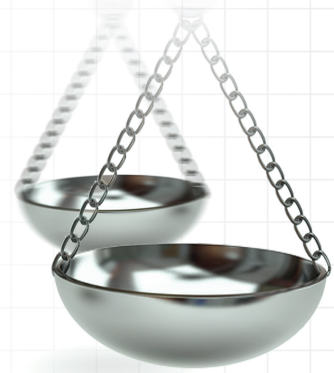
Systematic Review



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Comparative efficacy and safety of dabrafenib in combination with trametinib versus competing adjuvant therapies for high-risk melanoma

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Aim: To conduct a systematic literature review of high-risk resectable cutaneous melanoma adjuvant therapeutics and compare safety and efficacy. **Methods:** The systematic literature review included randomized controlled trials investigating: dabrafenib plus trametinib (DAB + TRAM), nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy and interferons. Outcomes included overall survival (OS), relapse-free survival, distant metastasis-free survival and safety. All outcomes were synthesized using Bayesian network meta-analysis. **Results:** Across relapse-free survival, distant metastasis-free survival and OS, DAB + TRAM had the lowest estimated hazards of respective events relative to all other treatments (exception relative to nivolumab in OS). Differences were significant relative to placebo, chemotherapy, interferons and ipilimumab. **Conclusion:** DAB + TRAM has improved efficacy over historical treatment options (ipilimumab, interferons and chemotherapy) and comparable efficacy with other targeted and immune checkpoint inhibitors.

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Keywords: adjuvant melanoma • dabrafenib • network meta-analysis • systematic literature review • trametinib

The incidence of melanoma has continued to increase in recent years [1–3]. It is estimated that in 2019, there will be 96,480 new cases of melanoma and an estimated 1.2% of all cancer deaths will be caused by melanoma in the USA [3]. It is considered to be one of the most aggressive forms of skin cancer, with a poor prognosis, particularly if the disease progresses to metastasis [4,5].

Though surgical excision is the treatment of choice for most early-stage melanoma patients, a subgroup of patients are at a higher risk of disease recurrence. Increasing tumor thickness, an increased mitotic rate, presence of ulceration and lymph node involvement, are some of the high-risk features associated with disease relapse [6]. In such patients, systemic adjuvant therapy is generally indicated after surgical resection of the tumor to minimize the risk of relapse. Until last decade, IFN-α was the only approved option in the adjuvant setting. However, its use is complicated by its unfavorable tolerability profile and limited efficacy [7,8].

Recent gene profiling studies have found that about 40–55% of melanoma patients have oncogenic *BRAF* mutations [9–12]. *BRAF* is a serine/threonine protein kinase, encoded on chromosome 7q34, that activates the MAP kinase/ERK-signaling pathway and is activated by Ras [9–11,13]. Over 90% of *BRAF* mutations observed in melanoma are at codon 600, and among these, over 90% are a single nucleotide mutation resulting in substitution of glutamic acid for valine (*BRAF*V600E: nucleotide 1799 T > A; codon GTG > GAG). The second most common mutation is *BRAF*V600K substituting lysine for valine, that represents 9–15% (GTG > AAG) [9–11,13]. Patients with *BRAF* positive mutations and a tumor thickness of 1 mm or more have shown poorer outcomes with conventional treatment strategies [9–12. Finding therapies targeted at *BRAF* is a challenging but promising field of research.

Future Medicine

The adjuvant treatment landscape for surgically resected high-risk melanoma has changed significantly in the past few years, with different targeted therapies and immune checkpoint inhibitors being approved for this patient population. These include: ipilimumab, dabrafenib plus trametinib combination, nivolumab and pembrolizumab [14–18]. Amongst the targeted therapies, dabrafenib plus trametinib combination has been approved (by US FDA [17] and EMA [14]) for the adjuvant treatment of patients with *BRAF* V600E- or V600K-positive stage III melanoma following complete resection, while vemurafenib is currently under evaluation in the adjuvant setting [14,15,17,19].

Head-to-head evidence from randomized controlled trials (RCTs) of dabrafenib plus trametinib is lacking for comparisons with other emerging treatments of interest in adjuvant melanoma. An understanding of the comparative efficacy and safety of competing therapeutics is critical to evidence-based medicine and to optimize decision making by clinicians and policy-makers. Despite the lack of head-to-head evidence, network meta-analyses (NMA) can be used to make indirect comparisons and to simultaneously review the therapeutic landscape [20–23]. These methods use the evidence base of RCTs comparing the interventions with each other and select common comparators, as identified through a systematic literature reviews (SLR).

The present study was undertaken to estimate the relative treatment effects in terms of relapse-free survival (RFS), distant metastasis-free survival (DMFS), overall survival (OS), and safety between different interventions for the adjuvant treatment of resected high-risk cutaneous melanoma. The study involved two components: 1) an SLR to identify RCTs assessing the comparative efficacy and safety of treatments for high-risk cutaneous melanoma with RFS/disease-free survival (DFS), DMFS and OS as the end points of interest, and 2) an NMA to assess the comparative efficacy and safety of dabrafenib plus trametinib in comparison with relevant interventions such as other targeted therapies, chemotherapy and immune checkpoint inhibitors as adjuvant therapy in the treatment of high-risk surgically resected melanoma patients.

Materials & methods

SLR

An SLR was conducted in accordance with the guidance published by the Center for Reviews and Dissemination and the Cochrane review [24,25]. MEDLINE, EMBASE and Cochrane Library databases were searched from inception until 13 July 2017, and were later updated on 27 July 2017 to include adjuvant chemotherapies and exclude cancer vaccines. This was done to match with the current treatment practices across North America and Europe. In May 2018, a Phase III study on pembrolizumab (KEYNOTE-054 study, published in April 2018) [26] was included in the SLR given that pembrolizumab is one of the key comparators of interest to dabrafenib plus trametinib. Another update in September 2018 included 40-month follow-up data from COMBI-AD trial [27] (for RFS) and 24-month data from CheckMate-238 study [28] (RFS and DMFS for stage III subgroup and RFS for *BRAF* subgroup). The search included terms for cutaneous melanoma, combined with the generic and brand names of interventions of interest, and study design filter for RCTs published by Scottish Intercollegiate Guidelines Network (SIGN) [29]. Each search strategy is provided in the Supplementary Data.

In addition, conference proceedings from the American Society of Clinical Oncology (2016 and 2017), European Society of Medical Oncology (2015 and 2016) and Society for Melanoma Research (2015 and 2016) were searched for relevant abstracts and other conference materials. Clinical trial registries of European Medicines Agency, FDA and the ClinicalTrials.gov register were also searched for unpublished results from clinical trials. Finally, with respect to systematic searches, the references in reviewed articles were analyzed to find further relevant publications.

Eligibility criteria were defined in terms of the population, interventions, comparisons, outcomes and study design criteria (see Supplementary Table). The target population of interest for this review was patients with completely resected, *BRAF* V600E/K mutation-positive, high-risk cutaneous melanoma. High-risk cutaneous melanoma was defined *a priori* as patients with stage IIB, IIC and IIIA–C cutaneous melanoma as per American Joint Committee on Cancer (AJCC)-7 staging system criteria. It was anticipated that not many studies would have been published in the target population of interest (less than five studies). Consequently, for the purpose of this SLR, the study population was defined as patients with completely resected, high-risk cutaneous melanoma independent of the *BRAF* mutation status. It was assumed that the target population (completely resected, *BRAF* V600E/K mutation-positive, high-risk cutaneous melanoma) is a subset of broader study population (completely resected, high-risk cutaneous melanoma independent of *BRAF* mutation status) and that any effects observed in the study population would apply to the target population. Eligible treatment regimens included: dabrafenib plus trametinib, nivolumab, pembrolizumab, ipilimumab, vemurafenib, chemotherapy and IFN-α, as monotherapy or part of a combination therapy. At all places in this manuscript, the term 'biological therapies' refers to targeted therapies (dabrafenib plus

trametinib and vemurafenib), and immune checkpoint inhibitors (ipilimumab, nivolumab and pembrolizumab) except for IFN-α. Outcomes of interest included: RFS, DMFS, OS any adverse events (AE), serious adverse events (SAE), and discontinuations due to AEs or any cause. Only RCTs with ten or more patients per treatment arm were eligible, as smaller trials are typically not sufficiently powered to detect meaningful differences.

With respect to study selection, two reviewers, working independently, reviewed all abstracts and proceedings identified by the search according to the selection criteria, with the exception of outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible after title-abstract screening were then screened at a full-text stage by the same two reviewers. Any discrepancies in the decisions during title-abstract and full-text screening stages were resolved by mutual discussion between the reviewers. If needed, a third reviewer was included to reach consensus for any remaining discrepancies. The full-text studies that fulfilled the study eligibility criteria were included for the data extraction. The process of study identification and selection were summarized with a PRISMA flow diagram [30].

All data were extracted independently by the same two reviewers and data discrepancies were resolved by mutual discussion or where necessary, through arbitration by third reviewer. Study-level data, patient characteristics, treatment details, and efficacy and safety end points were extracted from the included trials. The following study characteristics were extracted: study title, first author, publication year, trial ID, National Clinical Trial code, region, countries in which patients were enrolled, study design, trial phase, blinding, number patients randomized and completed trial, trial duration, initiation and completion dates, treatment arms, follow-up duration, inclusion/exclusion criteria, outcomes reported and study quality assessment. The following intervention characteristics were extracted: treatment regimen, treatment dose, method of administration, frequency of administration, duration of treatment and concomitant/background therapies. Patient characteristics included: age, sex, race and ethnicity, AJCC stage, *BRAF* mutation status, sentinel node biopsy, positive sentinel (and/or) node biopsy, clinical detectable nodal metastases, disease duration, disease recurrence, Eastern Cooperative Oncology Group (ECOG)/Karnovsky score, comorbidities and prior therapies. Outcomes included: OS, RFS, DFS, DMFS, any discontinuations, any AE, SAEs, treatment-related AEs TRAEs, discontinuation due to AEs and overall discontinuations.

For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm was extracted. For time-to-event outcomes, hazard ratios (HR) and associated information regarding uncertainty were extracted. Kaplan–Meier curves were extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time.

Initially, studies in high-risk cutaneous melanoma were included, irrespective of the definition of 'high-risk' reported in these studies. Later, patient characteristics and inclusion criteria from these studies were re-assessed and matched with the study defined criteria for high-risk melanoma. If the patient population matched with the AJCC-7 staging categories of interest, the study was extracted and included for further analysis.

Study quality assessment was done using Cochrane Collaboration's Risk of Bias tool by the same two reviewers [31]. This instrument was used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Further details, as well as results, are presented in the Supplementary Data.

Statistical analyses

A feasibility assessment for the NMA was performed in two steps. First, we determined if the network of evidence was connected as this is a key requirement to NMA. Second, we assessed the distribution of study and patient characteristics that may affect treatment effects across direct comparisons (i.e., effect modifiers) of the evidence networks by comparing their distributions both within and between comparisons. This second step was to determine whether any adjustments would be required and/or feasible within the NMA.

All analyses were performed in a Bayesian framework. The NMA of reported HRs in terms of RFS/DFS, OS and DMFS, assuming proportional hazards between treatments, was performed using a regression model with a contrast-based normal likelihood for the log HR (and corresponding standard error) of each trial. Analyses using time-varying HRs fit with fractional polynomials were also conducted; however, results of these analyses are not presented here. Fractional polynomial NMA involves using splines to best fit the HRs over time. They can at times be limited in their ability to properly fit the data, with first-order polynomials not being able to adapt to the changes over time and second-order polynomials being too flexible and behaving oddly, particularly in the tails. This was an evidence base in which the fractional polynomials failed to properly reflect the input data, which is why analyses with proportional HRs were preferred. Further details on these models are provided in the Supplementary Data.

For binary outcomes (any AE, SAE, DAE, any discontinuation), the NMA was performed based on the proportion of patients experiencing the event of interest using a regression model with a binomial likelihood and logit link. For all analyses Normal non-informative prior distributions for the parameters were used with a mean of 0 and a variance of 10,000. Relative treatment effects were expressed as HRs for time-to-event outcomes and as odds ratios (ORs) for dichotomous outcomes.

Both fixed- and random-effects models were considered. If there was insufficient evidence to estimate between-study heterogeneity, fixed-effects models were used. Meta-regression was deemed to be not feasible for the evidence base and was therefore not used. In order to address the heterogeneity between studies in terms of disease stage and *BRAF* mutation status; the following sub-group analyses were planned: stage III (AJCC ed.7) resectable melanoma independent of *BRAF* mutation status; and high-risk (AJCC-7 IIB–C and IIIA–C) *BRAF* mutation positive resectable melanoma.

The deviance information criterion was used to compare the goodness-of-fit of competing survival models [32]. Prior to the actual NMA, the consistency between direct and indirect comparisons was evaluated for networks that include closed loops. A synthesis of direct evidence only was performed using independent-means models where pooled estimates for all the different direct comparisons was obtained simultaneously [33]. Additionally, relative treatment effects for all the possible comparisons in the network based on indirect evidence only were assessed with 'edge-splitting' [33]. This involved repeatedly performing an NMA, where for every analysis the direct evidence for a particular comparison was removed from the dataset.

Overall survival is a critical outcome that is often the primary driver of health economic analyses. The current evidence base lacks OS outcome data for some key comparators, including nivolumab and pembrolizumab. The NMA for OS was conducted in two manners. First using the data as reported in the evidence base and second using RFS as a surrogate for OS. The justification and model for using RFS as a surrogate for OS was developed through the same evidence base (i.e., with targeted and immune checkpoint inhibitors), following the work done in an interferon only evidence base [34,35].

The parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo method as implemented in the JAGS software packages. A first series of iterations from the JAGS sampler were discarded as 'burn-in' (typically 40,000) and the inferences were based on additional iterations (typically 80,000) using two chains. Convergence of the chains were confirmed by the Gelman–Rubin statistics. These analyses were called upon from R version 3.3.3 (Vienna, Austria), which served to produce all analyses and graphical outputs.

Results

Evidence base

Figure 1 summarizes the results of the literature search. The initial literature search identified 11,136 records. 14 additional records were identified through manual search of gray literature resources and bibliographic searches (eight conference abstracts, one trial registry, one podium presentation, three full-text publications and unpublished data provided by Novartis). After initial screening of titles and abstracts, 118 full texts were assessed for study eligibility. Of these, 62 citations were excluded primarily due to outcomes outside the population, interventions, comparisons, outcomes and study design, leaving 55 citations in 37 studies that met the study eligibility criteria [26–28,36–71]. Of the 37 included studies, nine studies included a mix of stage II–IV patients and did not report on results for the study defined high-risk melanoma subgroup (matched AJCC-7 IIB–C and IIIA–C) and hence, were excluded from the dataset. The list of studies excluded at full-text screening, and the reason for their exclusion, is provided in the Supplementary Data.

The majority of RCTs were multicenter, eight were exclusively conducted in the USA, and 17 were conducted in the European countries. Open-label study design was implemented in 31 studies, while the remaining six studies used a double-blind study design; no studies were in Phase I, four were in Phase II, 23 were in Phase III and 10 did not report on the clinical trial phase. With respect to inclusion/exclusion criteria, disease staging criteria was not specified in 11 studies while two studies had disease stage according to criteria other than AJCC; the remaining studies used AJCC edition five through seven for melanoma staging. 13 studies included patients with stage II–III disease, seven studies included patients with stage III disease only, three studies included patients with stage III–IV disease and one study included patients with stage II–IV disease. Performance score was required to be ECOG 0-2, ECOG 0-1, Karnofsky ≥70% and Karnofsky ≥80%, in one, 16, two and one studies, respectively. The median age across trials ranged from 38 to 56 years with proportion of males between 50 and 65%. The study design,

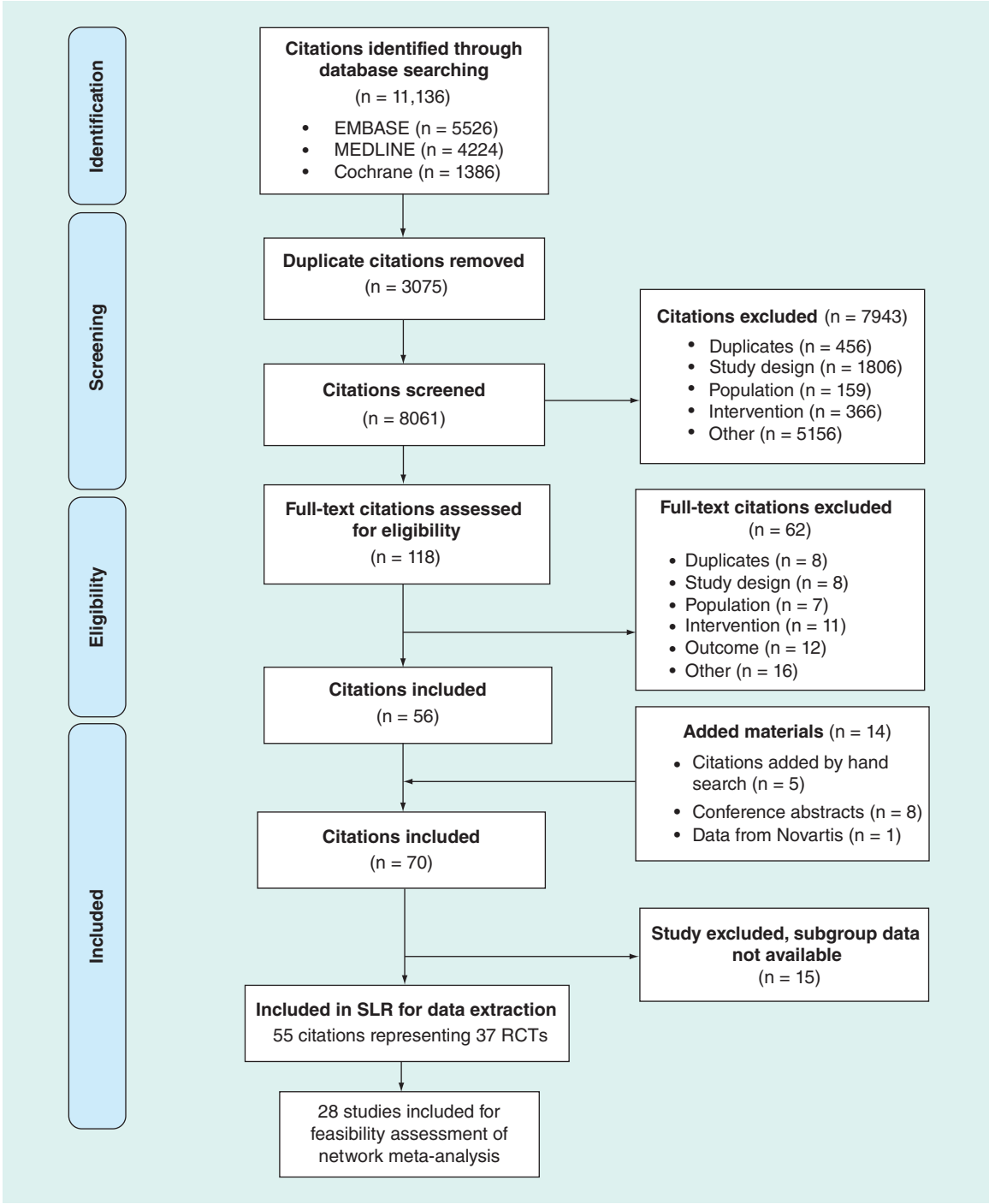

Figure 1. PRISMA study flow diagram.
RCT: Randomized control trial; SLR: systematic literature reviews.

treatment characteristics and baseline characteristics are summarized in the Supplementary Data. Overall, the trials were considered to have low risk of bias based on the assessment using Cochrane Collaboration's tool.

In order to obtain meaningful comparisons, the interferon treatment arms were aggregated into low-dose (LD) IFN-α-2a, rIFN-α-2b, pegylated (PEG)-IFN-α-2a, PEG-IFN-α-2b and high-dose, intermediate-dose (ID) and LD IFN-α-2b (see Supplementary Data). Due to the aggregation of interferon regimens, six trials comparing the same type of interferon but at a different schedule, were treated as single-arm and excluded from the NMA [39,50,61,64–66].

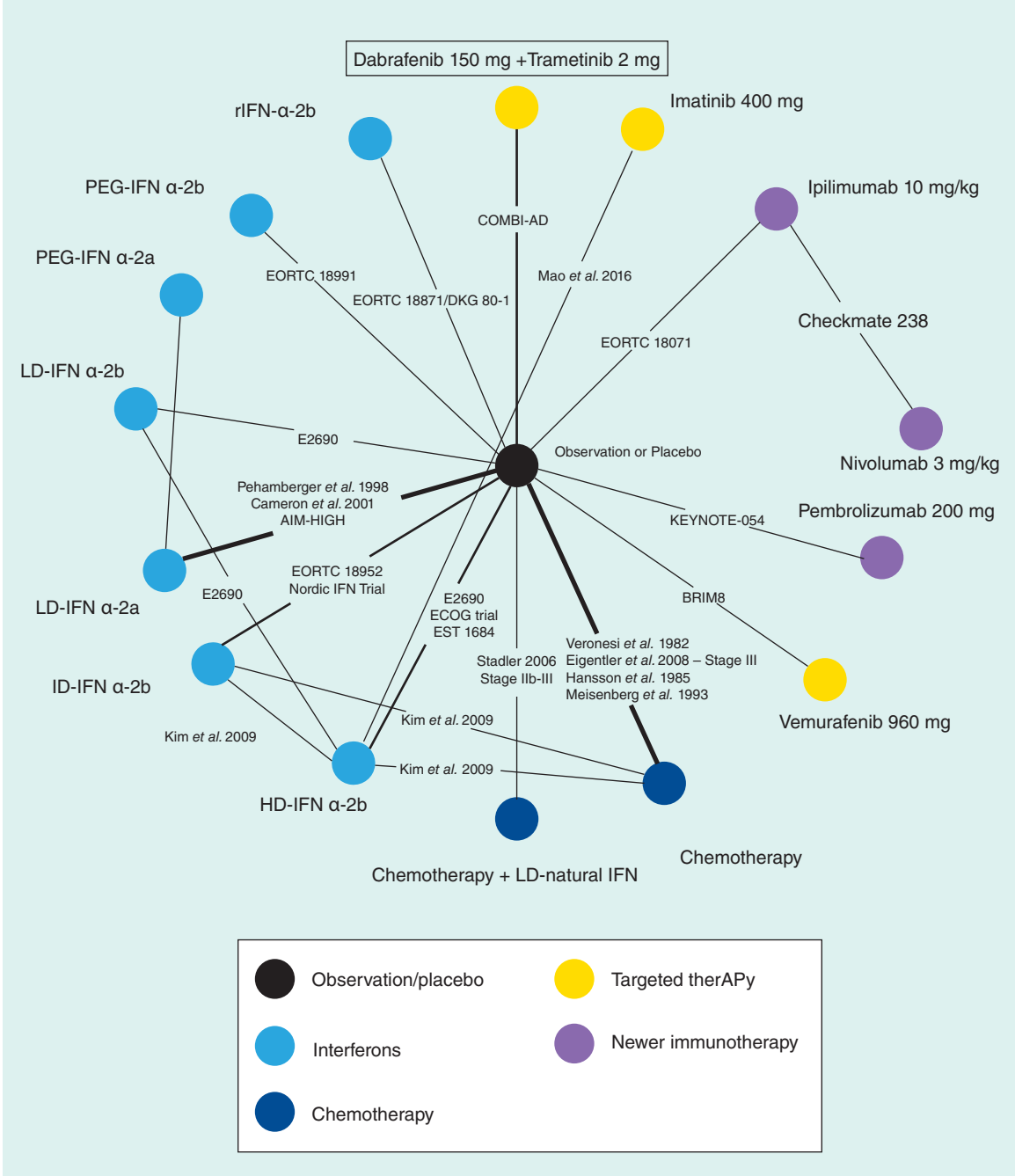

Figure 2. Network of evidence for high-risk melanoma (American Joint Committee on Cancer-7 IIB–C and IIIA–C) independent of *BRAF* mutation status, irrespective of outcomes of interest. The details of interferon dose categories are presented in Supplementary Data.
HD: High dose; ID: Intermediate dose; IFN: Interferon; LD: Low-dose; PEG: Pegylated; rIFN: Recombinant interferon.

Likewise, 'observation or placebo' label was used for 19 trials with 'observation' as comparator and five trials as 'placebo' comparator. A summary of the decisions regarding treatment groupings is presented in the Supplementary Data.

Feasibility assessment

The overall network of included interventions, connected at placebo, is presented in Figure 2. Among the biological therapies, head-to-head comparisons were only available between nivolumab and ipilimumab (CheckMate 238

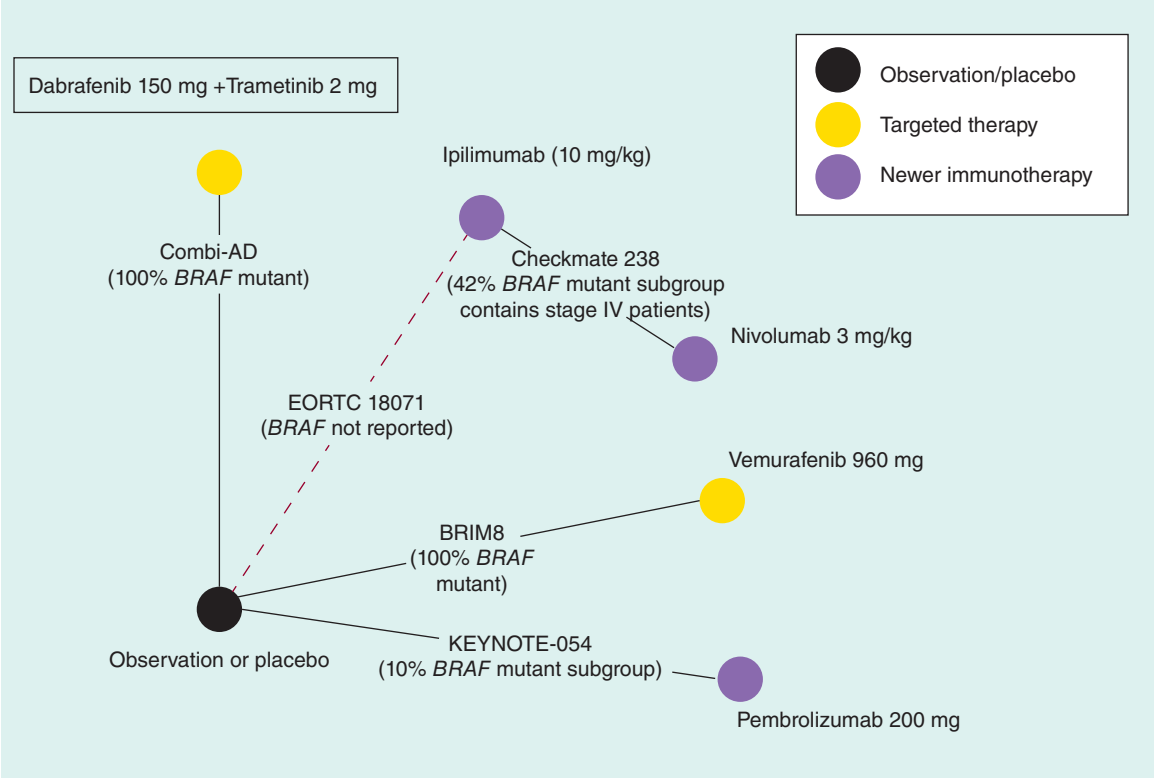

Figure 3. High-risk (American Joint Committee on Cancer-7 IIB–C and IIIA–C) melanoma *BRAF* mutation positive status – network of randomized controlled trials for relapse-free survival/disease-free survival; subgroup analysis.
The dotted line in red represents connection via EORTC 18071 study comparing ipilimumab and placebo; however, *BRAF* mutation status was unknown in these patients.

trial) [71]. The interferon treatment arms were adequately informed while the targeted and immune checkpoint inhibitors were supported by evidence from single trial each, except ipilimumab which was studied in two trials. Patient baseline characteristics were similar across the included trials except for some variation in disease stage. As shown in Figure 3, the network was also connected for the subgroup of *BRAF* positive high-risk melanoma patients for relapse-free survival. Evidence netwoks by each outcome for overall population and for the subgroups are presented in the Supplementary Data.

Completely resected high-risk melanoma independent of *BRAF* mutation status

The RFS/DFS data were reported in 18 trials evaluating 14 interventions in the high-risk melanoma (AJCC ed.7 stage IIB–C and IIIA–C) patients independent of *BRAF* mutation status. Figure 4 displays estimated HRs from the fixed-effects NMA for dabrafenib plus trametinib relative to other treatments for RFS/DFS. As can be seen, dabrafenib plus trametinib was estimated to lead to a lower risk of disease relapse compared with all other treatments in the network. There was strong evidence of a benefit relative to most comparators, including: ipilimumab, chemotherapy, all interferons and placebo. The evidence was weaker relative to nivolumab, pembrolizumab and vemurafenib.

Figure 4 also displays the estimated HRs from the fixed-effects NMA for dabrafenib plus trametinib relative to other treatments for DMFS. DMFS was reported in seven trials evaluating nine treatments. The DeCOG trial [44] was disconnected from the network of evidence, which ultimately consisted of six trials and seven treatments. The constant HR fixed-effects NMA results again suggested a lower risk of distant metastatic disease for dabrafenib plus trametinib relative to all other treatments, with strong evidence relative to placebo, ipilimumab, ID IFN-α-2b and PEG IFN-α-2b compared with dabrafenib plus trametinib. Similarly, evidence was weaker relative to nivolumab and vemurafenib.

15 trials reported on OS that included 11 interventions in the high-risk melanoma (AJCC-7 stage IIB–C and IIIA–C) group, independent of *BRAF* mutation status. Similar to the analyses of RFS and DMFS, dabrafenib plus

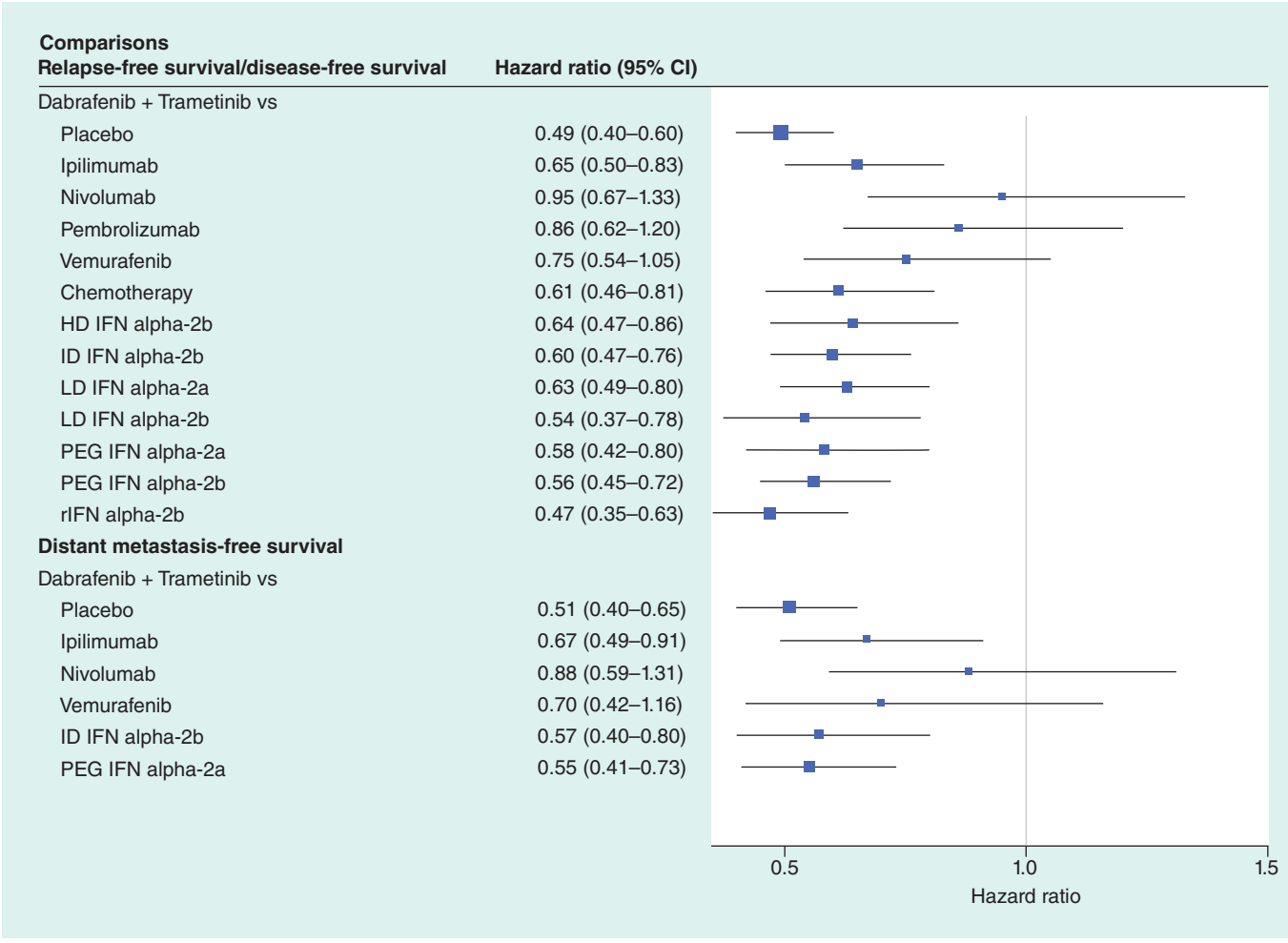

Figure 4. High-risk melanoma (American Joint Committee on Cancer-7 stage IIB–C and IIIA–C) independent of *BRAF* mutation status – hazard ratios estimated from fixed-effects network meta-analyses for relapse-free survival/disease free survival; base-case.

trametinib patients had better survival relative to all other treatments reporting survival. Figure 5 presents the results of the fixed-effects NMA using observed OS data. There was strong evidence of improved survival for dabrafenib plus trametinib relative to: placebo, ID IFN-α-2b, LD IFN-α-2a, LD IFN-α-2b, PEG IFN-α-2a, PEG IFN-α-2b and rIFN-α-2b. The evidence was weaker relative to ipilimumab, chemotherapy, chemotherapy plus LD-natural interferon and high-dose IFN-α-2b. Notably, nivolumab, pembrolizumab and vemurafenib were not included in this analysis.

When using RFS as a surrogate for OS, the evidence base for OS was expanded to 15 trials and included 11 interventions in the high-risk, AJCC-7 stage IIB–C and IIIA–C matched all-comers population. Five additional trials reported RFS but not OS (BRIM8 [59], CheckMate 238 [71], Pehamberger 1998 [67], KEYNOTE-054 [26] and E2690) [55]. In these trials, OS HRs were imputed based on the linear regression model established *a priori* between RFS and OS created from same evidence base (OS = 0.03 + 0.91 log HR for RFS with a correlation coefficient of correlation = 0.74, manuscript under consideration). For all the remaining trials, the true OS HRs were included in the NMA. This allowed for OS comparisons between dabrafenib plus trametinib versus nivolumab, vemurafenib and pembrolizumab. The imputed OS results, as shown in Figure 5, were comparable between dabrafenib plus trametinib versus vemurafenib, nivolumab and pembrolizumab. All other comparisons were in line with the main OS analysis except for comparison between dabrafenib plus trametinib and PEG IFN-α-2a, where the results were no longer statistically significant in favor of dabrafenib plus trametinib. These results should be interpreted with caution, given the differences in study populations across the included trials in terms of disease severity and *BRAF* mutation status, in the RFS versus OS surrogacy estimations.

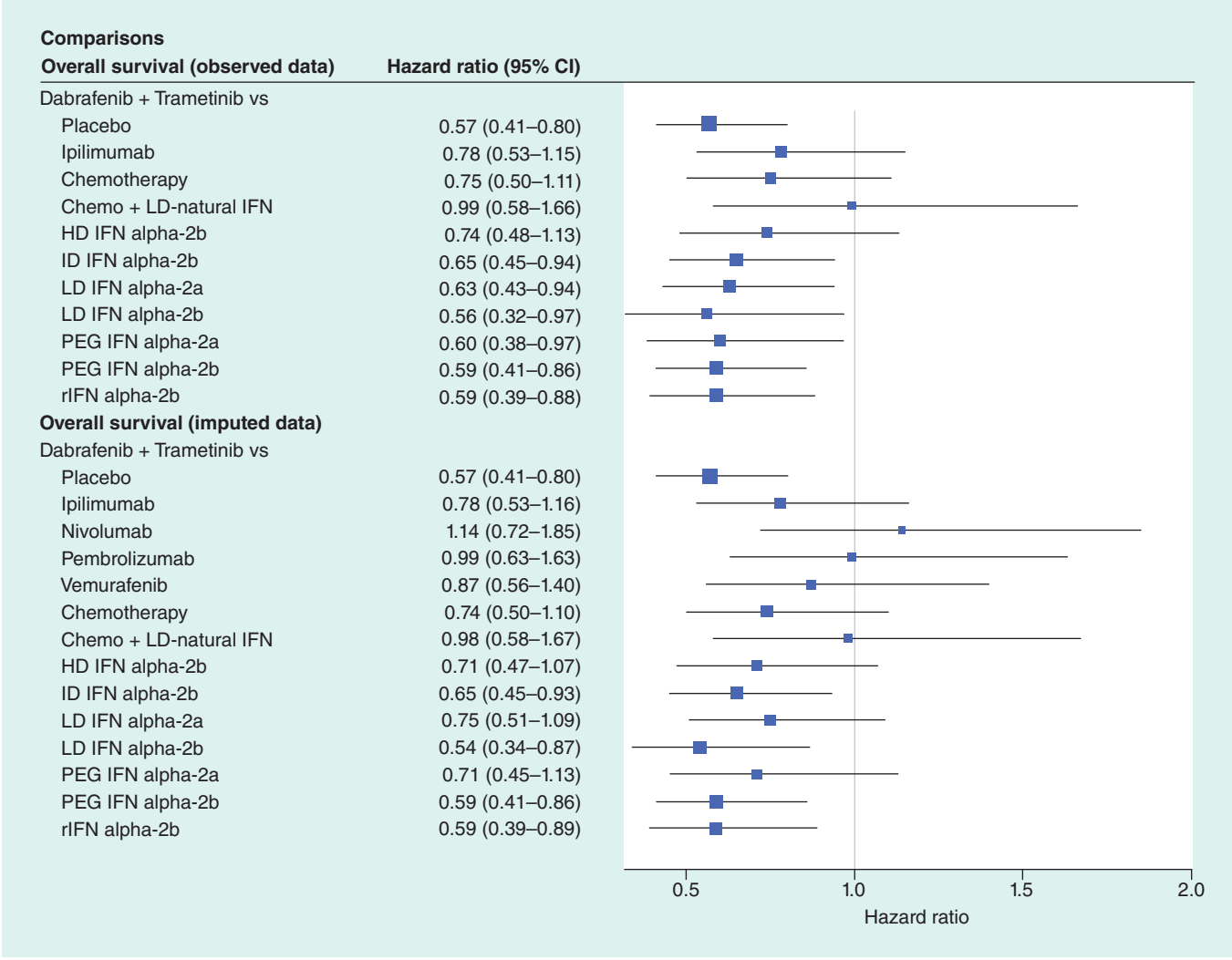

Figure 5. High-risk melanoma (American Joint Committee on Cancer-7 stage IIB–C and IIIA–C) independent of *BRAF* mutation status – hazard ratios estimated from fixed-effects network meta-analyses for overall survival; base-case.

Safety events in terms of any AE and SAE were reported in five trials (six treatments) and three trials (three treatments), respectively. The odds of experiencing any AE were statistically significantly higher with dabrafenib plus trametinib relative to placebo (OR: 4.52; 95% credible interval [CrI]: 2.47–8.93) and pembrolizumab (OR: 3.00; 95% CrI: 1.39–6.73) while being statistically significantly lower than with vemurafenib (OR: 0.11; 95% CrI: 0.01–0.68). It was comparable with nivolumab and ipilimumab. There were also higher odds of SAEs with dabrafenib plus trametinib when compared with placebo (OR: 4.92; 95% CrI: 3.44–7.21) and nivolumab (OR: 4.51; 95% CrI: 2.61–7.89).

Dabrafenib plus trametinib had statistically significantly lower DAEs when compared with ID IFN-α-2b (OR: 0.30; 95% CrI: 0.15–0.71) and PEG-IFN-α-2b (OR: 0.08; 95% CrI: 0.04–0.20), while it was not distinguishable relative to all other interferons, pembrolizumab, ipilimumab, vemurafenib and chemotherapy. Both placebo and nivolumab had lower odds of DAEs relative to dabrafenib plus trametinib. When considering discontinuations overall, there was strong evidence that dabrafenib plus trametinib had lower odds of discontinuations than pembrolizumab, ipilimumab, placebo and all included interferons. The odds of any discontinuations for dabrafenib plus trametinib were similar with respect to chemotherapy and nivolumab. All results of the safety analyses are presented in the Supplementary Data.

Table 1. High-risk (American Joint Committee on Cancer-7 IIB–C and IIIA–C) melanoma *BRAF* mutation positive status.

Observation or Placebo*	2.04 (1.68–2.48)*	1.32 (1.11–1.55)*	1.80 (1.27–2.54)*	1.85 (1.22–2.81)*	1.54 (1.18–2.01)*
0.49 (0.40–0.59)*	**Dabrafenib + Trametinib***	0.64 (0.50–0.83)*	0.88 (0.59–1.31)	0.91 (0.57–1.44)	0.75 (0.54–1.05)
0.76 (0.65–0.90)*	1.55 (1.21–2.01)	**Ipilimumab**	1.37 (1.01–1.86)*	1.41 (0.90–2.21)	1.17 (0.86–1.59)
0.56 (0.39–0.79)*	1.14 (0.77–1.69)	0.73 (0.54–0.99)*	**Nivolumab***	1.03 (0.60–1.77)	0.85 (0.55–1.32)
0.54 (0.36–0.82)*	1.10 (0.70–1.75)	0.71 (0.45–1.11)	0.97 (0.56–1.67)	**Pembrolizumab***	0.83 (0.51–1.37)
0.65 (0.50–0.85)*	1.33 (0.96–1.85)	0.86 (0.63–1.17)	1.17 (0.76–1.81)	1.21 (0.73–1.97)	**Vemurafenib***

Hazard ratios estimated from fixed-effects network meta-analyses for relapse-free survival/disease free survival; subgroup analysis. Each cell represents the comparison (hazard ratio and 95% credible interval) of the row treatment versus the column treatment. Deviance information criterion: 9.35; Deviance: 4.35.
*Statistically significant at the 0.05 significance level.

Stage III cutaneous melanoma independent of *BRAF* mutations

The constant HR NMA results for stage III all-comers subgroup were in line with the base-case results. Dabrafenib plus trametinib was estimated to have the best RFS, DMFS and OS estimates. There was strong evidence of this improvement relative to vemurafenib, ipilimumab, PEG IFN-α-2b and placebo. The evidence was weaker relative to nivolumab and pembrolizumab. OS comparisons with nivolumab, vemurafenib and pembrolizumab for this subgroup were only available in the imputed OS analysis, where dabrafenib plus trametinib was comparable with all these interventions (data will be made available upon request).

BRAF mutation positive resected high-risk cutaneous melanoma

The evidence network for *BRAF* mutation positive high-risk melanoma in biological therapies was disconnected between dabrafenib plus trametinib and nivolumab. No data were available from interferon or chemotherapy trials for this subgroup. To obtain meaningful comparisons, ipilimumab versus placebo arm from EORTC 18071 was used to connect CheckMate 238 trial (nivolumab vs ipilimumab) to the dabrafenib plus trametinib network. The network is presented in Figure 3. Two sources of heterogeneity in this population were: the EORTC 18071 trial was in all-comers population, and the CheckMate 238 *BRAF*-positive subgroup was based on mixed stage III and IV patients. Based on these assumptions, in *BRAF*-positive patients, dabrafenib plus trametinib had comparable RFS with respect to nivolumab, pembrolizumab and vemurafenib, while it was significantly better than placebo and ipilimumab (Table 1).

Discussion

Our study demonstrated that, among patients with high-risk resected cutaneous melanoma, adjuvant treatment with dabrafenib plus trametinib combination had the most favorable efficacy profile compared with conventional therapies (interferons and chemotherapy) and is comparable with the newer biological therapies (nivolumab, pembrolizumab and vemurafenib) in the current therapeutic landscape. With respect to ipilimumab, while the results favored dabrafenib plus trametinib combination in terms of prolonging relapse-free and DMFS, further investigations and longer term follow-up are warranted to observe a differential effect on OS. This is the first SLR and network meta-analysis among both interferons and newer biological therapies for high-risk resected cutaneous melanoma. Although our intended target population was high-risk resected *BRAF* mutation-positive cutaneous melanoma, we expanded the study population by removing the restriction on *BRAF* mutation status. The resulting evidence base was connected and allowed for NMA to be conducted. OS was under-reported, but use of RFS as a surrogate measure allowed comparisons to be made between biological therapies, including other *BRAF*-inhibitors and other PD1-checkpoint inhibitors. Results of the analyses were robust to sensitivity analyses when restricted to Stage III AJCC ed.7 matched high-risk adjuvant melanoma and restricted to the *BRAF* V600E/K-positive population. In fact, in the latter sub-population, there was an improved separation between the dabrafenib plus trametinib combination and other therapies. The evidence base for safety outcomes was much sparser, suggesting the dabrafenib plus trametinib combination was better than some, but worse than others.

Results from this study help corroborate results from previous meta-analyses in patients with high-risk melanoma. Given that this is the first SLR and NMA to include targeted and immune checkpoint inhibitor therapies, previous studies have been limited to interferons and chemotherapy. Previous results have reported significant RFS advantage (HR = 0.82) for patients receiving IFN-α while the effect on OS was marginal (HR = 0.89) [72]. Several other published meta-analysis in adjuvant interferon therapies have indicated either no benefit or marginal benefit of interferon in prolonging survival [73–76]. Besides, due to considerable toxic effects of interferon, its use in adjuvant

therapy setting is controversial. The results from our NMA strongly indicate that adjuvant therapy with dabrafenib plus trametinib can be considered a more efficacious alternative to the interferon and chemotherapy in patients with resected high-risk melanoma. The limited safety data also suggests that dabrafenib plus trametinib is more tolerable than interferons.

As previously mentioned, there was a notable difference between the target population and the study population. To help address this, we conducted a subgroup analysis in the target population, to provide insights (differences and/or similarities) into the relationship between the results in the target and study populations. Only two studies were restricted to 100% *BRAF* positive high-risk resectable melanoma patients: COMBI-AD study comparing dabrafenib plus trametinib to placebo and BRIM-8 comparing vemurafenib to placebo [59,60]. This is hardly surprising given that these were the only Phase III studies that focused on *BRAF*-inhibitors. The CheckMate-238 study comparing nivolumab to ipilimumab, also reported on HR for RFS in *BRAF* positive subgroup; however, patients in this subgroup had resectable stage III or resectable stage IV disease [71]. KEYNOTE-054 study in pembrolizumab had 43% *BRAF*-positive patients [26]. Another challenge was that the nivolumab versus ipilimumab comparison was not connected to dabrafenib plus trametinib network. Thus, in order to include nivolumab in the dabrafenib plus trametinib network, aggregate level matching NMA was performed wherein, ipilimumab versus placebo arm of EORTC 18071 trial, which does not report on *BRAF* status, was included [41]. These two allowances introduced additional heterogeneity in the *BRAF* mutation-positive network and as such, the observed effects might not be truly representative of relative treatment effects in this population and should be interpreted with caution. The results of this subgroup analysis suggest that we can interpolate the results from the study population to the target population.

This study has several strengths and limitations. The strengths of this SLR involved highly sensitive searches in key bibliographic databases as well as searches of recent conferences and clinical trial registries to identify unpublished completed trials with results. The review processes were guided by the predefined eligibility criteria established in the SLR protocol and involved two independent researchers for the identification of studies and data extraction.

There was a lack of *BRAF* mutant-specific results for the PD1-inhibitors. We tried to address this by including *BRAF*-all comers results in the principal analysis and confirming alignment with a subgroup analysis restricted to *BRAF*-positive patients. Another constraint was the lack of OS data for targeted and immune checkpoint inhibitor therapies outside of the dabrafenib plus trametinib combination; however, we were able to draw inference for OS for these therapies by using RFS as a surrogate on the basis of a separate study we had conducted. Despite this effort, use of a surrogate outcome for survival limits how the results can be interpreted. Next, while a large connected network was possible for efficacy outcomes, safety outcomes were much less frequently reported making it difficult to draw inference with respect to safety. Better inference could be drawn with respect to tolerability (discontinuation, overall and due to AEs), which suggested that the dabrafenib plus trametinib combination was comparatively comparable with immune checkpoint inhibitors and much more tolerable than interferons.

As always, the SLR is limited by the use of published data. Moreover, the May 2018 and July 2018 updates were not comprehensive SLR updates. As such, some of the studies of interest that were published between July 2017 and July 2018 could have been missed out. There is risk of publication bias as some clinical trials fail to be published while others are published in abstract form, which present limited information. However, an extensive search of conference abstracts was performed, which may mitigate this for recent trials.

The results from NMA suggested that adjuvant therapy with dabrafenib plus trametinib significantly prolongs the survival outcomes in high-risk resected cutaneous melanoma compared with interferon, ipilimumab and chemotherapy while the combination is comparable in efficacy to nivolumab and pembrolizumab. Further investigations from direct head-to head trials will be needed to confirm the results.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0061

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Summary points

Background

- Biological therapies (*BRAF*-, MEK- and PD1/PDL1-inhibitors) are a promising new set of adjuvant therapies for the treatment of high-risk completely resected melanoma.
- There has yet to be a systematic literature review and network meta-analysis of this therapeutic landscape.

Evidence base

- Systematic searches were conducted on 27 July 2017 and updated nonsystematically in May 2018 and July 2018.
- A total of 55 citations corresponding to 37 studies met the inclusion criteria and 28 studies were included in the analyses.
- Key included trials are COMBI-AD (dabrafenib plus trametinib), BRIM-8 (vemurafenib), CheckMate-238 (nivolumab and ipilimumab) and KEYNOTE-054 (pembrolizumab).

Relapse-free survival

- In high-risk melanoma (American Joint Committee on Cancer-7 stage IIB–C and IIIA–C) patients independent of *BRAF* mutation status, dabrafenib plus trametinib was estimated to lead to a lower risk of disease relapse compared with all other adjuvant treatment regimens in the network.
- There was strong evidence of a benefit relative to most comparators, including: ipilimumab, chemotherapy, all interferons and placebo. The evidence was weaker relative to nivolumab, pembrolizumab and vemurafenib.
- Results were similar when restricting to *BRAF* mutant positive high-risk cutaneous melanoma and restricting to stage III high-risk cutaneous melanoma.

Distant metastasis-free survival

- The evidence base was sparser for distant metastasis-free survival, relative to relapse-free survival; however, results were quite similar to relapse-free survival results.

Overall survival

- Overall survival (OS) was not reported for nivolumab, pembrolizumab and vemurafenib.
- Analyses ignoring these treatments suggest that dabrafenib plus trametinib have the highest OS with strong evidence of improvements relative to all interferons and placebo.
- We developed a statistical model to use relapse-free survival as a surrogate to OS (analysis published separately) and analyzed all treatments simultaneously. Dabrafenib plus trametinib improved survival relative to interferons and placebo and was comparable with other targeted and immune checkpoint inhibitors.

Safety & tolerability

- There were much fewer trials reporting safety data; however, dabrafenib plus trametinib did appear to lead to higher proportions of patients with adverse events than placebo and pembrolizumab, while leading to lower proportions relative to vemurafenib.
- Dabrafenib plus trametinib appeared to be more tolerable to interferons, but was not distinguishable from other targeted and immune checkpoint inhibitors. Nonetheless, when considering discontinuations overall, dabrafenib plus trametinib was positively distinguishable from pembrolizumab, ipilimumab as well as interferons.

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