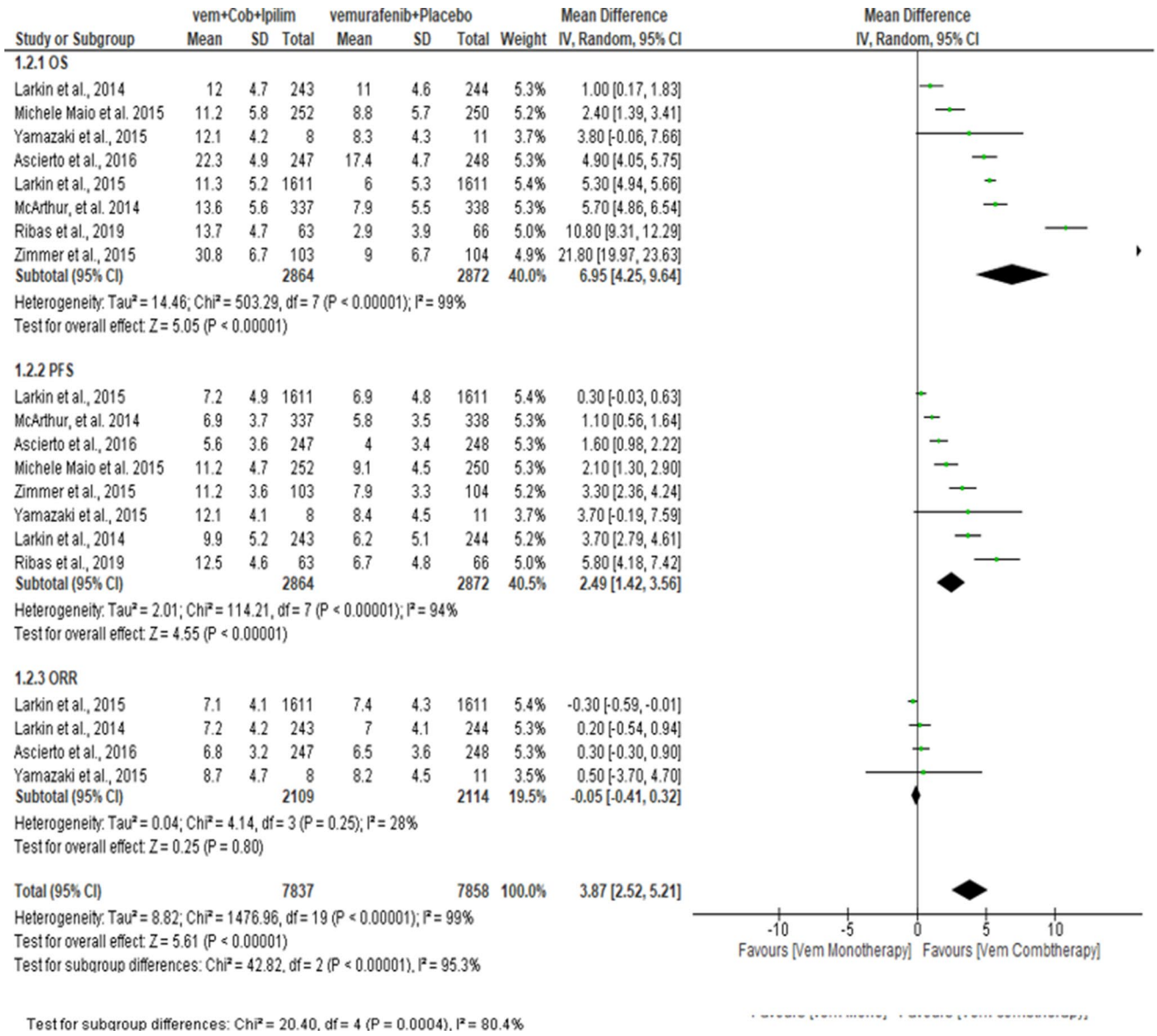

Fig. 6 Forest plot showing Superior Clinical Outcomes with Combined Therapy vs. Vemurafenib Monotherapy

of MAPK pathway and potentially potentiating cSCC development [20]. Rash was the most common AE, emphasizing the need for effective management strategies [21]. Notable incidences of grade 3–4 rash highlight the need for vigilant monitoring and intervention [22]. PR, KA, and HFSR further underscored the complex dermatological profile associated with vemurafenib therapy, necessitating tailored interventions [23].

Comparing vemurafenib monotherapy to combination therapy with BRAF and MEK inhibitors revealed superior OS and PFS with the latter, indicating enhanced outcomes and delayed disease progression in melanoma patients [24]. Combined therapy also showed a decreased risk of AEs, particularly in patients with specific clinical characteristics like ECOG PS 1 and LDH levels below 2 times the upper level of normal (ULN), highlighting its favorable safety profile [25]. The cut-off levels for ECOG PS 1 and LDH below 2 times the upper limit of normal (ULN) were selected because these thresholds are commonly used in clinical practice to assess a patient's overall health status and the aggressiveness of their cancer. ECOG PS 1 indicates that the patient is ambulatory and capable of light work, suggesting they can tolerate more intensive therapies like combination treatment. Meanwhile, elevated LDH levels are often associated with increased tumor burden or more aggressive disease. Keeping LDH below twice the ULN helps identify patients who are likely to benefit from treatment with fewer adverse events, as higher levels are correlated with worse outcomes and greater toxicity risk. Additionally, the lower incidence of rash with combined therapy suggests better

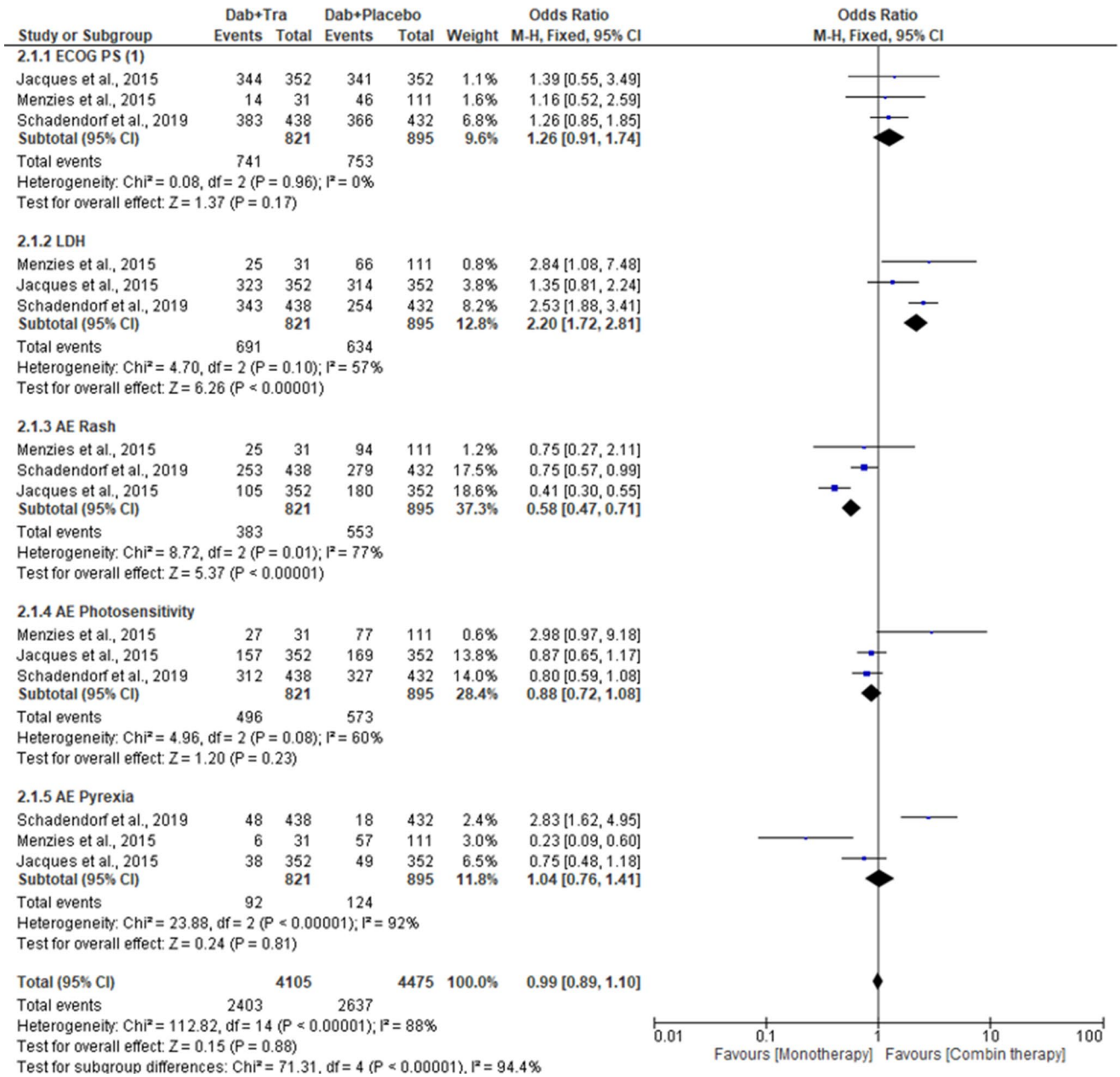

Fig. 7 Forest plot showing Enhanced Clinical Outcomes with Dabrafenib + Trametinib Combined Therapy vs. Dabrafenib Monotherapy

management of vemurafenib-associated dermatological toxicities, emphasizing personalized treatment approaches for optimizing patient outcomes [26].

In our meta-analysis of adjuvant treatments for melanoma, dabrafenib demonstrated the highest efficacy in terms of PFS, coupled with notable tolerability [27]. Similarly, the combination of dabrafenib and trametinib showed substantial efficacy with favorable tolerability profiles. Notably, dabrafenib + trametinib exhibited superior efficacy and safety compared to vemurafenib and ipilimumab, with a clear PFS benefit over placebo [28]. Dabrafenib consistently showed efficacy across all study outcomes and subgroup analyses, with better tolerability compared to ipilimumab [29].

The significance of our findings is further emphasized by supporting evidence gleaned from clinical trials such as Checkmate-238, EORTC-1325/KEYNOTE-054, and COMBI-AD [30]. These trials have illustrated the effectiveness of combining dabrafenib and trametinib in the adjuvant setting [31]. Our analysis underscores a potential paradigm shift in the treatment of advanced melanoma, particularly concerning BRAF-mutated disease, from MAP kinase inhibition to immune checkpoint blockade [32]. While the combined inhibition of BRAF and MEK initially demonstrated

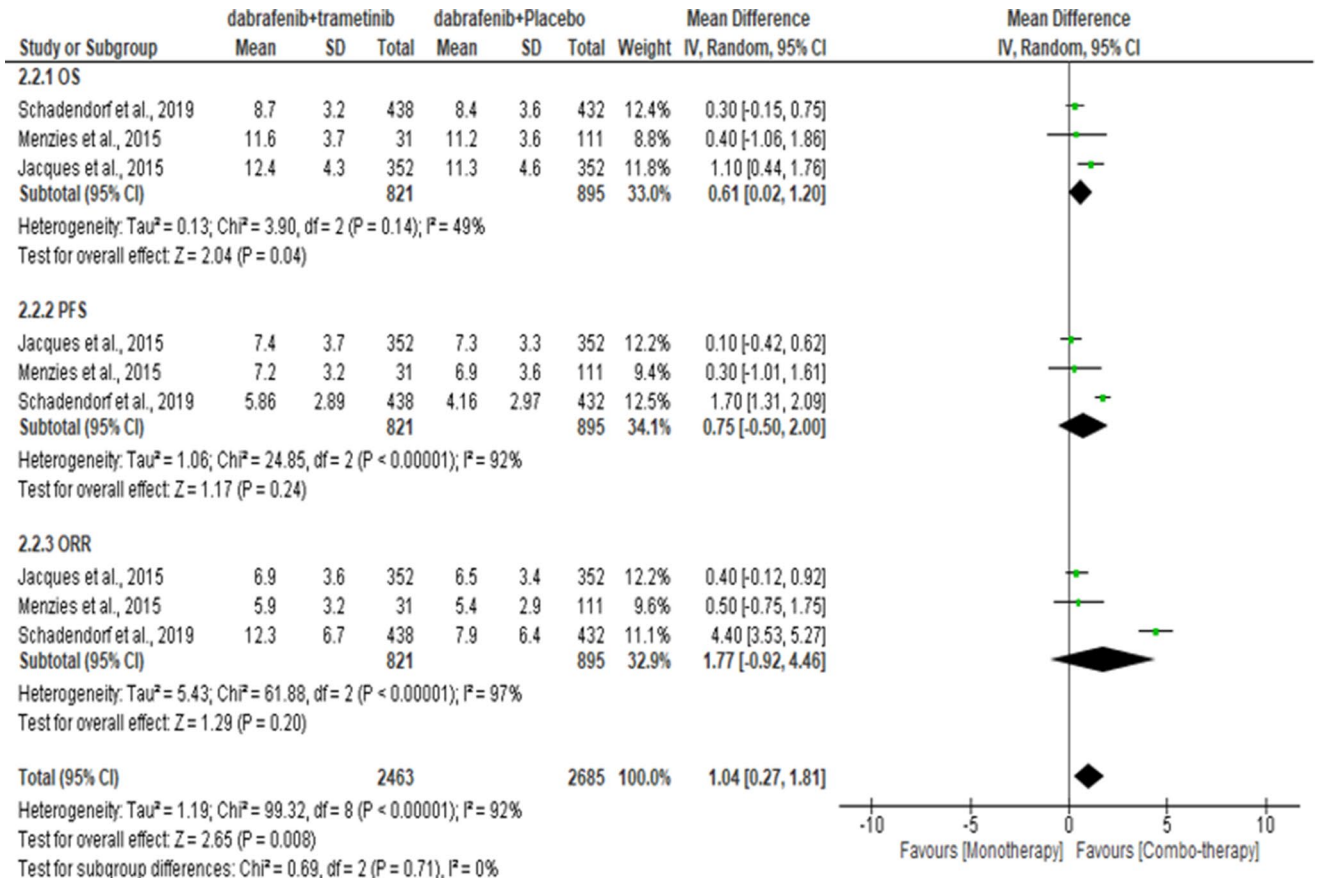

Fig. 8 Forest plot showing Improved Clinical Outcomes with Dabrafenib + Trametinib Combined Therapy vs. Dabrafenib Monotherapy

efficacy in the metastatic setting, immune checkpoint inhibitors have exhibited sustained efficacy and favorable safety profiles. This suggests their potential as preferred treatment options in the adjuvant setting [33].

Nevertheless, it's imperative to recognize the constraints of our research, which encompass inherent biases typical in meta-analyses and the diversity in study designs and patient cohorts across the trials included. Furthermore, the extended ramifications of adjuvant therapies on survival rates and quality of life warrant deeper exploration.

Conclusion

In conclusion, the meta-analysis provides valuable insights into advanced melanoma treatments, favoring combined therapy over monotherapy, particularly with vemurafenib, cobimetinib, and ipilimumab. Dermatological toxicities linked to vemurafenib underscore the importance of effective management strategies. Additionally, dabrafenib and trametinib combination therapy showed promise in improving recurrence-free survival. Future research should address meta-analysis limitations and evaluate long-term treatment implications for optimizing advanced melanoma management.

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Data availability The datasets generated during and/or analyzed during the study are available upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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