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Dual checkpoint inhibitor therapy versus dual targeted therapy of untreated metastatic BRAF-mutant melanoma: a systematic review of randomised controlled trials

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ABSTRACT

Objective Dual immune checkpoint inhibitor (ICI) therapy might improve the outcome of adult patients with untreated metastatic BRAF-mutant melanoma. We synthesised the evidence of its effect on overall survival (OS) and adverse events.

Design Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data sources MEDLINE and the Cochrane Library were searched through 15 May 2025.

Eligibility criteria for selecting studies We included randomised controlled trials (RCTs) assessing the effects of first-line dual ICI therapy compared with first-line dual targeted therapy (TT) on adult patients with metastatic BRAF-mutant melanoma. We considered articles in English or German language.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Time-to-event data were pooled using the generic inverse-variance method and expressed as HRs with 95% CIs. Dichotomous data were pooled using the Mantel-Haenszel method and expressed as risk ratios (RRs). Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). GRADE assessed the certainty of the evidence.

Results We identified two RCTs (305 participants) with parallel assignment and intention-to-treat analyses. The primary beneficial outcome was overall survival (OS), and OS favoured the first-line ICI group: HR 0.66 (95% CI 0.49 to 0.90) I^2=0%. In contrast, the primary adverse outcome was treatment-related adverse events of grade 3 or higher (TRAEs), and TRAE favoured the first-line TT group: RR 1.18 (95% CI 1.01 to 1.39) I^2=0%. The certainty of the evidence was graded as moderate.

Conclusions The evidence base is compatible with a favourable effect of first-line nivolumab plus ipilimumab for adults with untreated metastatic BRAF-mutant melanoma on survival and an unfavourable effect on toxicity when compared with first-line TT. Future RCTs could provide more data on therapy failure and quality of life.

PROSPERO registration number CRD420251006128.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present review is based on a comprehensive search, and we are confident that we included all randomised controlled trials (RCTs) that were available at the time of the search.
⇒ Study selection and risk of bias assessment are subjective, and we employed three independent reviewers.
⇒ We deduced the survival data from the Kaplan-Meier plots of the article, and we calculated the HR using data from the curve with numbers at risk given.
⇒ Switching between random and fixed effects did not change the direction of effect.
⇒ The two included RCTs reported various clinical stages of melanoma, which can bias the effect and applicability of the results.

INTRODUCTION

In this systematic review, the disease of interest is the untreated metastatic BRAF-mutant melanoma. Cutaneous melanoma arises from malignant transformation of melanocytes, the pigment-producing cells derived from the neural crest.[1] Although melanoma accounts for only a minority of skin cancers, it is responsible for the majority of skin cancer-related deaths.[2] Worldwide, cutaneous melanoma causes approximately 55 500 cancer deaths annually, accounting for about 0.7% of all cancer-related deaths.[3] Its incidence has been increasing since the early 1970s, particularly in predominantly fair-skinned populations.[2] Melanoma is primarily caused by DNA damage resulting from exposure to ultraviolet radiation.[4] Thus, sun exposure is the most important risk factor.[5] Approximately 40–50% of metastatic melanomas harbour activating mutations in the BRAF gene, most commonly the V600E mutation, which results in constitutive activation of the MAPK/ERK

signalling cascade and promotes uncontrolled cell proliferation and tumour progression.[6 7] Melanoma is highly immunogenic due to its high mutational burden, which leads to abundant neoantigen formation and makes it especially susceptible to immune checkpoint inhibition.[8] Additionally, spontaneous regressions and historical responsiveness to immunotherapy underscore its unique sensitivity to immune modulation.[9] Two main treatment modalities are approved for BRAF-mutant metastatic melanoma: immune checkpoint inhibitors (ICIs) and targeted therapies (TTs).[10]

In this systematic review, the test intervention of interest is the first-line dual ICI therapy, specifically the combination of nivolumab plus ipilimumab, and the control intervention is the first-line dual targeted cancer therapy.[10]

ICI therapy is an established treatment modality in melanoma. ICIs function by blocking inhibitory pathways, such as programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4), that normally suppress T-cell activation to maintain immune homeostasis. Tumours exploit these checkpoints to evade immune detection. Nivolumab is a monoclonal antibody targeting PD-1, a receptor on activated T cells that, when engaged by its ligands PD-L1 or PD-L2, inhibits T-cell activity. By blocking PD-1, nivolumab restores effector T-cell function and promotes tumour cell killing. The monoclonal antibody ipilimumab blocks CTLA-4 that regulates early T-cell activation, thereby enhancing T-cell priming and proliferation. As a consequence, checkpoint inhibitor therapy is associated with a higher risk of immunological adverse effects including autoimmune diseases and various inflammatory diseases such as colitis, thyroiditis and hypophysitis.[11]

TT refers to a form of precision oncology designed to inhibit specific molecular pathways that are essential for tumour cell proliferation, survival and metastasis. In the context of this systematic review, dual TT refers to the combined inhibition of two key signalling molecules: BRAF and MEK. The BRAF V600E mutation, a thymine-to-adenine transversion at nucleotide 1799 in exon 15, results in the substitution of valine (V) with glutamic acid (E) at codon 600. This mutation leads to constitutive activation of the BRAF kinase, driving uncontrolled MAPK/ERK pathway signalling and tumour growth.[6 7] BRAF functions upstream of MEK in the MAPK cascade, and MEK activation further promotes cell proliferation and survival.[10 11] Dual inhibition of BRAF and MEK has been shown to improve response rates, delay resistance and reduce toxicity compared with BRAF inhibition alone. Approved combinations include encorafenib plus binimetinib, vemurafenib plus cobimetinib and dabrafenib plus trametinib.[10] Concerning these combinations, adverse events occur predominantly in the cutaneous system, with rash, photosensitivity and hyperkeratosis being the most frequent reported toxicities, followed by fever and gastrointestinal symptoms.[12]

Table 1 Inclusion criteria

Item	Description
Study design	Randomised clinical trials with parallel assignment
Participants*	Adults with untreated, metastatic BRAF V600 mutated melanoma
Intervention	First-line dual immune checkpoint inhibitor therapy ► Nivolumab (PD-1 inhibitor) PLUS Ipilimumab (CTLA-4 inhibitor).
Comparators	First-line dual targeted therapy of cancer ► Encorafenib PLUS binimetinib. ► Vemurafenib PLUS cobimetinib. ► Dabrafenib PLUS trametinib.
Outcomes	Primary beneficial outcome ► Overall survival. Primary adverse outcome ► Treatment-related adverse events grade III or higher. Secondary outcomes ► Progression-free survival. ► Brain metastases-free survival. ► Survival after brain metastases were detected after randomisation.
Publication type	Article publications in peer-reviewed journals ► Not considered: abstract publications including meeting abstracts, ongoing studies, trial registry results, comments, letters, narrative reviews, opinions, systematic reviews, meta-analyses and duplicate publications. ► If costs or health-related quality of life were the only outcomes, then these studies were also not considered.

*In departing from the protocol, we included brain metastasis.
BRAF: human gene that encodes one of three RAF kinase proteins which are part of the serine/threonine-protein kinase family. V600E indicates a specific mutation of the BRAF gene in which valine (V) is substituted by glutamic acid (E) at amino acid 600.
CTLA-4, cytotoxic T-lymphocyte associated protein 4; PD-1, programmed cell death protein 1; RAF, rapidly accelerated fibrosarcoma.

Objective

This systematic review aimed to assess the effects of dual ICI therapy versus dual targeted cancer therapy in adult patients with untreated metastatic BRAF-mutant melanoma.

METHODS

While preparing this systematic review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[13] The PROSPERO registration number is CRD420251006128.

Inclusion criteria

An overview of the inclusion criteria is shown in table 1. We included article publications of randomised controlled

trials (RCTs) with parallel assignment in peer-reviewed journals. The population of interest was adult patients with an untreated, metastatic BRAF V600 mutated melanoma, including patients with brain metastases. Interventions and comparators were taken from recommendations of the recent European consensus-based interdisciplinary guideline for melanoma.[10] The intervention of interest was the dual checkpoint inhibitor therapy, specifically the combination of the PD-1 inhibitor nivolumab plus the CTLA-4 inhibitor ipilimumab. The comparator was the dual target therapy specifically either the combination of encorafenib plus binimetinib or the combination of vemurafenib plus cobimetinib or the combination of dabrafenib plus trametinib. Outcomes are described in a separate section below. No language restrictions were applied during the database search.

Exclusion criteria

We did not consider comments, letters, narrative reviews, opinions, systematic reviews, meta-analyses and duplicate publications. Unless associated with included trials, we did not consider abstract publications including meeting abstracts, ongoing studies and trial registry results. If costs or health-related quality of life were the only outcomes, then these studies were excluded.

Search strategy

We performed an unrestricted electronic literature database search in MEDLINE (via PubMed, US National Library of Medicine) on 12 November 2025, and the respective search strategy is listed in online supplemental table 1. Due to automated term mapping, use of an asterisk (*) as a wild card for truncation, different spelling or use of synonyms was not necessary. We conducted an additional electronic literature database search in the Cochrane Central Register of Controlled Trials (CENTRAL) (via The Cochrane Library, Wiley) on 12 November 2025, and the respective search strategy is listed in online supplemental table 2. MeSH terms were combined with text terms to ensure a comprehensive and up-to-date search. We searched in online trial registries on 12 November 2025 without applying limits. For searching in ClinicalTrials.gov (CT.gov, https://clinicaltrials.gov/, US National Library of Medicine), we used the query Condition/disease: “melanoma metastatic” | Intervention/treatment: “checkpoint Inhibitor, immune” | Age: “adult (18 - 64)” or “older adult (65+)” | Study phase: “phase 2” or “phase 3” | Study type: “interventional” | Title and/or title acronym: “immunotherapy or targeted therapy”. For searching in the International Clinical Trials Registry Platform (ICTRP, https://trialsearch.who.int, WHO), we used the query “Melanoma metastatic Immunotherapy Targeted therapy”. We searched reference lists of recent publications, Google, and we used PubMed tools including *similar articles* and *clinical queries*. The search on 12 November 2025 is an update of a previous search which was conducted on 5 May 2025. We limited the search for meeting abstracts by relying on the presearched results retrieved from CENTRAL which includes subject-related abstracts from Embase.

Study selection

We planned to use a translation tool for the inclusion of different language articles, though this was not necessary. We applied independent study selection, data extraction and judgement by multiple observers. SB imported the bibliographic data into Excel (Microsoft) and SB and FP independently selected relevant studies in a two-step screening process. In the first step of safe exclusion (title and/or abstract screening), we excluded references if both reviewers agreed that those references were not relevant to this systematic review. If at least one reviewer was not sure about excluding a reference, then this reference was regarded as potentially relevant, and it was assigned to full-text assessment. We calculated Cohen’s kappa coefficient to measure the inter-rater reliability[14] and characterised the resulting values as follows: 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement.[15]

In the second step of safe inclusion (full-text assessment), SB and FP independently assessed the potentially relevant article or abstract publications. We included references if both reviewers agreed that those references were relevant to this systematic review. If at least one reviewer was not sure about including a reference, then we initiated a discussion. If the discussion was not satisfactory, then a third reviewer (KBA) joined the evaluation to clarify whether inclusion criteria were truly met. We calculated Cohen’s kappa coefficient to measure the inter-rater reliability[14] and characterised the resulting values as follows: 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement.[15] If a reference was not deemed of interest, then we ascribed an exclusion reason according to the following decreasing order of priority: population, intervention, comparator, outcomes, study design. If we agreed on the inclusion of a specific study, then we included all available publications associated with this study. One of the publications of an included study was denoted the primary reference for the study, and the other publications were checked to see whether they contained important additional information.

Outcomes

The primary beneficial outcome was overall survival (OS). Synonymous terms to define the event include overall mortality, all-cause mortality, all-cause death, all deaths, survival free of death. Overall mortality was defined as death from any cause, and the measure of effect was the HR. The primary adverse outcome was serious treatment-related adverse events (TRAEs) reported at any time during the study. Seriousness of the TRAE was defined by grade 3 or higher of the Common Terminology Criteria for Adverse Events (CTCAE) V.4.0 (2009).[16] Secondary outcomes include progression-free survival, brain metastases-free survival and survival after brain metastases which were detected after randomisation. In those time-to-event analyses, the measure of effect was the HR.

Data extraction and analysis

SB and FP independently extracted characteristics of the study design, participants, interventions and outcomes into Word (Microsoft). Differences in opinions were resolved by discussion and the assistance of KBA. The main extracted data fields included the study characteristics as follows: registry number; study name; design; study locations; enrolment; inclusion, exclusion and assignment criteria for study participants to enter; median age and sex proportion of study participants; type of intervention; type of comparator; outcomes relevant for this systematic review.

Concerning the time-to-event data, we applied the statistical method *inverse variance*, the analysis model *random effects* and the effect measure HR. We reproduced the survival functions by deducing survival data from the Kaplan-Meier survival curves depicted in the corresponding figures. We used the Excel tool provided by Tierney[17] to estimate the logHR (HR) and its SE HR by using the 'data from curve with numbers at risk given', which is based on the method by Parmar.[18] We made sure that the constructed graph and the published graph were alike. Fortunately, the authors reported well-prepared graphs with sufficient information on the numbers of participants at risk, and we did not detect important missing information. Data were analysed using the Cochrane Review Manager V.5 (The Cochrane Collaboration).

Concerning dichotomous data, we applied the statistical method *Mantel-Haenszel*, the analysis model *random effects* and the effect measure *risk ratio* (RR). We extracted the total number of analysed participants in each treatment group and the number of participants with an event. We made sure that the resulting figures matched those reported in both the text and the tables of the articles. Data were analysed using the Cochrane Review Manager V.5 (The Cochrane Collaboration).

Subgroups and heterogeneity

We assessed clinical reasons for heterogeneity and estimated the percentage heterogeneity between trials that cannot be ascribed to sampling variation using the index of heterogeneity (I^2 statistic).[19] An I^2 statistic equal to or greater than 50% was regarded as substantial heterogeneity. The following sensitivity analyses were planned to explain at least parts of the statistical heterogeneity: studies with low risk of bias versus high/unclear risk of bias; removal of studies with deviant data. We assessed the robustness of the results by comparing the random effects model versus the fixed effects model. Since we expected a small number of studies that enrolled patient within comparable time periods, we did not plan subgroup analyses.

Risk of bias assessment

Two authors independently appraised the risk of bias of the included studies. SB drafted an appraisal, and FP checked the draft against the text of the included articles. Differences in opinions were resolved by discussion and the assistance of KBA. We used the items suggested by the Cochrane's tool for assessing risk of bias,[20] which included seven items for assessment as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias (funding bias). In general, if an item met one of the requested criteria, we judged a low risk of bias; if an item was not addressed, we judged an unclear risk of bias; and if an item was negated, we judged a high risk of bias. With respect to an open-label study, we judged a high risk of bias for blinding items. Concerning incomplete outcome data, we judged an unclear risk of bias if the missing data did not appear sufficient to have a clinically relevant impact on the effect estimate. Concerning other bias, we judged a low risk of bias if the funding was not industry based. Since only two studies were included, we did not assess the publication bias by visual inspection of the corresponding funnel plot.[21]

Grading the certainty of evidence

We adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to define the certainty of a body of the identified evidence as described in the Cochrane Handbook for Systematic Reviews of Interventions.[22] We established the initial level of certainty based on study design, considered lowering the level of certainty based on risk of bias, inconsistency, indirectness, imprecision and publication bias, and we rated the certainty in an estimate of effect across those considerations as high, moderate, low or very low. For the primary beneficial outcome and the primary adverse outcome, two review authors (FP, KBA) independently assessed the quality of the evidence by using the GRADE considerations.

Patient and public involvement

None.

RESULTS

Search results

We retrieved 180 references from electronic databases, 86 from PubMed and 94 from the Cochrane Library. Of the 94 references from the Cochrane Library, 89 references were retrieved from the CENTRAL and 5 references from the Cochrane Database of Systematic Reviews. We retrieved one study in the clinical trials database ClinicalTrials.gov and eight from the clinical trials platform ICTRP. The respective PRISMA flow chart is shown in online supplemental figure 1. We did not find information on other studies in references lists of recent reviews and included publications, and we did not find other studies by searching Google. Of the 189 imported references, 153 references were excluded and 36 references were deemed potentially relevant in the first step of the

Table 2 Included studies (n=2), associated references (n=9)

Study ID	Info	Reference
DREAMseq	Primary reference for the study	Atkins MB, Lee SJ, Chmielowski B, Tarhini AA, Cohen GI, Truong TG, *et al* Combination dabrafenib and trametinib vs combination nivolumab and ipilimumab for patients with advanced BRAF-mutant melanoma: the DREAMseq trial-ECOG-ACRIN EA6134. J Clin Oncol. 2023;41(2):186–197.
	NCT02224781	Atkins MB. Dabrafenib and trametinib followed by ipilimumab and nivolumab or ipilimumab and nivolumab followed by dabrafenib and trametinib in treating patients with stage III-IV BRAFV600 melanoma (https://clinicaltrials.gov/ct2/show/NCT02224781).
	2022 ASCO meeting	Jensen RE, Zheng Y, Atkins MB, Chmielowski B, Tarhini AA, Truong TG, *et al* Early quality of life (QOL) and symptom analysis from the DREAMseq phase III randomised control trial of combination immunotherapy vs targeted therapy in patients (pts) with BRAF-mutant metastatic melanoma (MM) (ECOG-ACRIN EA6134). J Clin Oncol. 2022;40(Suppl 16):9559.[25]
SECOMBIT	Primary reference for the study	Ascierto PA, Mandala M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, *et al* Sequencing of ipilimumab plus nivolumab and encorafenib plus binimetinib for untreated BRAF-mutated metastatic melanoma (SECOMBIT): a randomised, three-arm, open-label phase II trial. J Clin Oncol. 2023;41(2):212–221.
	NCT02631447	Ascierto PA. Sequential combo immuno and target therapy (SECOMBIT) study (https://clinicaltrials.gov/ct2/show/NCT02631447).
	Follow-up report and brain metastases	Ascierto PA, Mandala M, Ferrucci PF, Guidoboni M, Rutkowski P, Ferraresi V, *et al* Sequencing of checkpoint or BRAF/MEK inhibitors on brain metastases in melanoma. NEJM Evid. 2024;3(10):EVIDoa2400087.[28]
	Follow-up report and biomarker	Ascierto PA, Casula M, Bulgarelli J, Pisano M, Piccinini C, Piccin L, *et al* Sequential immunotherapy and targeted therapy for metastatic BRAF V600 mutated melanoma: 4-year survival and biomarkers evaluation from the phase II SECOMBIT trial. Nat Commun. 2024;15(1):146.[29]
	2021 ESMO Meeting	Ascierto PA, Mandala M, Ferrucci PF, Rutkowski P, Guidoboni M, Arrance Fernandez AM *et al* LBA40 SECOMBIT: The best sequential approach with combo immunotherapy (ipilimumab (I) / nivolumab (N))and combo target therapy (encorafenib (E)/binimetinib (B))in patients with BRAF mutated metastatic melanoma: A phase II randomised study. Ann Oncol. 2021;32(Suppl 5):S1316-S1317.[30]
	2017 ASCO Meeting	Ascierto PA, Dummer R, Melero I, Palmieri G, Giannarelli D, Abrami E, *et al* SECOMBIT (sequential combo immuno and target therapy study): A three arms prospective, randomised phase II study to evaluate the best sequential approach with combo immunotherapy (ipilimumab (I) /nivolumab (N))and combo target therapy (encorafenib (E)/binimetinib (B)) in patients with metastatic melanoma and BRAF mutation. J Clin Oncol. 2017;35 (15_suppl):TPS9598.[31]

ASCO, American Society of Clinical Oncology; DREAMseq, Doublet, Randomized Evaluation in Advanced Melanoma Sequencing; ESMO, European Society for Medical Oncology; NCT, ClinicalTrials.gov identifier (National Clinical Trial number).; SECOMBIT, Sequential Combo Immuno and Target Therapy.

screening. Of the 36 potentially relevant references, 9 references associated with two RCTs were included. In the first step, the two reviewers (SB, FP) disagreed on 22 references, and Cohen's kappa indicated a moderate agreement, and the respective two-by-two table is shown in online supplemental table 3. In the second step, the two reviewers (SB, FP) disagreed on seven references, and Cohen's kappa indicated again a moderate agreement, and the respective two-by-two table is shown in online supplemental table 4. The disagreements about reference inclusion led to a discussion, and a third reviewer (KBA) joined the study selection process. It was decided that nine different publications were to be included corresponding to two RCTs (table 2). Of those nine publications, three reported about the study *Doublet, Randomized Evaluation in Advanced Melanoma Sequencing (DREAMseq)*[23–25] and six about the study *Sequential Combo Immuno and Target Therapy (SECOMBIT)*.[26–31] The exclusion reasons for every 1 of the 27 excluded references are listed in online supplemental table 5.

Baseline data

Table 3 provides an overview of study characteristics of the included studies trials *DREAMseq* and *SECOMBIT*. *DREAMseq* recruited participants from the USA and *SECOMBIT* from Europe, mainly Italy. In the intervention arm, both studies applied first-line nivolumab plus ipilimumab in participants with metastatic or unresectable melanoma until progressive disease. One study applied first-line encorafenib plus binimetinib in the comparator arm and the other study applied first-line dabrafenib plus trametinib. In the case of progressive disease, the

Table 3 Inclusion criteria and design of the included trials

	DREAMseq	SECOMBIT
Registries	NCT02224781	NCT02631447
Study name	Doublet, Randomized Evaluation in Advanced Melanoma Sequencing (DREAMseq)	Sequential Combo Immuno and Target Therapy (SECOMBIT)
Design	Allocation: randomised; intervention model: crossover assignment; masking: none. The study is a two-arm, two-step, open-label, randomised phase III trial.	Allocation: randomised; intervention model: parallel assignment; masking: none. Patients were randomly assigned 1:1:1 across treatment arms in a phase II, open label randomised trial.
Sponsor	National Cancer Institute, Bethesda, Maryland, USA	Fondazione Melanoma Onlus, Napoli, Italy
Investigator	ECOG and American College of Radiology Imaging Network Cancer Research Group, Philadelphia, Pennsylvania, USA	Fondazione Melanoma Onlus, Napoli, Italy
Study locations	843 locations in the USA	30 locations in Europe: Italy 15, Austria 4, Spain 3, UK 2, France 1, Germany 1, Greece 1, Poland 1, Sweden 1, Switzerland 1
Enrolment	Launched in 2015 Recruitment status: active, not recruiting Last updated posted: 18 May 2025	November 2016 to May 2019 Recruitment status: completed Last updated posted: 7 June 2024
Population	265 patients of either sex aged ≥18 years were randomly assigned; histologically confirmed stage III (unresectable) or AJCC clinical stage IV melanoma with the BRAF V600 mutation; treatment naïve for metastatic disease; ECOG performance status 0 or 1.	209 patients of either sex aged ≥18 years were randomly assigned; histologically confirmed stage III (unresectable) or AJCC clinical stage IV melanoma with the BRAF V600 mutation; treatment naïve for metastatic disease; ECOG performance status 0 or 1.
Treatment overview	Ipilimumab plus nivolumab until PD was applied in arm A (step 1); this treatment was followed by dabrafenib plus trametinib until second PD in Arm C (step 2). Dabrafenib plus trametinib until PD was applied in Arm B (step 1); this treatment was followed by ipilimumab plus nivolumab until second PD in Arm D (step 2).	Ipilimumab plus nivolumab until PD was applied in Arm B (step 1); this treatment was followed by encorafenib plus binimetinib until second PD (step 2). Encorafenib plus binimetinib until PD was applied in Arm A (step 1); this treatment was followed by ipilimumab plus nivolumab until second PD (step 1). In a third Arm C, patients received a sandwich or induction/maintenance treatment which consisted of encorafenib plus binimetinib for 8 weeks followed by ipilimumab plus nivolumab until PD followed by encorafenib plus binimetinib until second PD. Data from this arm were not extracted for the purpose of this systematic review.
Intervention	133 participants received ipilimumab (1 mg/kg IV once every 3 weeks for four doses) plus nivolumab (3 mg/kg IV once every 3 weeks for four doses) until PD in arm A (ICI).	71 participants received ipilimumab (3 mg/kg IV once every 3 weeks) plus nivolumab (1 mg/kg IV once every 3 weeks three to four cycles, then 3 mg/kg every 2 weeks) until PD in arm B (ICI).
Comparator	132 participants received dabrafenib (150 mg orally two times per day) plus trametinib (2 mg orally once daily) until PD in arm B (TT).	69 participants received encorafenib (450 mg orally once daily) plus binimetinib (45 mg orally two times per day) until PD in arm A (TT).
Outcome: primary	Overall survival	Overall survival
Outcome: secondary	Progression-free survival Overall response rate and duration of response Adverse events based on CTCAE	Progression-free survival Overall response rate and duration of response Adverse events based on CTCAE Biomarkers evaluation
Crossover from step 1 to step 2	20% (27 of 133) from ICI to TT versus 35% (46 of 132) from TT to ICI	51% (36 of 71) from ICI to TT versus 52% (36 of 69) from TT to ICI
Median follow-up	27.7 months	56 months

Continued

Table 3 Continued

	DREAMseq	SECOMBIT
Kaplan-Meier interval	60 months	72 months

.AJCC, American Joint Committee on Cancer; BRAF, human gene that encodes a protein known as serine/threonine-protein kinase B-Raf (rapidly accelerated fibrosarcoma); CTCAE, Common Terminology Criteria for Adverse Events (V.4.0, 2009); ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; IV, intravenous; PD, progressive disease; TT, targeted therapy; V600, mutation of the BRAF gene in which valine (V) is substituted by glutamic acid (E) at amino acid 600.

treatment was crossed over. With respect to outcomes, both studies reported OS, progression-free survival and TRAEs grade III and higher based on the CTCAE V.4.0 (2009).[16] *DREAMseq* added grade V. These grades of adverse events severity were defined as follows. Grade III: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living: refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden. Grade IV: life-threatening consequences; urgent intervention indicated. Grade V: death related to adverse events. A considerable number of participants crossed over from one arm to the other. An overview of the characteristics of the study participants is listed in online supplemental table 6, which did not differ significantly between treatment arms. An overview of the characteristics of the interventions is listed in online supplemental table 7.

Outcomes

The primary beneficial outcome of OS was assessed by applying the HR as the effect measure (table 4). The estimated pooled HR favoured the ICI arm when compared with the TT arm: HR 0.66 (95% CI 0.49 to 0.90) I^2=0% (figure 1).

The primary adverse outcome of TRAEs was assessed by applying the RR as the effect measure (table 4). The estimated pooled RR favoured the TT arm when compared with the ICI arm: TR 1.18 (95% CI 1.01 to 1.39) I^2=0% (figure 2).

The secondary outcome of progression-free survival was assessed by applying the HR as the effect measure (table 4). The estimated pooled HR favoured the ICI arm when compared with the TT arm: HR 0.69 (95% CI 0.54 to 0.89) I^2=0%, and the respective forest plot is shown in online supplemental figure 2.

Brain metastases

The authors of the *SECOMBIT* trial compared the brain metastases-free survival in the ICI arm versus the TT arm. We assessed the brain metastases-free survival by applying the HR as the effect measure, though the data could be extracted only from a single study, and the respective information is listed in online supplemental table 8. The HR did not favour any treatment arm: HR 0.56 (95% CI 0.29 to 1.07), and the respective forest plot is shown in online supplemental figure 3. During the *SECOMBIT* trial, new brain metastases were detected in about 16% (11 of 70) participants in the ICI arm and in about 33% (23 of 69) participants in the TT arm. The authors compared the survival of participants with brain metastases detected after randomisation in the ICI arm versus the TT arm. One participant of the 71 participants in the ICI arm had already brain metastases at baseline and was therefore not considered in this analysis. We assessed the survival of participants with brain metastases detected after randomisation by applying the HR as the effect measure, though the data could be extracted only from a single study, and the respective information is listed in online supplemental table 8. The HR did not favour any treatment arm: HR 0.66 (95% CI 0.31 to 1.41), and the respective forest plot is shown in online supplemental figure 4. Most of the participants who

Table 4 Outcomes (ICI vs TT)

	DREAMseq	SECOMBIT	Pooled estimate
OS	HR 0.61 (95% CI 0.41 to 0.91)*	HR 0.75 (95% CI 0.46 to 1.22)†	HR 0.66 (95% CI 0.49 to 0.90), I^2=0%
TRAEs	(75 of 126) versus (68 of 130)* RR 1.14 (95% CI 0.91 to 1.42)	74% (51 of 69) versus (41 of 69)‡ RR 1.24 (95% CI 0.98 to 1.58)	RR 1.18 (95% CI 1.01 to 1.39), I^2=0%
PFS	HR 0.73 (95% CI 0.54 to 1.00)*	HR 0.62 (95% CI 0.40 to 0.95)†	HR 0.69 (95% CI 0.54 to 0.89), I^2=0%

*OS and PFS extracted from Kaplan-Meier curves, TRAE data extracted from section *Safety* and table 4 of the article by Atkins *et al*.[23]
†OS and PFS data extracted from Kaplan-Meier curves of the article by Ascierto 2024.[28]
‡TRAE data extracted from table 2 of the article by Ascierto *et al*.[26]
.DREAMseq, Doublet, Randomized Evaluation in Advanced Melanoma Sequencing; ICI, immune checkpoint inhibitor(s); OS, overall survival; PFS, progression-free survival; RR, risk ratio; SECOMBIT, Sequential Combo Immuno and Target Therapy; TRAE, treatment-related adverse event; TT, targeted therapy of cancer.

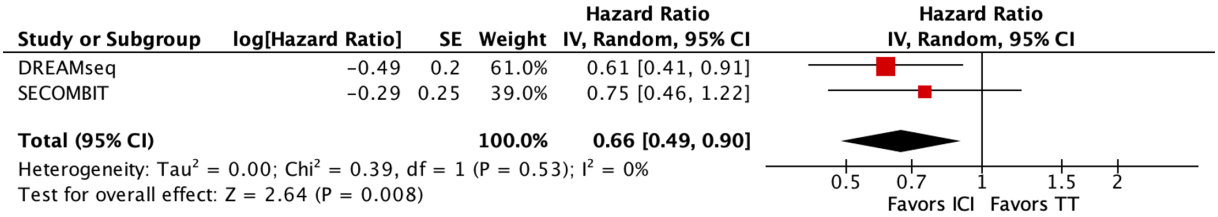

Figure 1 Forest plot for overall survival comparing first-line dual ICI therapy versus first-line dual targeted therapy. Data are HRs (data from curve with numbers at risk given) with 95% CI. I^2: index of heterogeneity (the smaller the value, the lesser the heterogeneity). DREAMseq, Doublet, Randomized Evaluation in Advanced Melanoma Sequencing; ICI, immune checkpoint inhibitor; IV, inverse variance (statistical method); P, probability; Random, random effects (analysis model); SE, SE of log (HR); SECOMBIT, Sequential Combo Immuno and Target Therapy; TT, targeted therapy.

did not crossover from step 1 to step 2 died within 6 months (65.2% in the ICI arm vs 78.1% in the TT arm), and many had brain metastases.

Risk of bias assessment

We conducted 14 assessments per reviewer, seven items for any of the two included RCTs. SB drafted judgement and explanations, and FP cross-checked all items, and the results are listed in online supplemental table 9. Each assessment contains a statement whether a low, unclear or high bias was judged and adds a reasonable explanation for the respective decision. The reports of both studies were similar and subsequently the risk of bias assessment led to comparable results: two times low, two times high and three times unclear risk of bias. There were five times unclear or high risk of bias. The treatment consisted of drugs given orally or intravenously. It is conceivable that blinding of participants and personnel (performance bias) as well as blinding of outcome assessment (detection bias) could have been impossible, and we judged a high risk of bias if blinding was not attempted. The number of participants who crossed over was considerable. This might partially be explainable by the sequential design of the study and the severity of the disease. We were unsure whether the attrition in a certain treatment arm could have a clinically relevant impact on the observed effect size. Thus, we judged an unclear risk of bias. All two RCTs received funding independent from industry. The risk of bias summary and graph are shown in online supplemental figure 5.

Grading the certainty of evidence

We established an initial level of high certainty due to the randomised study design. There was an unclear risk of bias concerning selection bias and a high risk of bias concerning performance bias and detection bias in both studies. Thus, we downgraded by one level. There was no unexplained heterogeneity or inconsistency of results, and there was no indirectness of evidence. The studies included an appropriate number of participants and reported wide CIs for the main outcomes. Thus, there was not an imprecision of results. There are two positive studies, and it appears that studies showing no effect or harm have not been published. The studies reported a specific intervention on a specific disease, and there is no for-profit interest in the intervention. Thus, there was no clear indication of a publication bias. The final level of certainty rating was: Moderate ⊕⊕⊕◯.

DISCUSSION

Summary of the main findings

We included the two RCTs *DREAMseq* and *SECOMBIT* in a meta-analysis. The primary beneficial outcome was favourable for the first-line nivolumab plus ipilimumab arm, while the primary adverse outcome was favourable for the first-line dual TT arm.

Overall completeness and applicability of evidence

The peer-reviewed article publications of the two included RCTs were published first in 2023, and we presume that the principal treatment procedures probably do not deviate considerably from the current practice. The studies were conducted by academic institutions, and a financial conflict of interest was not obvious. The risk of bias assessment of the two studies resulted in similar judgements. A high risk

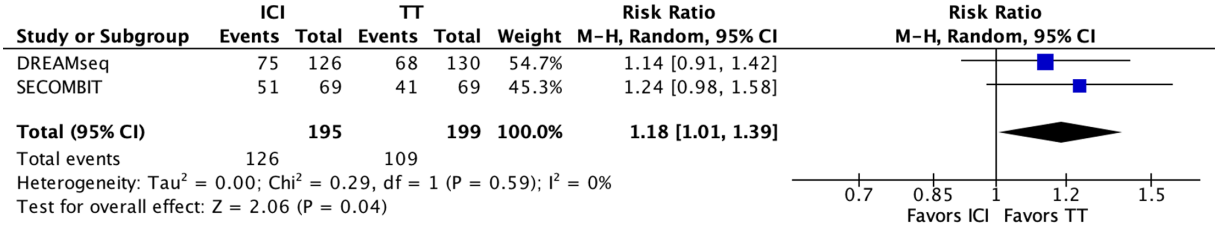

Figure 2 Forest plot for treatment-related adverse events (CTCAE grade 3–5) comparing first-line dual ICI therapy versus first-line dual targeted therapy. Data are risk ratios with 95% CIs. CTCAE, Common Terminology Criteria for Adverse Events (V.4.0, 2009); DREAMseq, Doublet, Randomized Evaluation in Advanced Melanoma Sequencing; I^2, index of heterogeneity (the smaller the value the lesser the heterogeneity); ICI, immune checkpoint inhibitor; M-H, Mantel-Haenszel (statistical method); P, probability; Random, random effects (analysis model); SECOMBIT, Sequential Combo Immuno and Target Therapy; TT, targeted therapy.

was judged for performance bias and detection bias because we believed that masking would have been possible. Both studies reported the use of intention-to-treat analyses, and we presume only a minor attrition. Also, both studies reported the flow diagram according to Consolidated Standards of Reporting Trials,[32] though information on random sequence generation and allocation concealment was not described as required. We recommend minding these issues in future study updates.

Subgroups and heterogeneity

We do not see reasons to assume a significant clinical heterogeneity because the characteristics of the participants were balanced, and the treatment plans were adapted to standard dosages. Statistical heterogeneity was low with respect to the primary outcome.

Limitations of the evidence contained in this paper

We focused on the new treatment recommendations of the European consensus-based interdisciplinary guideline for melanoma. Previous recommendations were regarded as outdated. This was especially true for single-drug treatments. Therefore, the evidence depended on new studies. These studies had to implement the current conception of a treatment that could promise a survival benefit. Therefore, we expected a small number of studies for inclusion from the outset. This turned out to be true, and we identified only two relevant RCTs.

Strengths and limitations

The present review is based on a comprehensive search, and we provide detailed study characteristics and interpretations. Study selection is a subjective procedure, and we employed three independent reviewers. We documented the divergence of opinion in a fourfold table and by calculating the Kappa value. Risk of bias assessment is also subjective, and we used the Cochrane definitions and examples regarding low, high and unclear risk of bias to make judgements based on a well-accepted standard. Concerning the quantitative analyses, we used the random effects model because of potential heterogeneity inherent in clinical study data. Switching to a fixed effects model did not change the direction of results. We reproduced the seminal figures such as survival data instead of just copying from the article. This allows us to discover errors if present. Deducing those data from Kaplan-Meier plots may be imprecise. We primarily relied on the methods for calculating the HR with data from curves with numbers at risk given. We compared the results to the alternative method with data from curve read where wished and assuming constant censoring. The first method means that you know the exact number of participants for each time interval, but you have a limited number of those intervals. The second method means that you only know the total number of participants at randomisation. You may create as many time intervals as wished, but the number of participants for each new time interval is estimated by an algorithm. It was reassuring that the results after application of both methods did not really differ. The two included RCTs reported various clinical stages of melanoma which can bias the effect and applicability of the results.

Agreements and disagreements with other studies or reviews

We found five systematic reviews published within the last 5 years which are concerned with related topics.[33–37] Three of those are network meta-analyses.[33 36 37] None mentioned the RCTs included in this work. These five reviews used search dates ranging from 13 January 2019 to 5 March 2023, while the peer-reviewed article publications of the *DREAMseq* and *SECOMBIT* were both first published on 10 January 2023. Two updates of *SECOMBIT* were published on 2 January 2024 and in October 2024. We did not find a Cochrane Review on the topic of this systematic review. There have been no meta-analyses published that evaluated the dual checkpoint inhibitor therapy versus the dual TT of untreated metastatic BRAF-mutant melanoma in a systematic way. Our review substantially updates and improves the previous work in this area. In an editorial commentary on the two studies included in this systematic review,[38] it was concluded that the combination of ipilimumab plus nivolumab is the preferred option at first-line setting versus the combination of BRAF plus MEK inhibitors. Toxicity was reported to be usually manageable after TT but was high grade in more than 50% of patients after the combination of nivolumab and ipilimumab. This statement is consistent with the observation in this systematic review that there is an advantage in the first line combination of ipilimumab plus nivolumab group on OS and progression-free survival but a disadvantage on severe TRAEs.

Outlook

We believe that further RCTs are needed to clarify the optimal role and sequencing of dual checkpoint inhibitor therapy versus dual TT in the first-line treatment of metastatic BRAF-mutant melanoma. In this context, the best treatment strategy, whether to start with ICIs ('ICI first'), TT ('TT first') or upfront triplet therapy, remains to be defined.[10] Comprehensive prospective studies should also include long-term evaluations of OS, reasons for treatment failure, TRAEs and health-related quality of life, as these factors are critical for informed clinical decision-making. Future research is needed to understand why a substantial proportion of patients do not respond to immunotherapy.[38]

CONCLUSIONS

The evidence base is compatible with a favourable effect on survival and an unfavourable effect on toxicity of first-line nivolumab plus ipilimumab for adults with untreated metastatic BRAF-mutant melanoma, when compared with first-line TT. Future RCTs could provide more data on treatment failure and quality of life.

Contributors FP: created the design, developed the search strategy, performed literature search and drafted the work; SB: performed study selection, data analysis and critically revised the work; KBA: performed study inclusion and risk of bias; MH: contributed a clinical perspective and critically reviewed the work. FP is the guarantor.

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