Meta-Analysis

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Comparative efficacy of dabrafenib + trametinib versus treatment options for metastatic melanoma in first-line settings

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Aim: The objective was to systematically review the literature and assess the relative efficacy of agents approved in first-line settings via network meta-analysis. **Materials & methods:** A literature review was conducted via searching different medical databases. The eligibility criteria included Phase II or III randomized controlled trials that had enrolled treatment-naive adult patients with advanced/metastatic melanoma. **Results:** The network meta-analysis results suggested that dabrafenib + trametinib significantly prolongs the survival outcomes compared with the monotherapies and had comparable efficacy profile compared with encorafenib + binimetinib and cobimetinib + vemurafenib. In comparison with immunotherapies, the results varied for progression-free survival and overall survival. **Conclusion:** Long-term survival data of dabrafenib + trametinib establishes the combination as one of the preferred treatment options for previously untreated melanoma patients.

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Keywords: BRAF mutation • first-line • immunotherapies • metastatic melanoma • targeted agents

Melanoma represents only 3–5% of all skin cancers, but is an aggressive form of skin cancer that may spread to any organ. Melanoma is reported as the 19th most common cancer worldwide, with estimated age-standardized incidence rates of 3.1 per 100,000 individuals [1]. As per the SEER estimates, the incidence of malignant melanoma is rapidly increasing in the US, being the fifth most common malignancy accounting for 5.6% of all new cancer cases [2]. In the US, the rate of new cases (2013–2017) of melanoma of skin was estimated at 22.7 per 100,000 men and women per year, while the death rate (2014–2018) was 2.3 per 100,000 men and women per year [2]. Cutaneous melanoma has the greatest mortality rate among all forms of melanoma, and is one of the malignancies with the highest potential of dissemination. The prognosis of patients with metastatic melanoma is grim, with a 5-year survival rate between 5 and 19%, and is dictated by the location and the number of metastases [3]. Mutations in the v-Raf murine sarcoma viral oncogene homolog B gene (*BRAF*) gene, which codes for a serine/threonine kinase involved in the MAPK pathway, are the most frequent mutations observed in melanoma (40–66%) and occur early in the pathogenesis of the disease [4–9]. Of the activating *BRAF* mutations, the *BRAF* V600E mutation (valine at the 600 position exchanged for glutamic acid) is reported in about 90% of cases, while the *BRAF* V600K mutation is reported in 5–6% of cases [10]. The *BRAF* V600E mutation confers the ability of *BRAF* to activate mitogen-activated protein kinase (*MEK*, the only known downstream target of *BRAF*) independent of *RAS*.

Thus, targeted inhibition of both *BRAF* and *MEK* has been of significant therapeutic interest for the treatment of melanoma, both as adjuvant and metastatic therapies [4]. Such interest has been heightened by evidence suggesting that patients with the *BRAF* mutation have a worse prognosis than those with the wild-type gene. Concomitant inhibition of *BRAF* and *MEK* may prevent or delay the drug resistance that arises through reactivation of the MAPK pathway. In preclinical studies, combining a *BRAF* inhibitor and a *MEK* inhibitor blocked rebound phospho-ERK (*pERK*) signaling in *BRAF*-mutant melanoma cells and enhanced cell death [11].

Future Medicine

Since 2011, a number of targeted therapies, including *BRAF* inhibitors and *MEK* inhibitors, and checkpoint inhibitors, such as anticytotoxic T-lymphocyte-associated antigen 4 (anti-CTLA-4) antibodies and antiprogrammed (anti-PD-1) antibodies, have been approved by the US FDA in the US because of their significant survival benefit, and have emerged as new standard therapies. The treatment landscape for metastatic melanoma is changing rapidly with the recent development of newer agents that have demonstrated better efficacy than traditional chemotherapy. The first generation of agents (i.e., vemurafenib, dabrafenib and ipilimumab) demonstrated significantly improved response rates and outcomes compared with conventional therapies. Vemurafenib and dabrafenib were developed to inhibit *BRAF* V600 mutations. Despite high initial response rates, half of the patients treated with *BRAF*-targeted monotherapies relapse within 6 months due to development of drug resistance. Hence, *BRAF*/*MEK* inhibitor combination therapies with dabrafenib + trametinib, vemurafenib + cobimetinib, and the recently approved encorafenib + binimetinib improved efficacy outcomes in patients with metastatic melanoma in first-line settings. Immune checkpoint inhibitors have transformed the treatment algorithm for unresectable or metastatic disease, notably the PD-1 inhibitors pembrolizumab and nivolumab and the combined use of nivolumab and ipilimumab.

The National Comprehensive Cancer Network (NCCN) guidelines recommend *BRAF*/*MEK* inhibitor combination therapies of dabrafenib + trametinib, vemurafenib + cobimetinib and encorafenib + binimetinib for patients with *BRAF* V600 mutations. The guidelines also recommend immunotherapy agents (i.e., pembrolizumab, nivolumab and nivolumab + ipilimumab) for the treatment of patients with metastatic melanoma in first-line settings [12]. However, the European Society for Medical Oncology (ESMO) guidelines recommend immunotherapies upfront (i.e., pembrolizumab, nivolumab, and nivolumab + ipilimumab) in first-line settings irrespective of the *BRAF* mutation status, and *BRAF*/*MEK* inhibitor combination therapies of dabrafenib + trametinib, vemurafenib + cobimetinib and encorafenib + binimetinib are recommended for patients who are not suitable for immunotherapies [13].

The first-line treatment options considered for the review included targeted therapies as monotherapies (e.g., dacarbazine, vemurafenib and dabrafenib) or combination (e.g., dabrafenib + trametinib, encorafenib + binimetinib and cobimetinib + vemurafenib) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab and nivolumab + ipilimumab). Head-to-head evidence from the RCTs between the first-line agents in metastatic melanoma is lacking and thus the optimal treatment is unknown. An understanding of the comparative efficacy of agents is important for evidence-based medicine and help in decision making for clinicians and policy-makers. Network meta-analyses (NMA) is an effective technique to assess the relative efficacy of therapeutic agents in absence of head-to-head trials. Hence, NMA methodology was utilized to achieve the estimates of the relative treatment effect of dabrafenib + trametinib versus all possible comparisons. The review also reported the qualitative safety data reported across the trials.

Materials & methods

Literature search

A systematic literature review (SLR) was conducted via a search of key biomedical databases, in other words, MEDLINE® and Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) in May 2020. MEDLINE In-Process was also searched to ensure that nonindexed citations were retrieved. Search terms were related to each specific facet of disease, study design and interventions. The searches were limited to English-language articles only. Additionally, proceedings from selected conferences (American Society of Clinical Oncology, International Melanoma Congress of the Society for Melanoma Research and European Society for Medical Oncology) during the period from 2017–2019 were searched for abstracts to retrieve the latest studies that had not yet been published in journals as full-text articles or to supplement results of previously published studies.

Study selection

A protocol was prepared prior to conducting the systematic review defining the inclusion and exclusion criteria. The SLR included Phase II or III RCTs that had enrolled treatment-naive adult patients with unresectable lymph node metastasis (American Joint Committee on Cancer TNM stage IIIC) or distant metastatic (American Joint Committee on Cancer tumor [T] nodes [N] metastases [M] stage IV) melanoma. At least one of the interventions compared in the trial was either a targeted inhibitor (*BRAF* or *MEK* or a combination of both) or an immune checkpoint inhibitor (CTLA-4 or PD-1 or a combination of both). Although the population of interest was patients with *BRAF*-mutated melanoma, no restriction was applied on study eligibility by *BRAF* mutation status as immunotherapies have largely been assessed either in a mixed population or in a *BRAF* wild-type population. To

identify relevant publications meeting the inclusion criteria, citations were first screened based on the abstract and title citation by two independent reviewers, and any discrepancies between the reviewers were reconciled by a third independent reviewer. Thereafter, the eligibility criteria were applied to the full text of the articles.

Data extraction

Studies that met the eligibility criteria at the second screening stage were extracted. Data extraction was done related to study and patient characteristics as well as treatments and outcomes (progression-free survival [PFS], overall survival [OS] and adverse events [AEs]). For PFS and OS, the hazard ratio (HR) and CIs were extracted wherever reported. The longest follow-up data for PFS and OS were extracted from multiple citations of the same trial and utilized for analysis.

Data analysis

The NMA allows estimation of the relative treatment effect of multiple interventions based on both head-to-head comparisons within trials and indirect comparisons across trials simultaneously. It is an extension of the classical pairwise meta-analysis. The general idea was to include all evidence at hand about a specific research question in one single model. An NMA can include all treatments as well as interventions that have not been investigated head-to-head using Bayesian method.

A set of Bayesian, hierarchical models were developed to perform the NMA analyses. Bayesian NMAs were conducted to estimate the HRs with corresponding 95% credible interval for PFS and OS. Analyses were conducted based on the reported HRs between trial arms. In the case of multi-arm trials (i.e., trials with three or more interventions), adjustments were made to reflect the correlations between relative treatment effects by converting log-HRs to log-hazards. Both fixed-effect and random-effect models were fitted to the data using the Markov Chain Monte Carlo methods and conducted under the Bayesian paradigm. The models were adapted from National Institute for Health and Care Excellence technical support document 2 [14]. A three-chain model with noninformative priors was run for 100,000 iterations with a burn-in of 30,000 model iterations. Model fit was assessed according to the deviance information criteria (DIC).

Consistency & heterogeneity test

Inconsistency was evaluated by edge-splitting, an approach that estimates relative treatment effects based on direct evidence (i.e., pairwise comparisons between treatment nodes) and indirect evidence (i.e., relative treatment effects estimated using only indirect evidence) separately. If a model is consistent, the direction and statistical importance of the effect will be maintained. Models were programmed in R v3.6.2 (www.r-project.org) using R2OpenBUGS package and Rstudio (version 1.1.456).

Study and patient characteristics that may impact treatment effects were assessed. Heterogeneity arises when treatment effects differ across studies due to observable or unobservable differences in design or population. Observable heterogeneity can be assessed by estimating the effect of study-level covariates on treatment effects. First, heterogeneity was qualitatively assessed based on the inclusion and exclusion criteria of each study. Thereafter, a meta-regression analysis was performed for the baseline characteristics of Eastern Cooperative Oncology Group performance status (ECOG PS), LDH level and *BRAF* mutation status. A meta-regression analysis can help explain between-study heterogeneity and minimize inconsistency.

Results

Evidence identified

Figure 1 presents the preferred reporting items for systematic reviews and meta-analyses diagram depicting the flow of studies included at each step of the review. A systematic search of the databases yielded 9826 separate references, of which 1332 references were found to be duplicates and were removed. Following the first pass of the remaining 8494 citations, 564 potentially relevant references were identified for the second stage of screening. Of these 564 citations, 404 citations were excluded for not meeting the eligibility criteria. Following full-text screening and linking of multiple publications, 15 studies (reported in 163 publications) were included for extraction. Of these 15 studies, eight studies assessed targeted therapies (monotherapies or combination therapies), while seven studies assessed immunotherapies (monotherapies, combination with chemotherapy or PD-1 inhibitor + CTLA-4 inhibitor).

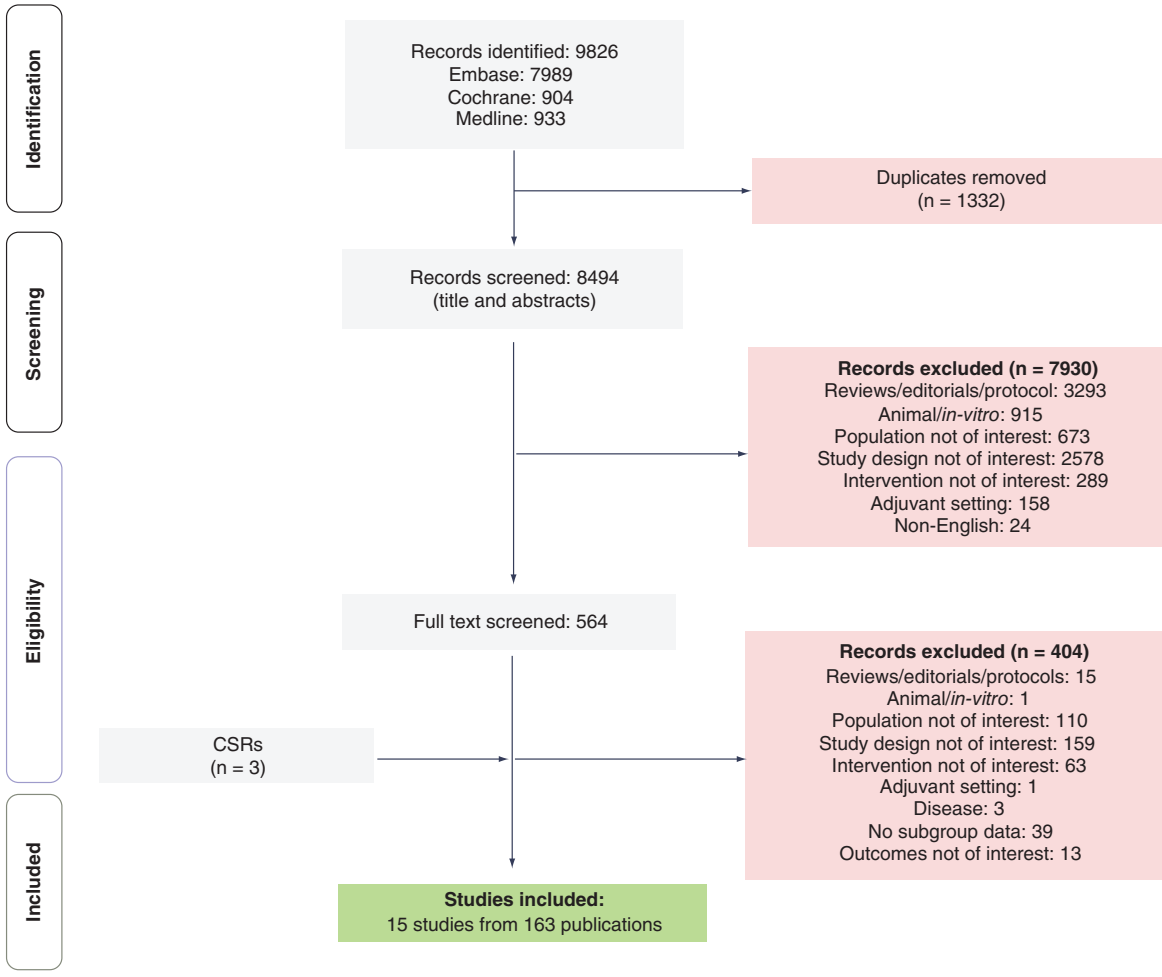

Figure 1. Preferred reporting items for systematic reviews and meta-analysis study flow diagram.
CSR: Clinical study report; PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Dabrafenib 150 mg twice daily (b.i.d.) + trametinib 2 mg once daily (o.d.) was assessed in three trials (COMBI-v [15], COMBI-d [16] and BRF113220 [17]), while one trial each assessed encorafenib 450 mg + binimetinib 45 mg (COLUMBUS [18]) and cobimetinib 60 mg o.d. + vemurafenib 960 mg b.i.d. (coBRIM [19]). One trial each assessed trametinib 2 mg od versus chemotherapy (METRIC), dabrafenib 150 mg b.i.d. versus dacarbazine 1000 mg/m2 (BREAK-3 [20]) and vemurafenib 960 mg b.i.d. versus dacarbazine 1000 mg/m2 (BRIM-3 [21]).

Among the immunotherapies, nivolumab 1 mg/kg every 3 weeks (q3w) + ipilimumab 3 mg/kg q3w was assessed in two trials (CheckMate 067 [22] and CheckMate 069 [23]) and ipilimumab 10 mg/kg q3w + dacarbazine 850 mg/m2 intravenous q3w was assessed in two trials (CA184-013 [24] and CA184-024 [25]). One trial assessed nivolumab 3 mg/kg every 2 weeks (q2w) versus dacarbazine 1000 mg/m2 q3w (CheckMate 066 [26]), while one trial assessed ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg [27]. In KEYNOTE-006, outcomes were reported for two doses of pembrolizumab (10 mg/kg q3w or 10 mg/kg q2w) versus ipilimumab 3 mg/kg, but a recent publication reported results for pooled doses of pembrolizumab in treatment-naive patients [28]; hence, the HRs for the pooled doses were utilized for the NMA.

Study & patient characteristics

Table 1 presents the details of RCTs and patient baseline characteristics. All the included studies were Phase III studies except three trials, BRF113220 [17], CA184-013 [24] and CheckMate 069 [23], which were Phase II studies. All the included studies had a multicenter-international setting (more than one country) except one trial, in other words, CA184-013 [24], which was conducted at multiple centers in the US. Of the included studies, seven were double-blinded, three were assessor-blinded and five were open-labeled.

Table 1. Details of randomized controlled trials and patient baseline characteristics.

Study name	Treatment	n	Trial design	Median age (years)	Male (%)	ECOG PS (%)		LDH levels (%)		*BRAF* mutation status (%)		Ref.
						ECOG PS 0	ECOG PS 1	LDH (≤ULN)	LDH (>ULN)	Mutation positive	Mutation negative	
CSR 2019 (COMBI-d trial)	Dabrafenib	212	DB, MI, AC, Phase III	57	54	71	29	64	34	100	–	[16]
	Dabrafenib + trametinib	211		55	53	74	26	64	36	100	–	
CSR 2019 (COMBI-v trial)	Dabrafenib + trametinib	352	OL, MI, AC, Phase III	55	59	71	29	66	34	100	–	[15]
	Vemurafenib	352		54	51	70	30	68	32	100	–	
CSR 2019 (BRF113220 trial)	Dabrafenib	53	OL, MI, AC, Phase II	50	54	63	37	–	50	100	–	[17]
	Dabrafenib + trametinib	55	58	63	65	35	–	41	100	–		
Robert 2019 (METRIC trial)	Chemotherapy	108	AB, MI, AC, Phase III	54	49	64	36	61	39	100	–	[29]
	Trametinib	214	55	56	64	36	63	36	100	-		
Liszkay 2019 (COLUMBUS trial)	Encorafenib + binimetinib	192	OL, MI, AC, Phase III	57	60	71	29	71	29	100	–	[18]
	Encorafenib	194		54	56	72	28	76	24	100	–	
	Vemurafenib	191		56	58	73	27	73	27	100		
Dreno 2018 (coBRIM trial)	Cobimetinib + vemurafenib	247	DB, MI, AC, Phase III	56	59	76	24	–	46	79	–	[19]
	Vemurafenib	248		55	56	67	33	–	43	83	–	
Hauschild 2020 (BREAK-3 trial)	Dabrafenib	187	AB, MI, AC, Phase III	53	60	66	33	64	36	100	–	[20]
	Dacarbazine	63		50	59	70	25	68	30	100	–	
Chapman 2017 (BRIM-3 trial)	Dacarbazine	338	OL, MI, AC, Phase III	52	54	68	32	42	58	100	–	[21]
	Vemurafenib	337		56	59	68	32	42	58	–	–	
Hersh 2011 (CA184-013 trial)	Ipilimumab + dacarbazine	35	OL, M, AC, Phase II	60	74	–	–	77	23	–	–	[24]
	Ipilimumab	37		66	57	–	–	73	27	–	–	
Maio 2015 (CA184-024 trial)	Dacarbazine	252	DB, MI, AC, Phase III	56	59	71	29	56	44	–	–	[25]
	Dacarbazine + ipilimumab	250		58	61	71	29	63	37	–	–	
Larkin 2019 (CheckMate 067 trial)	Ipilimumab	315	DB, MI, AC, Phase III	62	64	71	29	62	37	31	69	[22]
	Ipilimumab + nivolumab	314	61		66	73	26	63	36	32	68	
	Nivolumab	316	60		64	75	25	62	35	32	68	
Hodi 2016 (CheckMate 069 trial)	Ipilimumab	47	DB, MI, AC, Phase II	67	68	79	21	77	23	21	79	[23]
	Ipilimumab + nivolumab	95		64	66	83	15	74	25	23	77	
Ascierto 2019 (CheckMate 066 trial)	Dacarbazine	208	DB, MI, AC, Phase III	66	60	58	40	60	36	–	100	[26]
	Nivolumab	210		64	58	70	29	57	38	–	100	
Robert 2019 (KEYNOTE-006 trial)†	Pembrolizumab 10 mg/kg q2w	279	AB, MI, AC, Phase III	61	58	70	30	70	29	35	63	[28]
	Pembrolizumab 10 mg/kg q3w	277		63	63	68	32	63	35	35	64	
	Ipilimumab 3 mg/kg	278		62	58	68	32	64	33	39	61	
Ascierto 2017†	Ipilimumab 10 mg/kg	365	DB, MI, AC, Phase III	62	60	72	28	61	36	22	62	[27]
	Ipilimumab 3 mg/kg	362		62	64	70	30	60	38	22	65	

†Data presented for overall population.
AB: Assessor blind; AC: Active controlled; *BRAF*: v-Raf murine sarcoma viral oncogene homolog B; CSR: Clinical study report; DB: Double-blind; ECOG PS: Eastern Cooperative Oncology Group performance status; M: Multicenter; MI: Multicenter-International; q2w: Every 2 week; q3w: Every 3 week; ULN: Upper limit of normal.

Table 2. Clinical evidence identified across the trials.

Trial name	Treatment	Comparator	PFS (HR, 95% CI)	OS (HR, 95% CI)	Ref.
CSR 2019 (COMBI-d trial)	Dabrafenib + trametinib	Dabrafenib	0.73 (0.59–0.91)	0.80 (0.63–1.01)	[16]
CSR 2019 (COMBI-v trial)	Dabrafenib + trametinib	Vemurafenib	0.62 (0.52–0.74)	0.70 (0.58–0.84)	[15]
CSR 2019 (BRF113220 trial)	Dabrafenib + trametinib	Dabrafenib	0.44 (0.28–0.67)	0.76 (0.49–1.18)	[17]
Robert 2019 (METRIC trial)	Trametinib	Chemotherapy	0.44 (0.28–0.69)	0.81 (0.55–1.18)	[29]
Liszkay 2019 (COLUMBUS trial)	Encorafenib + binimetinib	Vemurafenib	0.51 (0.39–0.67)	0.61 (0.48–0.79)	[18]
	Encorafenib + binimetinib	Encorafenib	0.75 (0.56–1.00)	0.81 (0.61–1.06)	
Dreno 2018 (coBRIM trial)	Cobimetinib + vemurafenib	Vemurafenib	0.58 (0.46–0.72)	0.70 (0.55–0.90)	[19]
Hauschild 2020 (BREAK-3 trial)	Dabrafenib	Dacarbazine	0.37 (0.23–0.57)	0.76 (0.48–1.21)	[20]
Chapman 2017 (BRIM-3 trial)	Vemurafenib	Dacarbazine	0.38 (0.32–0.46)	0.81 (0.70–1.0)	[21]
Maio 2015 (CA184-024 trial)	Ipilimumab + dacarbazine	Dacarbazine	0.76 (0.63–0.93)	0.69 (0.57–0.84)	[25]
Larkin 2019 (CheckMate 067 trial)	Nivolumab + ipilimumab	Nivolumab	0.79 (0.64–0.96)	0.83 (0.67–1.03)	[22]
	Nivolumab + ipilimumab	Ipilimumab	0.42 (0.35–0.51)	0.52 (0.42–0.64)	
Hodi 2016 (CheckMate 069 trial)	Nivolumab + ipilimumab	Ipilimumab	0.36 (0.22–0.56)	0.74 (0.43–1.26)	[23]
Ascierto 2019 (CheckMate 066 trial)	Nivolumab	Dacarbazine	0.42 (0.33–0.53)	0.46 (0.36–0.59)	[26]
Robert 2019 (KEYNOTE-006 trial)	Pembrolizumab	Ipilimumab	0.54 (0.44–0.67)	0.73 (0.57–0.92)	[28]
Ascierto 2017	Ipilimumab 10 mg/kg	Ipilimumab 3 mg/kg	-	0.85 (0.65–1.10)	[27]

CSR: Clinical study report; HR: Hazard ratio; OS: Overall survival; PFS: Progression-free survival.

In terms of line of therapy, 11 studies had data on treatment-naive patients, while four studies had data on a mixed patient population (first- and second-line patients). Of these four studies, three reported subgroup data for first-line settings [27–29], while one study, in other words, the Columbus trial, did not report segregated data for first-line and second-line settings [18]. However, the NCCN and ESMO guidelines recommend the combination of encorafenib + binimetinib in the first-line setting; hence, this trial was included as a source for indirect comparison.

The median age of patients in all the included studies was generally >50 years, indicating a higher incidence of metastatic melanoma among the older population. ECOG PS was reported in all the included studies (except the CA184-013 trial). The majority of the patients (>60%) from the included studies had an ECOG PS of 0 or 1 at baseline, thus implying that the majority of patients in the included studies were either asymptomatic or symptomatic, but completely ambulatory. Elevated serum LDH has been identified as an independent and highly significant predictor of survival outcome among patients with stage IV disease. The proportion of patients with LDH levels more than the upper limit of normal ranged from 23.0 [23,24] to 58.0% [21]. In terms of *BRAF* mutation status, seven trials included populations that were entirely *BRAF* mutation positive, five trials included mixed patient populations, and two trials did not reported information related to *BRAF* mutation status [24,25]. One trial, in other words, CheckMate 066, included 100% of patients with *BRAF* wild-type status [26].

Clinical evidence

The SLR identified long-term PFS and OS reported in different trials (Table 2). The COMBI-d, COMBI-v, and BRF113220 trials reported landmark 5-year PFS and OS data for dabrafenib + trametinib versus the respective comparators. The 5-year analysis showed that dabrafenib + trametinib continued to demonstrate clinically meaningful reductions in the risk of progression or death compared with the *BRAF* inhibitors dabrafenib or vemurafenib, administered as monotherapy [15,16]. The median OS achieved by dabrafenib + trametinib treated patients was 25.8, 26.0 and 25.0 months for COMBI-d [16], COMBI-v [15] and BRF113220 [17] trial, respectively.

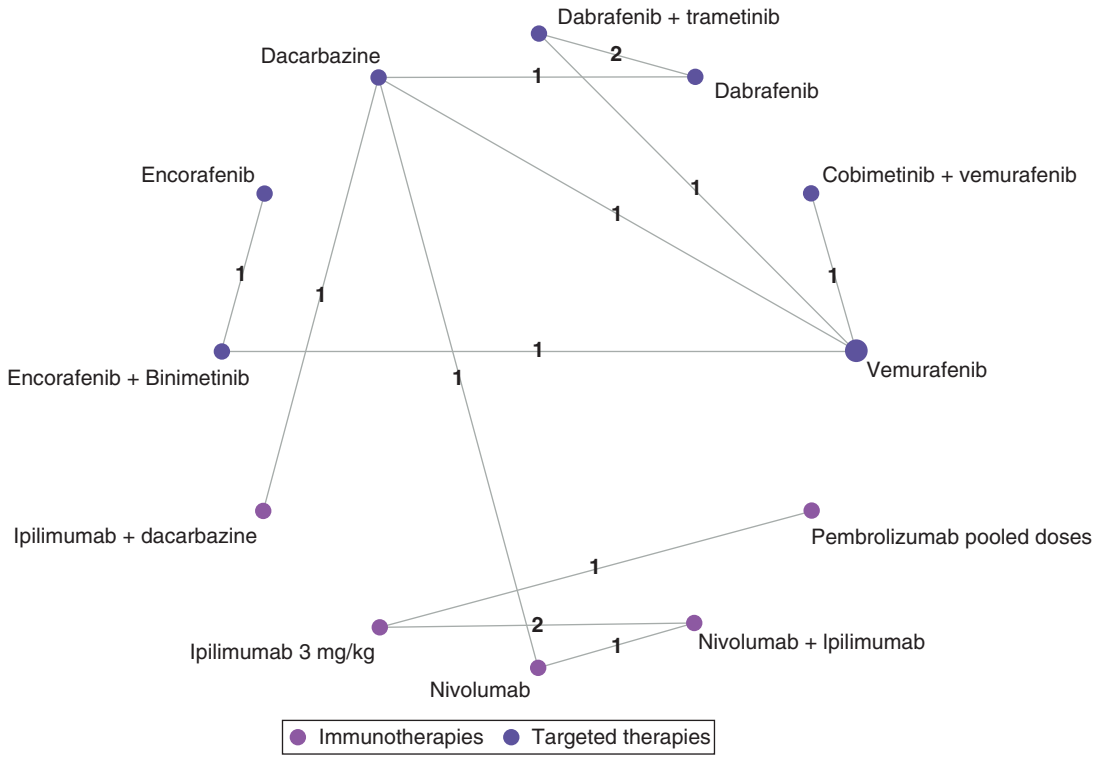

Figure 2. Master network diagram of trials contributing to analysis for progression-free survival and overall survival. Numerical values presents the number of studies.
OS: Overall survival; PFS; Progression-free survival.

The COLUMBUS trial reported the 4-year landmark analysis of PFS and OS for encorafenib + binimetinib versus vemurafenib [18]. The coBRIM trial also reported 4-year survival analysis results for cobimetinib + vemurafenib versus vemurafenib monotherapy [19]. The results were found to be significantly in favor of the combination therapies.

The CheckMate 067 trial [22] recently reported 5-year PFS and OS data for nivolumab + ipilimumab versus nivolumab and ipilimumab monotherapies. The results were significantly in favor of the combination therapy versus monotherapies, with OS not yet reached with the combination therapy. The recently published KEYNOTE-006 trial [28] update analysis provided *5-year* survival results for pooled doses of pembrolizumab versus ipilimumab in treatment-naive patients. Two-year PFS and OS results for the combination of nivolumab + ipilimumab versus ipilimumab monotherapy were reported in the CheckMate 069 trial. The median survival had not been reached with nivolumab + ipilimumab, significantly in favor of the combination therapy versus monotherapy. CA184-013 [24] study reported only median OS data but HR were not reported.

Network meta-analysis

Figure 2 presents the network diagram of trials contributing to the analysis for PFS and OS. A total of 13 and 14 studies contributed to the analysis for PFS and OS, respectively. In most of the cases, all comparisons were informed by a single trial.

Progression-free survival

Since data for most of the comparisons were derived from a single trial, and the DICs for the fixed-effect and random-effect models were similar, the fixed-effect model was selected as the appropriate fit. Figure 3 presents the forest plot of PFS for dabrafenib + trametinib versus the comparators.

Among the targeted therapies, the NMA results showed that dabrafenib + trametinib was associated with a significantly better PFS compared with dacarbazine (HR: 0.24 [95% CI: 0.19–0.3]), vemurafenib (HR: 0.62 [95% CI: 0.52–0.73]) and dabrafenib (HR: 0.66 [95% CI: 0.55–0.79]). The NMA results showed no significant

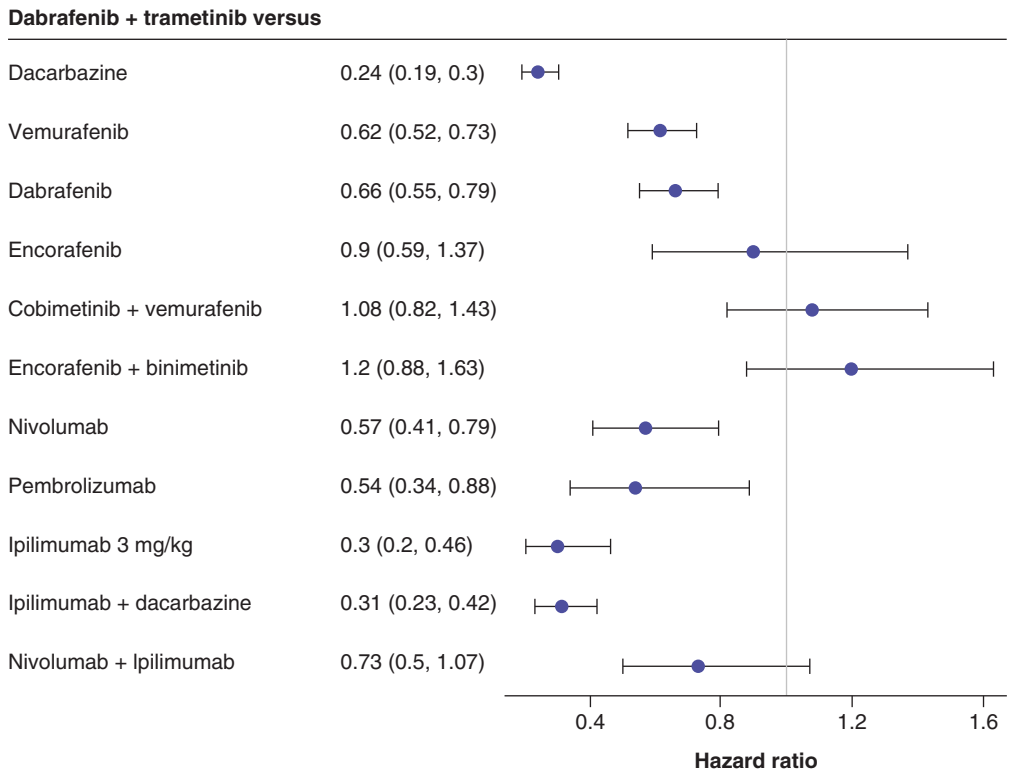

Figure 3. Summary plot of progression-free survival for dabrafenib + trametinib versus comparators (intention-to-treat population).
ITT: intention-to-treat; PFS: Progression-free survival.

difference in PFS between dabrafenib + trametinib and the other two *BRAF/MEK* inhibitor combinations, i.e, encorafenib + binimetinib (HR: 1.20 [95% CI: 0.88–1.63]) and cobimetinib + vemurafenib (HR: 1.08 [95% CI: 0.82–1.43]). It is important to highlight the heterogeneity across the trials assessing dabrafenib + trametinib and encorafenib + binimetinib, wherein the trials assessing dabrafenib + trametinib had treatment-naive populations, while the COLUMBUS trial assessing encorafenib + binimetinib had a mixed patient population, in other words, treatment-naive and pretreated patients.

The NMA results showed that dabrafenib + trametinib was associated with a significantly better PFS compared with ipilimumab (HR: 0.30 [95% CI: 0.20–0.46]), ipilimumab + dacarbazine (HR: 0.31 [95% CI: 0.23–0.42]), pembrolizumab (HR: 0.54 [95% CI: 0.34–0.88]) and nivolumab (HR: 0.57 [95% CI: 0.41–0.79]). However, the NMA results showed that the combination of dabrafenib + trametinib was associated with a numerically better PFS compared with nivolumab + ipilimumab but statistical significance was not achieved (HR: 0.73 [95% CI: 0.50–1.07]).

Overall survival

Similar to PFS, since most of the data for comparison of OS were derived from a single trial, and the DICs for the fixed-effect and random-effect models were similar, the fixed-effect model was selected as the appropriate fit. Figure 4 presents the forest plot of OS for dabrafenib + trametinib versus the comparators. Among the targeted therapies, the NMA results showed that dabrafenib + trametinib was associated with a significantly better OS compared with dacarbazine (HR: 0.59 [95% CI: 0.47–0.74]), vemurafenib (HR: 0.70 [95% CI: 0.59–0.83]) and dabrafenib (HR: 0.79 [95% CI: 0.65–0.95]). The NMA results showed no significant difference in OS between dabrafenib + trametinib and the other two *BRAF/MEK* inhibitor combinations, in other words, encorafenib + binimetinib (HR: 1.14 [95% CI: 0.84–1.54]) and cobimetinib + vemurafenib (HR: 1.0 [95% CI: 0.74–1.35]). Dabrafenib + trametinib was associated with a numerically better OS compared with ipilimumab 3 mg/kg (HR: 0.83 [95% CI: 0.54–1.29]) and ipilimumab + dacarbazine (HR: 0.85 [95% CI: 0.63–1.15]). However, pembrolizumab and nivolumab were numerically better compared with dabrafenib + trametinib but statistical significance was not

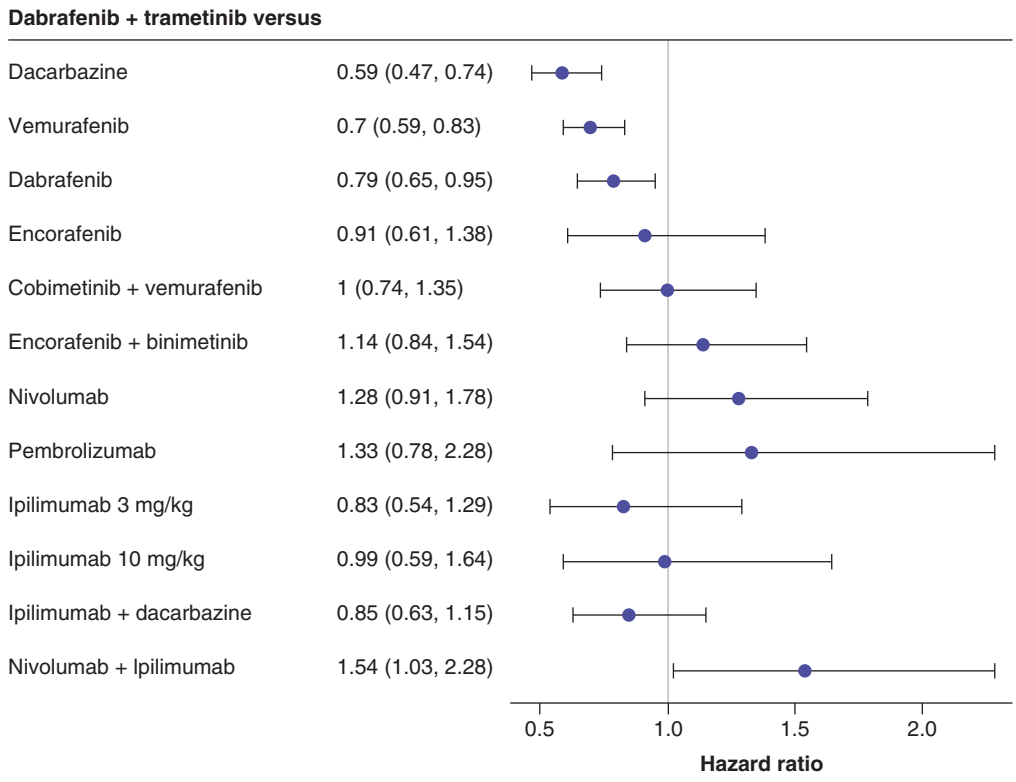

Figure 4. Summary plot of OS for dabrafenib + trametinib versus comparators (intention-to-treat population).
OS: Overall survival.

achieved. The combination of nivolumab + ipilimumab was associated with a significantly better OS compared with dabrafenib + trametinib (HR: 1.54 [95% CI: 1.03–2.28]).

Consistency

To assess inconsistency, direct and indirect treatment effects were estimated for dabrafenib + trametinib versus vemurafenib and for dabrafenib + trametinib versus dabrafenib. The results of the edge-splitting exercise revealed evidence of inconsistency, although the mean treatment effect was similar. For both PFS and OS, HR of dabrafenib + trametinib versus vemurafenib was significant via mixed treatment comparison (MTC) approach, but significance was not achieved via indirect treatment comparison (ITC) approach. HR for PFS via MTC was found to be 1.61 (95% CI: 1.36–1.9), while HR was 1.6 (95% CI: 0.95–2.71) via ITC; for OS, HR was found to be 1.43 (95% CI: 1.2–1.7) via MTC and HR was 1.39 (95% CI: 0.82–2.37) via ITC. In addition, HR for PFS related to comparison of dabrafenib + trametinib versus dabrafenib was significant via MTC (HR: 1.51 [95% CI: 1.26–1.81) but not significant via ITC (HR: 1.52 [95% CI: 0.91–2.55]). The point estimates demonstrated a consistent direction of the effect.

To assess heterogeneity, ECOG PS, LDH level and *BRAF* mutation status were considered for the meta-regression analysis. None of the variables significantly affected the results except *BRAF* mutation status for PFS. To assess the robustness of the results in the base-case analysis, a sensitivity analysis was conducted after removing the CheckMate 066 trial that included a 100% *BRAF* wild-type population. Results from the sensitivity analysis were similar to the base-case results.

Safety

NMA was not performed with respect to safety outcomes, although the safety outcomes are discussed qualitatively (Table 3). The combination of *BRAF* + *MEK* inhibitors is highly effective for the treatment of metastatic melanoma; however, AEs occur with all the combinations in patients treated with combination therapies. Five-year analysis of the COMBI-d, COMBI-v and BRF113220 trials showed that the most common AEs associated with the combination therapy of dabrafenib + trametinib were pyrexia, nausea, diarrhea, chills, headache, fatigue, vomiting, hypertension

Table 3. Summary of safety data reported across the studies.

Study name	Treatment	n	Any AE (%)	Any grade 3/4 AE (%)	Any SAE (%)	Any dose interruptions/ modifications (%)	Any dose reductions (%)	Ref.
CSR 2019 (COMBI-d trial)	Dabrafenib + trametinib	209	97.0	51.7	47.0	56.0	28.0	[16]
	Dabrafenib	211	97.0	51.7	38.0	37.0	14.0	
CSR 2019 (COMBI-v trial)	Dabrafenib + trametinib	350	99.0	60.6	49.0	55.0	33.0	[15]
	Vemurafenib	349	99.0	66.5	40.0	56.0	39.0	
CSR 2019 (BRF113220 trial)	Dabrafenib + trametinib	55	100.0	67.3	71.0	73.0	60.0	[17]
	Dabrafenib	53	100.0	47.2	28.0	34.0	25.0	
Robert 2019 (METRIC trial)	Trametinib	211	99.1	53.0	24.6	39.0	33.0	[29]
	Chemotherapy	99	92.9	38.0	20.2	25.3	10.0	
Liszkay 2019 (COLUMBUS trial)	Encorafenib + binimetinib	192	98.4	68.2	34.0	45.8	11.5	[18]
	Encorafenib	194	99.5	67.7	34.0	63.5	27.1	
	Vemurafenib	186	100.0	65.6	37.0	52.7	22.6	
Dreno 2018 (coBRIM trial)	Vemurafenib + cobimetinib	247	99·2	73.0	37.0	–	–	[19]
	Vemurafenib	246	98·0	60.0	28.0	–	–	
Hauschild 2020 (BREAK-3 trial)	Dabrafenib	187	98.9	46.0	32.6	37.0	24.0	[20]
	Dacarbazine	59	93.2	42.0	23.7	27.0	17.0	
Chapman 2017 (BRIM-3 trial)	Vemurafenib	336	99.0	71.1	49.0	47.3	33.3	[21]
	Dacarbazine	287	93.0	42.2	18.0	15.6	15.2	
Hersh 2011 (CA184-013 trial)	Dacarbazine + ipilimumab	36	–	23.0	–	–	–	[24]
	Ipilimumab	40	–	13.0	–	–	–	
Maio 2015 (CA184-024 trial)	Dacarbazine + ipilimumab	247	98.8	56.3	68.8	–	–	[25]
	Dacarbazine	251	94.0	27.5	48.2	–	–	
Larkin 2019 (CheckMate 067 trial)	Nivolumab + ipilimumab	313	96.0	59.0	–	–	–	[22]
	Ipilimumab	311	86.0	28.0	–	–	–	
	Nivolumab	313	86.0	22.0	–	–	–	
Hodi 2016 (CheckMate 069 trial)	Nivolumab + ipilimumab	94	91.0	54.0	–	–	–	[23]
	Ipilimumab	46	93.0	19.0	–	–	–	
Ascierto 2019 (CheckMate 066 trial)	Dacarbazine	205	95.2	17.6	–	–	–	[26]
	Nivolumab	206	92.7	15.0	–	–	–	

AE: Adverse event; SAE: Serious adverse event.

and arthralgia [15–17]. The coBRIM trial illustrated that the most common AEs (≥20%, all grade) associated with the combination of vemurafenib + cobimetinib included rash, arthralgia, diarrhea, fatigue, nausea, pyrexia, decreased appetite, photosensitivity reaction, alanine aminotransferase and aspartate aminotransferase increase, and serious retinopathy [19]. The COLUMBUS trial reported that the most common AEs associated with the combination of encorafenib + binimetinib included rash, arthralgia, diarrhea, fatigue, vomiting, nausea, constipation, blood creatine phosphokinase increase and vision blurred [18]. Five-year analysis results from the CheckMate 067 trial demonstrated that most common AEs associated with nivolumab + ipilimumab were rash, pruritus, arthralgia, diarrhea, fatigue, nausea, vomiting, pyrexia, decreased appetite, photosensitivity reaction, alanine aminotransferase and aspartate aminotransferase increase, hypothyroidism, and serious retinopathy.

The most common grade 3/4 AEs associated with dabrafenib + trametinib were found to be pyrexia, neutropenia and hypertension, while combination of cobimetinib + vemurafenib was associated with grade 3/4 liver toxicity, rash, arthralgia, squamous cell carcinomas and diarrhea. Combination of encorafenib + binimetinib was associated with grade 3/4 (≥5%) hypertension, blood creatine phosphokinase increase and gamma-glutamyl transferase increase. The CheckMate 067 trial reported that the most common treatment-related grade 3 AE associated with nivolumab + ipilimumab was diarrhea, while the most common grade 4 AE was increased lipase.

Discussion

Recent advances in targeted therapies and immune checkpoint inhibitors have revolutionized the treatment paradigm for patients with advanced or metastatic melanoma. Dabrafenib + trametinib has been the first choice of physicians for treating patients with advanced or metastatic melanoma in many countries; however, with the introduction of newer *BRAF* + *MEK* inhibitors and immunotherapies, it has become challenging to select the optimal therapy. Furthermore, no head-to-head trials are available to assess the efficacy and safety profile of either targeted therapies or immunotherapies among themselves. Hence, we aimed to conduct an NMA to assess the relative efficacy of the available treatment options, and an SLR was conducted with prespecified criteria to identify studies assessing agents for the treatment of metastatic melanoma in first-line settings.

This SLR identified 15 studies assessing different treatment options for patients with metastatic melanoma in first-line settings. The baseline study and patient characteristics across the studies were found to be similar except for *BRAF* mutation status. The SLR identified long-term survival data associated with various combination therapies, and subsequently an NMA was conducted by using the HRs reported for the latest study data cut-offs.

Dabrafenib + trametinib was found to be associated with a significantly better PFS compared with monotherapies, in other words, dacarbazine, ipilimumab, pembrolizumab, nivolumab, vemurafenib and dabrafenib. The efficacy profiles of all three *BRAF* + *MEK* inhibitor combination therapies were similar with regard to PFS and OS. These results were in line with a previously conducted meta-analysis that also reported no significant difference between the combination therapies [30]. Moreover, a recent Scottish Medicines Consortium submission also stated that the efficacy profile of encorafenib + binimetinib was similar to that of dabrafenib + trametinib [31].

Dabrafenib + trametinib was associated with a numerically better PFS compared with nivolumab and ipilimumab monotherapies but combination of nivolumab and ipilimumab was associated with a significantly better OS compared with dabrafenib + trametinib (HR: 1.54 [95% CI: 1.03–2.28]). The NMA results correspond to a recently published systematic review and meta-analysis that stated that dabrafenib + trametinib was the preferred treatment for PFS, while the combination of nivolumab + ipilimumab was the preferred option for OS [32]. However, there were few differences in this SLR versus the previously conducted NMA by Zoratti and colleagues: this NMA was not only conducted at the category level but also at the molecule level; the NMA was conducted on recent data cut-offs and the NMA involved a comparison versus encorafenib + binimetinib.

This SLR has several strengths and limitations. The strengths of this SLR involve a search of key bibliographic databases as well as searches of recent conferences. The review adopted a standard methodology following predefined eligibility criteria established in the protocol and involved two independent researchers for the identification of studies and data extraction. The SLR identified long-term survival data reported according to different data cut-offs. There were few limitations associated with the SLR, such as heterogeneous baseline parameters, in other words, the inclusion of some mixed population trials, where subgroup results were not reported separately for *BRAF*-mutated and *BRAF* wild-type patients. These trials were included to form a connected network that linked targeted therapies and immunotherapies. Additionally, evidence suggests that immunotherapies demonstrate efficacy irrespective of *BRAF* mutation status. Second, the inclusion of the COLUMBUS trial, which included treatment-naive and pretreated patient populations. The trial did not report segregated data for first-line and second-line settings [18]. However, the NCCN and ESMO guidelines recommend the combination of encorafenib + binimetinib in the first-line setting; hence, this trial was included to have an indirect comparison. Owing to these heterogeneous factors, the NMA results should be interpreted with caution. The results from this meta-analysis are based on a sparse network of evidence as most comparisons were informed by a single trial; hence, the results should not be generalized to a broader patient population.

The results from the NMA suggest that dabrafenib + trametinib significantly prolongs survival outcomes compared with the monotherapies and has a comparable efficacy profile versus the other two *BRAF* + *MEK* inhibitors. In comparison with immunotherapies, the results varied for PFS and OS; hence, it is difficult to derive any conclusion. The treatment landscape for metastatic melanoma has evolved; however, clinical decision-

making is still based on factors, such as toxicity profile, *BRAF* mutation status and patient medical history (e.g., comorbidities, ECOG PS and tumor burden). This SLR may facilitate evidence-based decision-making and support the optimization of treatment and outcomes in everyday clinical practice.

Summary points

Background

- *BRAF* V600-mutation positive patients have worse prognosis, with higher mortality, than the general metastatic melanoma population.
- The treatment landscape for metastatic melanoma is changing rapidly with the recent development of newer agents that have demonstrated better efficacy than traditional chemotherapy.
- Many effective first-line treatment options are available for advanced *BRAF*-mutated melanoma, but there are no head-to-head randomized trials of these agents, and thus the optimal treatment is unknown.

Evidence base

- A systematic literature review was conducted via a search of key biomedical databases on May 2020.
- A total of 15 studies meeting the inclusion criteria were included in the review.
- Of these 15 studies, eight studies assessed targeted therapies (monotherapies or combination therapy), while seven studies immunotherapies (monotherapies, combination with chemotherapy or PD-1 inhibitor + CTLA-4 inhibitor).

Key findings

- Network meta-analysis results showed that dabrafenib + trametinib was associated with significantly better progression-free survival and overall survival (OS) compared with dacarbazine, vemurafenib and dabrafenib.
- No significant difference for progression-free survival and OS between dabrafenib + trametinib and other two *BRAF*/*MEK* combinations in other words, encorafenib + binimetinib and cobimetinib + vemurafenib.
- Combination of nivolumab and ipilimumab was associated with significantly better OS compared with dabrafenib + trametinib.

Author contributions

J Wu was responsible for providing insights and review of the analysis as well as writing/editing of manuscript. B Ratto, J Das and M Kalra were responsible for conceptualization, conducting review/analysis and writing of the manuscript.

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