SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS OF EFFECTIVENESS AND SAFETY OUTCOMES IN ADVANCED MELANOMA

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ABSTRACT

BACKGROUND

Although a myriad of novel treatments entered the treatment paradigm for advanced melanoma, there is a lack of head-to-head evidence. We conducted a network meta-analysis (NMA) to estimate each treatment's relative effectiveness and safety.

METHODS

A systematic literature review (SLR) was conducted in Embase, MEDLINE, and Cochrane to identify all phase-III randomised controlled trials (RCTs); timeframe: January 1, 2010 to March 11, 2019. We retrieved evidence on treatment-related grade 3/4 adverse events, progression-free survival (PFS), and overall survival (OS). Evidence was synthesised using a Bayesian fixed-effect NMA. Reference treatment was dacarbazine. In accordance with RCTs, dacarbazine was pooled with temozolomide, paclitaxel, and paclitaxel plus carboplatin. To increase homogeneity of the study populations, RCTs were only included if patients were not previously treated with novel treatments.

RESULTS

The SLR identified 28 phase-III RCTs involving 14,376 patients. Nineteen (seventeen) treatments were included in the effectiveness (safety) NMA. For PFS, dabrafenib plus trametinib (hazard ratio [HR] PFS: 0.21) and vemurafenib plus cobimetinib (HR PFS: 0.22) were identified as most favourable treatments. Both had, however, less favourable safety profiles. Five other treatments closely followed (dabrafenib [HR PFS: 0.30], nivolumab plus ipilimumab [HR PFS: 0.34], vemurafenib [HR PFS: 0.38], nivolumab [HR PFS: 0.42], and pembrolizumab [HR PFS: 0.46]). In contrast, for OS, nivolumab plus ipilimumab (HR OS: 0.39), nivolumab (HR OS: 0.46), and pembrolizumab (HR OS: 0.50) were more favourable than dabrafenib plus trametinib (HR OS: 0.55) and vemurafenib plus cobimetinib (HR OS: 0.57).

CONCLUSIONS

Our NMA identified the most effective treatment options for advanced melanoma and provides valuable insights into each novel treatment’s relative effectiveness and safety. This information may facilitate evidence-based decision making and may support the optimisation of treatment and outcomes in everyday clinical practice.

INTRODUCTION

The incidence of cutaneous melanoma has been increasing the past decades. The World Health Organization estimates around 132,000 new cases worldwide each year [1]. Although most patients are diagnosed at the local stage and have a rather favorable prognosis, advanced (unresectable stage III and stage IV) melanoma is associated with poor survival outcomes. Treatment options have been limited for many years. In March 2011, however, the Food and Drug Administration approved the CTLA-4 immune checkpoint inhibitor ipilimumab [2]. Ipilimumab was the first novel treatment that demonstrated improved survival (median overall survival [OS] of 10.1 months compared to 6.4 months for patients receiving glycoprotein 100 peptide vaccine [GP100] [3]). Since then, the treatment landscape rapidly changed as a myriad of novel treatments and combinations of treatments became available for patients with advanced melanoma. Although these novel regimens showed superior effectiveness in pivotal phase-III randomised controlled trials (RCTs), direct head-to-head comparisons remain scarce. In specific, there is a lack of comparative evidence between the different immune check-point inhibitors (anti-CTLA-4 and anti-PD-1) and mitogen-activated protein kinase pathway inhibitors (BRAFi and MEKi).

It is, therefore, not possible to evaluate the relative effectiveness and safety of each specific novel treatment using direct evidence from RCTs. A network meta-analysis (NMA) of available RCTs can provide such comparative evidence. NMAs will become increasingly important as there is a low incentive to initiate RCTs comparing treatment options with market approval [4,5]. Although performing NMAs is relatively new, the method has quickly gained popularity exemplified by the use of the method in clinical guidelines, Cochrane reviews and a recent call for a more widespread use by the WHO [4-7]. NMAs combine direct and indirect evidence to rank-order competing treatments that were never directly compared head-to-head in an RCT. This also implies that indirect evidence can alter the effectiveness estimates from the RCT because NMAs use evidence from all RCTs included in the network that inform the treatment effect. Therefore, relative effectiveness estimates obtained by an NMA are more robust than outcomes of one single RCT [8].

Although previous studies reported NMA outcomes in advanced melanoma, most of them were conducted before the introduction of immunotherapies and targeted therapies [9-11]. Two more recent studies [12,13] compared effectiveness across treatment classes (e.g., immunotherapies versus targeted therapies), but both studies were conducted earlier in time. More crucially, both studies did not investigate the relative effectiveness for treatments within the same class (e.g., nivolumab versus pembrolizumab within the immunotherapy class and vemurafenib versus dabrafenib within the BRAFi class).

We investigated the relative effectiveness and safety of each systemic treatment option. We performed a systematic literature review (SLR) to identify all phase-III RCTs in patients with advanced cutaneous melanoma and synthesised this evidence by means of an NMA to evaluate the relative effectiveness (progression-free survival [PFS] and OS) and safety (treatment-related adverse events [TRAEs]) of each systemic treatment. This provides relevant information to develop evidence-based clinical guidelines, to support medical decision

making in everyday clinical practice, and to facilitate economic analyses evaluating the relative cost-effectiveness of all treatment options.

METHODS

SYSTEMATIC LITERATURE REVIEW

A systematic literature search was performed, according to PRISMA guidelines [14], in the databases Embase®, MEDLINE®, and Cochrane® to identify relevant phase-III RCTs (appendix A.1 provides the search strategy). The time frame of the search was January 1, 2010 to March 11, 2019. Title and abstract were first screened, followed by full text assessing for eligibility. Each step was independently conducted by two researchers, results were compared and differences were resolved by consensus. Studies were included if they described a phase-III RCT of a systemic treatment for unresectable stage III and/or stage IV cutaneous melanoma. Exclusion criteria were: non-cutaneous melanoma, disease stage other than unresectable stage III and IV, study-design other than phase-III RCT (e.g., observational or review), subgroup analyses only, and non-English. Reference lists of published RCTs, reviews, and meta-analyses were manually screened to ensure the inclusion of all phase-III RCTs in advanced melanoma.

DATA EXTRACTION AND RISK OF BIAS ASSESSMENT

Data were extracted using a standardised data collection form in Excel. The following data were extracted: publication details (year of publication and first author), trial details (national clinical trial [NCT] number, follow-up duration, intervention and comparator, and number of patients), patient characteristics (age, disease status, treatment status [treatment naive versus previously treated], and type of previous treatment), safety outcomes (counts/percentages of patients experiencing at least one grade 3/4 TRAE, and effectiveness outcomes (median and hazard ratios [HRs] including 95% confidence intervals [CI] for PFS and OS). Data of the most recent citation was reported in case extended follow-up was available. In case extended follow-up did not report on all outcomes (PFS, OS, and TRAE), the latest reported follow-up was retrieved for each outcome.

In case TRAE count data, HRs and/or CI for PFS and OS were not reported, the first author was approached by email. If this data remained unavailable, HR and/or CI for PFS and OS were estimated following the step-wise methodology as described by Tierney et al. [15]. If TRAE count data remained unavailable, studies were excluded in the safety NMA. The quality of the studies was assessed by means of the Cochrane collaboration's tool for assessing risk of bias in randomised trials [16].

NETWORK META-ANALYSIS

A network was created from the identified treatment options which were head-to-head compared in the RCTs. To increase homogeneity between the studies, studies were only included in the main network if patients were either treatment naive or only previously treated with 'older' treatments which never demonstrated efficacy [9,17,18] (i.e., dacarbazine, temozolomide, fotemustine, carboplatin, interleukin-2, sorafenib, interferon, and cytokine). Thereby, we assumed that all trials within the main network investigated first line treatment and that previously receiving an 'older ineffective' treatment has no impact on current RCT outcomes. The impact of this assumption was explored by including all identified treatment options within a

full extended network, irrespectively of receiving previous treatment (extended network and results presented in the online appendix).

The NMA was conducted in WinBUGS in accordance with methods adopted by NICE [19-22] as well as recommended by ISPOR [23,24]. A random-effect model was deemed inappropriate as the number of studies was too low in comparison to the number of treatments (i.e., only 1 RCT provided direct evidence between most treatment nodes). Therefore, a Bayesian fixed-effect model was used to estimate the HR of a treatment's relative effectiveness for PFS and OS, and the relative risk (RR) for experiencing a grade 3/4 TRAE. For all comparisons, the following mathematical formula was used for estimating the HR for PFS and OS of treatment a versus b: $\widehat{HR_{a,b}} = e^{(\partial_b - \partial_a)}$. The mathematical formula for estimating the RR of TRAEs of treatment a versus b was: $\widehat{RR_{a,b}} = e^{(\partial_b - \partial_a)}$. In all the estimations, uninformative priors were used implying that before seeing the data all parameter values are deemed likely but on average the treatments are considered having no effect.

Dacarbazine was selected as reference treatment ($\partial_{REF} = 0$) as it has been the standard treatment for advanced melanoma until 2010 [9,10]. In accordance with the included RCTs, dacarbazine was pooled in a reference group with temozolomide, paclitaxel, and paclitaxel in combination with carboplatin to establish the main network. Consequently, these treatments were assumed having an identical safety profile and clinical benefit. This assumption was based on three RCTs [25-27] in which a novel treatment was compared with the investigator's choice of chemotherapy (either dacarbazine [25-27], temozolomide [27], paclitaxel [25], or paclitaxel plus carboplatin [26]). This assumption was confirmed by clinical experts.

We corrected for the correlation between effect estimates in multi-arm trials using the methods as described by Franchini and colleagues [28]. The NMA was performed using a Markov Chain Monte Carlo simulation process iteratively applying RRs for TRAEs and HRs for PFS and OS which were derived from the 95% CIs. The NMA outcomes are probability distributions for the parameters of interest from which summary statistics such as means and standard deviations can be derived (multiple testing is not required). This allows straightforward interpretation of the outcomes (e.g. the probability that a hazard ratio has a certain value) which is in line with decision making theory [29]. From the outcomes of the Markov Chain Monte Carlo simulation process, we calculated the 95% credible interval (CrI) as well as the probability of being the best (PBB) treatment. For results for BRAF wild-type patients only, we excluded targeted therapies in the calculation of the PBB.

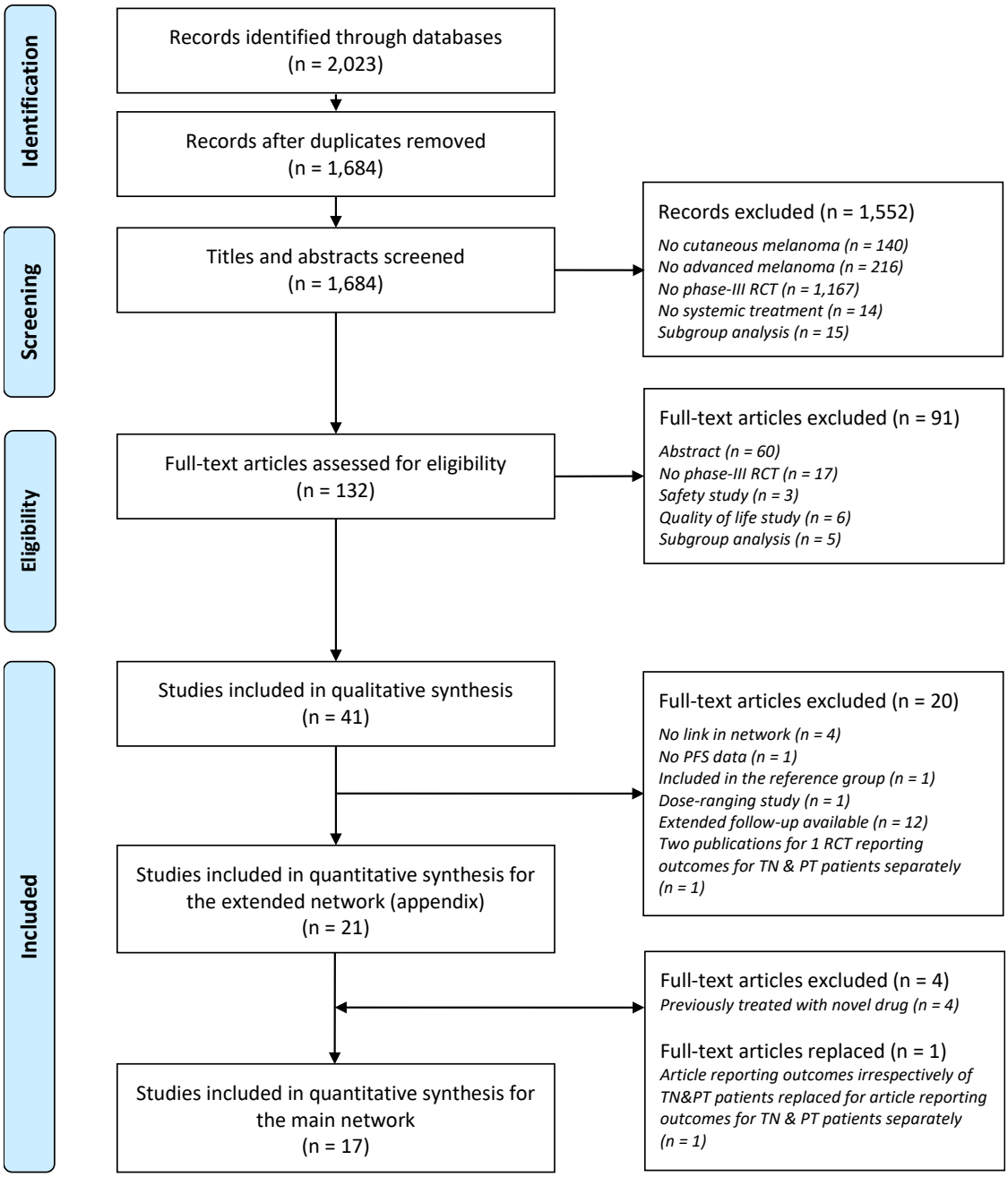
Convergence of the results was assessed using the Gelman and Rubin's diagnostic [30]. Model fit was assessed using overall residual deviance. Face validity was checked by comparing direct evidence from the RCTs with modelled outcomes. For further reading on NMA methodology, we refer to Caldwell et al. [6], Mills et al. [31], and Kanters et al. [7].

RESULTS

SYSTEMATIC LITERATURE REVIEW

The search identified 2,023 citations. After removing duplicates, 1,684 citations were retrieved from the electronic databases. Title and abstract screening resulted in the exclusion of 1,552 citations. Assessing full text resulted in the exclusion of another 91 citations. In total, 41 citations describing 28 RCTs were included for data extraction for the qualitative analysis. Figure 1 shows the PRISMA flow diagram.

FIGURE 1. PRISMA FLOW DIAGRAM



The 28 RCTs involved in total 14,376 advanced melanoma patients. The RCTs were conducted in treatment naive (TN) patients (11 RCTs), previously treated (PT) patients (4 RCTs) as well as in TN and PT patients within one trial (13 RCTs). Of the trials including PT patients (17 RCTs), most included patients previously treated with *'older'* treatments. Five of these 17 RCTs [32-36] included a percentage of patients previously treated with a novel treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, and anti-PD-1). One of these RCTs, however, reported outcomes in the first publication [32] irrespectively of line of treatment but reported outcomes differentiating between TN and PT patients in a follow-up publication [37]. The median/mean age of the patients was between 47 and 66 years. Follow-up time of the RCTs was often not reported (11 RCTs). In case it was reported, the method of computation greatly differed between the studies. Therefore, comparing reported follow-up times would be biased [38]. Nine RCTs published at least one extended follow-up publication. There was a large difference in the percentage of patients with a grade 3/4 TRAE (ranging from 9% in patients receiving nivolumab [26] to 84% in patients receiving Interleukin-2 plus GP100 [39]). Median PFS ranged between 1.5 months for dacarbazine [34] and/or paclitaxel [25] and 14.9 months for encorafenib plus binimetinib [36]; median OS ranged between 5.9 months for lenalidomide [40] and 37.6 months for nivolumab [41], and was not yet reached in four RCTs (i.e., dabrafenib [42], dabrafenib plus trametinib [43], nivolumab [44], pembrolizumab [32], and nivolumab plus ipilimumab [45]). None of the RCTs compared immunotherapy head-to-head with a BRAFi. Similar, none of the RCTs head-to-head compared the two anti-PD-1s, the three BRAFi's, or the three BRAFi plus a MEKi treatment combinations. Table 1 shows the summary characteristics extracted from the RCTs and appendix A.2 provides additional details of the SLR.

Appendix A.3 shows the details of the results of the risk of bias assessment. The overall risk of bias was relatively low. In case there was a risk of bias, this was mainly related to reporting bias, violation of the proportional hazard assumption, permission of treatment cross-over, and early stop of the study due to crossing predefined boundaries (e.g., futility, efficacy, or stopping boundary).

TABLE 1. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

NCT number	First author	Year	Intervention	Comparator	Treatment status	Number of patients in ITT population *Int vs Comp*		RR grade 3/4 TRAEs (95% CI)	HR for PFS (95% CI)	HR for OS (95% CI)
NCT 00057616	Eisen[a] [40]	2010	Lenalidomide	Placebo	PT	152	154	NR	NR	1.16 (0.86-1.59)
NCT 00094653	Hodi [3]	2010	A: Ipilimumab + GP100	C: GP100	PT	403	136	A vs B: 0.76 (0.52-1.11)	A vs B: 1.25 (1.06-1.49)	A vs B: 1.04 (0.83-1.30)
			B: Ipilimumab			137		A vs C: 1.53 (0.90-2.58)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.68 (0.55-0.85)
								B vs C: 2.02 (1.14-3.57)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.66 (0.51-0.87)
NCT 00087776	Bedikian[b] [46]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	TN	194	199	2.13 (1.72-2.64)	NR	NR
NCT 00005052	Patel[c] [47]	2011	Temozolomide	Dacarbazine	TN & PT	429	430	1.21 (0.99-1.47)	0.92 (0.80-1.06)	1.00 (0.86-1.17)
NCT 00324155	Robert [48]	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	TN	250	252	2.05 (1.63-2.57)	0.76 (0.63-0.93)	0.72 (0.59-0.87)
NCT 00019682	Schwartzen-truber[a] [39]	2011	Interleukin-2 + GP100	Interleukin-2	TN & PT	91	94	1.06 (0.92-1.23)	NR	NR
NCT 01227889	Hauschild [42]	2012	Dabrafenib	Dacarbazine	TN	187	63	NR	0.30 (0.18-0.51)	0.61 (0.25-1.48)
NCT 01359956	Daponte[a] [49]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	TN	64	70	A+B vs C+D: NR	A+B vs C+D: 0.93 (0.72-1.21)	A+B vs C+D: 0.93 (0.71-1.21)

			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b		68	58	B+D vs A+C: NR	B+D vs A+C: 0.96 (0.73-1.25)	B+D vs A+C: 0.92 (0.70-1.20)
NCT 00110019	Flaherty [50]	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	TN & PT	410	413	1.08 (1.01-1.17)	0.90 (0.78-1.03)	1.01 (0.87-1.18)
NCT 00522834	O'Day [51]	2013	Elesclomol + paclitaxel	Paclitaxel	TN & PT	325	326	1.23 (1.00-1.50)	0.89 (0.73-1.08)	1.10 (0.92-1.32)
NCT 00257205	Ribas [27]	2013	Tremelimumab	Temozolomide or dacarbazine	TN	328	327	1.40 (1.18-1.67)	0.94 (0.81-1.11)	0.88 (0.74-1.04)
NCT 00518895	Bedikian [52]	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	TN & PT	157	157	2.38 (1.68-3.36)	0.85 (0.67-1.09)	1.04 (0.81-1.34)
NCT 01006252	Hamid [53]	2014	Tasisulam	Paclitaxel	PT	168	168	NR	1.30 (1.01-1.66)	1.23 (0.89-1.69)
NCT 00769704	Andtbacka[a] [54]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	TN & PT	295	141	2.32 (0.99-5.41)	NR	0.79 (0.62-1.00)
NCT 00864253	Hersh [55]	2015	*nab*-Paclitaxel	Dacarbazine	TN & PT	264	265	NR	0.79 (0.63-0.99)	0.90 (0.71-1.13)
NCT 01597908	Robert [43]	2015	Dabrafenib + trametinib	Vemurafenib	TN	352	352	0.82 (0.73-0.94)	0.56 (0.49-0.69)	0.69 (0.53-0.89)
NCT 01689519	Ascierto [56]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	TN	247	248	1.13 (0.96-1.33)	0.58 (0.46-0.72)	0.70 (0.55-0.90)
NCT01515189	Ascierto[d] [57]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	TN & PT	365	362	1.87 (1.44-2.43)	0.89 (0.76-1.40)	0.84 (0.70-0.99)
NCT 01006980	Chapman [58]	2017	Vemurafenib	Dacarbazine	TN	337	338	1.75 (1.51-2.03)	0.38 (0.32-0.46)[e]	0.81 (0.70-1.00)
NCT 01763164	Dummer[f] [34]	2017	Binimetinib	Dacarbazine	TN & PT	269	133	NR	0.62 (0.47-0.80)	1.00 (0.75-1.33)

NCT 01721746	Larkin[f] [33]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	PT	272	133	0.41 (0.28-0.62)	1.00 (0.78-1.44)	0.95 (0.70-1.29)
NCT 01584648	Long [59]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	TN	211	212	0.95 (0.78-1.16)	0.71 (0.57-0.88)	0.75 (0.58-0.96)
NCT 01866319	Schachter[f] [32]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	TN & PT	279	278	A vs C: 0.87 (0.60-1.24)	A vs C: 0.61 (0.50-0.75)	A vs C: 0.68 (0.53-0.87)
			B: Pembrolizumab 3-weekly			277		B vs C: 0.85 (0.59-1.22)	B vs C: 0.61 (0.50-0.75)	B vs C: 0.68 (0.53-0.86)
NCT 00779714	Ugurel[f] [35]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	TN & PT	141	133	3.27 (1.94-5.50)	0.91 (0.70-1.18)	1.08 (0.80-1.45)
NCT 01866319	Carlino[g] [37]	2018	Pembrolizumab	Ipilimumab	TN & PT	TN: 65	TN: 63	TN: 0.95 (0.66-1.37)	TN: 0.57 (0.46-0.70)	TN: 0.69 (0.54-0.89)
						PT: 59	PT: 58	PT: 0.74 (0.42-1.31)	PT: 0.71 (0.53-0.94)	PT: 0.71 (0.51-0.99)
NCT 01909453	Dummer[f] [36]	2018	A: Encorafenib + binimetinib	B: Encorafenib	TN & PT	192	194	A vs B: 0.87 (0.75-1.02)[h]	A vs B: 0.77 (0.59-1.00)	A vs B: 0.81 (0.61-1.06)
				C: Vemurafenib			191	A vs C: 0.91 (0.77-1.07)[h]	A vs C: 0.51 (0.39-0.67)	A vs C: 0.61 (0.47-0.79)
								B vs C: 1.04 (0.90-1.21)[h]	B vs C: 0.68 (0.52-0.88)	B vs C: 0.76 (0.58-0.98)
NCT 01844505	Hodi [45]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	TN	314	316	A vs B: 2.64 (2.11-3.31)	A vs B: 0.79 (0.65-0.97)	A vs B: 0.84 (0.67-1.05)
				C: Ipilimumab			315	A vs C: 2.14 (1.75-2.62)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.54 (0.44-0.67)
								B vs C: 0.81 (0.62-1.06)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.65 (0.53-0.79)
NCT 01721772	Ascierto [60]	2019	Nivolumab	Dacarbazine	TN	210	208	0.86 (0.55-1.33)	0.42 (0.33-0.53)	0.46 (0.36-0.59)

NCT 01245062	Robert [61]	2019	Trametinib	Dacarbazine or paclitaxel	TN & PT	214	108	1.37 (1.04-1.81)	0.54 (0.41-0.73)	0.84 (0.63-1.11)

CI, confidence interval; Comp, comparator; HR, hazard ratio; Int, intervention; ITT, intention-to-treat; kg, kilogram; mg, milligram; NR, not reported; OS, overall survival; PFS, progression-free survival; PT, previously treated; RR, relative risk; TN, treatment naive; TRAEs, treatment-related adverse events.

[a]No link in main network;

[b]Not included in main network because data on progression-free survival was not presented;

[c]Temozolomide is pooled within the dacarbazine reference group;

[d]Dose-ranging study;

[e]Retrieved from McArthur et al. 2014 [62];

[f]Only included in extended network (see appendix A.7);

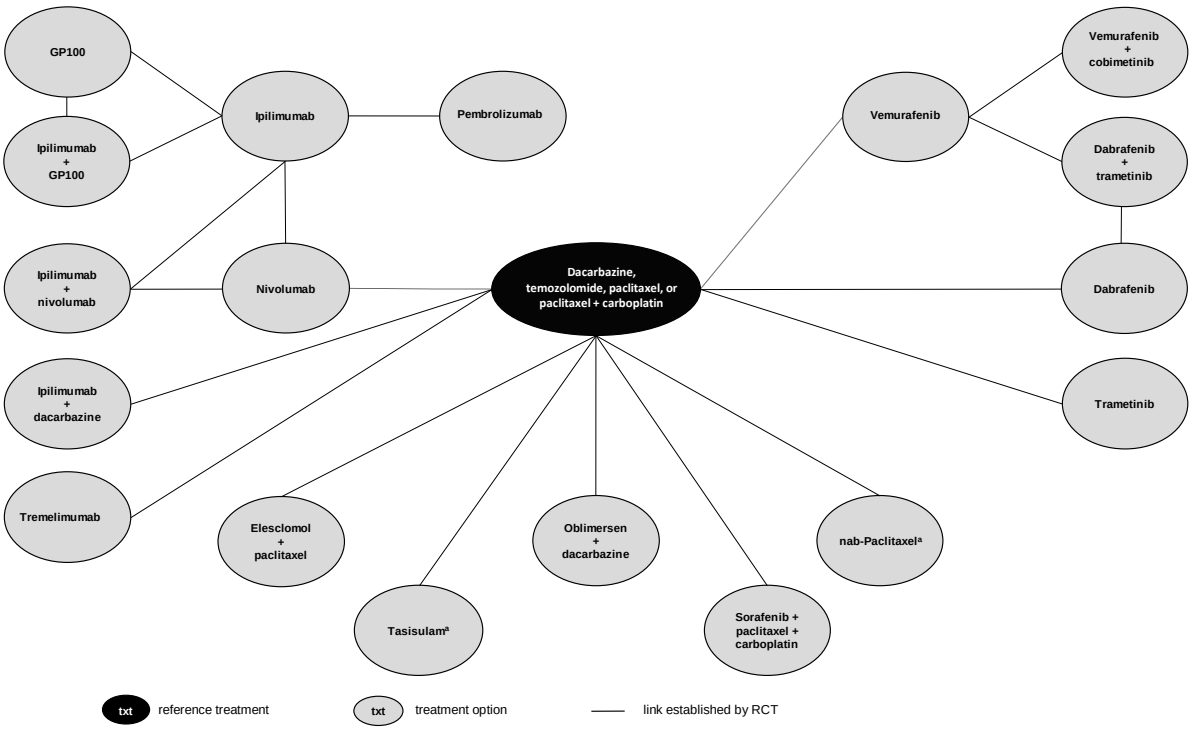
[g]Treatment line specific outcomes of Schachter et al. 2017 [32] (only included in main network);

[h]Retrieved from Dummer et al. 2018 [63].

NETWORK OF TREATMENT OPTIONS

The treatment options of the RCTs were connected in a network (see Figure 2). Out of the 28 identified RCTs, four [39,40,49,54] had no connection in the network. Another seven RCTs were excluded from the main network as one RCT [46] had no PFS data (only reported Time To Progression), one RCT [47] was included within the reference group (comparing temozolomide versus dacarbazine), one RCT [57] concerned a dose-ranging study, and four RCTs [33-36] included patients previously treated with a novel treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, and anti-PD-1). One RCT including TN and PT patients (Schachter et al. [32]) could be retained within the main network as the extended follow-up published the outcomes for TN and PT patients separately (Carlino et al. [37]). Consequently, a total of seventeen RCTs could be connected within the main network including nineteen treatment options: 1) carboplatin, paclitaxel plus sorafenib, 2) dabrafenib, 3) dabrafenib plus trametinib, 4) dacarbazine reference group (including: paclitaxel, paclitaxel plus carboplatin, temozolomide), 5) dacarbazine plus oblimersen, 6) elesclomol plus paclitaxel, 7) GP100, 8) ipilimumab, 9) ipilimumab plus dacarbazine, 10) ipilimumab plus GP100, 11) nanoparticle albumin–bound (nab-)paclitaxel, 12) nivolumab, 13) nivolumab plus ipilimumab, 14) pembrolizumab, 15) tasisulam, 16) trametinib, 17) tremelimumab, 18) vemurafenib, and 19) vemurafenib plus cobimetinib. Appendix A.4 shows RCT and NMA outcomes confirming face validity of our NMA results. Appendix A.5 provides estimates of NMA outcomes for each head-to-head comparison.

FIGURE 2. MAIN NETWORK OF TREATMENTS FOR ADVANCED MELANOMA



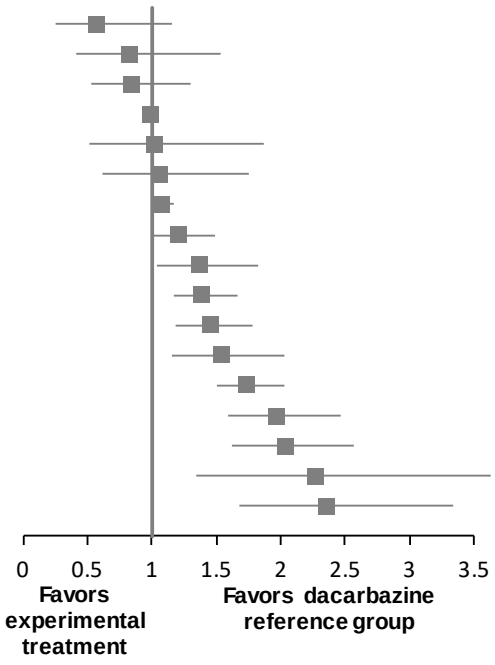
[a]Only included in network-meta analyses for progression-free and overall survival (not in safety analyses).

NETWORK META-ANALYSIS FOR TREATMENT-RELATED GRADE 3/4 ADVERSE EVENTS

Two RCTs [53,55] within the network did not report TRAE count data, therefore, the NMA for TRAE included fifteen RCTS (excluding tasisulam and nab-paclitaxel from the main network). Figure 3 presents the estimated RR for grade 3/4 TRAEs ranked according to RR compared to the dacarbazine reference group. GP100 was most favourable both in terms of RR for grade 3/4 TRAE (RR TRAE: 0.58 [95%CrI: 0.25-1.16]) and probability of being the best (PBB: 0.85). Although 95%CrI were overlapping with 1, two other options ranked better than the reference group: ipilimumab plus GP100 (PBB: 0.04; RR TRAE: 0.85 [95%CrI: 0.42-1.54]) and nivolumab (PBB: 0.05; RR TRAE: 0.86 [95%CrI: 0.54-1.30]). Pembrolizumab (RR TRAE: 1.04) and ipilimumab (RR TRAE: 1.08) were slightly less favourable than the dacarbazine reference group, but the 95%CrIs were overlapping with 1. The remaining eleven treatments had a greater risk for grade 3/4 TRAEs compared to the reference group (RR ranging from 1.08 to 2.38).

FIGURE 3. RESULTS OF THE NETWORK META-ANALYSIS FOR ADVERSE EVENTS

Treatment	PBB	RR TRAE vs reference group (95% CrI)
GP100	85%	0.58 (0.25-1.16)
Ipilimumab + GP100	4%	0.85 (0.42-1.54)
Nivolumab	5%	0.86 (0.54-1.30)
Dacarbazine reference group	**3%**	**1**
Pembrolizumab	2%	1.04 (0.52-1.87)
Ipilimumab	0%	1.08 (0.62-1.76)
Carboplatin + paclitaxel + sorafenib	0%	1.08 (1.01-1.17)
Elesclomol + paclitaxel	0%	1.23 (1.00-1.49)
Trametinib	0%	1.38 (1.04-1.83)
Tremelimumab	0%	1.40 (1.17-1.67)
Dabrafenib + trametinib	0%	1.46 (1.19-1.79)
Dabrafenib	0%	1.55 (1.16-2.03)
Vemurafenib	0%	1.75 (1.51-2.03)
Vemurafenib + cobimetinib	0%	1.98 (1.59-2.46)
Ipilimumab + dacarbazine	0%	2.05 (1.63-2.57)
Nivolumab + ipilimumab	0%	2.29 (1.35-3.64)
Dacarbazine + oblimersen	0%	2.38 (1.68-3.34)



NETWORK META-ANALYSIS FOR PROGRESSION-FREE SURVIVAL

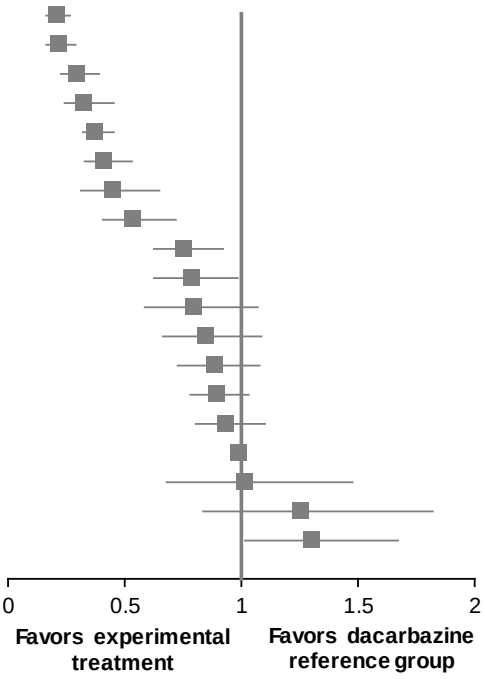
Figure 4 presents the estimated HRs for PFS ranked according to HR for PFS compared to the dacarbazine reference group. The two BRAFi plus MEKi combination treatments were identified as most favourable. Although dabrafenib plus trametinib had a higher probability of being the best treatment (PBB: 0.59) and a slightly more favourable HR for PFS (0.21) compared to vemurafenib plus cobimetinib (PBB: 0.40; HR PFS:

0.22), the 95%CrIs were similar (0.17-0.27 versus 0.17-0.29). Fifteen treatments ranked better than the dacarbazine reference group; the HRs for PFS ranged between 0.21 and 0.94. Seven treatments reduced the risk of progression by more than 50% including dabrafenib plus trametinib, vemurafenib plus cobimetinib, dabrafenib, nivolumab plus ipilimumab, vemurafenib, nivolumab, and pembrolizumab. Trametinib, ipilimumab plus dacarbazine and ipilimumab monotherapy reduced the risk of progression with 45%, 24% and 20%, respectively. All chemotherapies were less likely reducing the risk of progression, most of these HRs were overlapping with 1.

In BRAF wild-type patients, nivolumab plus ipilimumab ranked best (PBB: 0.97; HR PFS: 0.34 [95%CrI: 0.24-0.46]), followed by nivolumab monotherapy (PBB: 0.02; HR PFS: 0.42 [95%CrI: 0.33-0.53]) and pembrolizumab (PBB: 0.02; HR PFS: 0.46 [95%CrI: 0.31-0.65]).

FIGURE 4. RESULTS OF THE NETWORK META-ANALYSIS FOR PROGRESSION-FREE SURVIVAL

Treatment	PBB	HR PFS vs reference group (95% CrI)
Dabrafenib + trametinib	59%	0.21 (0.17-0.27)
Vemurafenib + cobimetinib	40%	0.22 (0.17-0.29)
Dabrafenib	0%	0.30 (0.23-0.40)
Nivolumab + ipilimumab	1%	0.34 (0.24-0.46)
Vemurafenib	0%	0.38 (0.32-0.45)
Nivolumab	0%	0.42 (0.33-0.53)
Pembrolizumab	0%	0.46 (0.31-0.65)
Trametinib	0%	0.55 (0.41-0.72)
Ipilimumab + dacarbazine	0%	0.76 (0.62-0.92)
nab -Paclitaxel	0%	0.80 (0.63-0.99)
Ipilimumab	0%	0.80 (0.59-1.07)
Dacarbazine + oblimersen	0%	0.86 (0.67-1.09)
Elesclomol + paclitaxel	0%	0.89 (0.73-1.08)
Carboplatin + paclitaxel + sorafenib	0%	0.90 (0.78-1.03)
Tremelimumab	0%	0.94 (0.80-1.10)
Dacarbazine reference group	**0%**	**1**
Ipilimumab + GP100	0%	1.02 (0.68-1.47)
GP100	0%	1.26 (0.84-1.82)
Tasisulam	0%	1.31 (1.01-1.67)



NETWORK META-ANALYSIS FOR OVERALL SURVIVAL

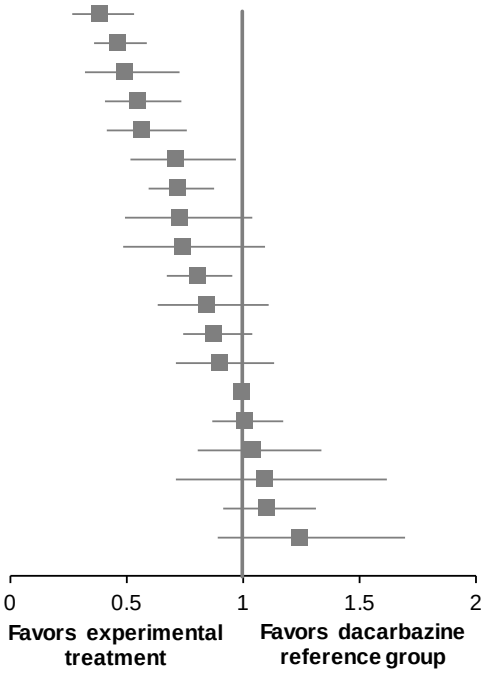
Figure 5 presents the estimated HRs for OS ranked according to HR for OS compared to the dacarbazine reference group. Three treatments reduced the risk of death by 50% or more. Nivolumab plus ipilimumab had the highest probability of being the best treatment (PBB: 0.82) and the most favourable HR for OS (0.39 [95%CrI: 0.27-0.54]). Although nivolumab monotherapy (PBB: 0.04) and pembrolizumab (PBB: 0.06) had a

somewhat less favourable HR for OS (0.46 and 0.50 respectively), the 95%CrI largely overlapped with nivolumab plus ipilimumab (nivolumab 95%CrI: 0.36-0.59; pembrolizumab 95%CrI: 0.33-0.73). The two BRAFi plus MEKi combination treatment options closely followed (dabrafenib plus trametinib: PBB: 0.05; HR OS: 0.55 [95%CrI: 0.41-0.74] and vemurafenib plus cobimetinib: PBB: 0.03; HR OS: 0.57 [95%CrI: 0.42-0.76]). Another eight treatments ranked better than the dacarbazine reference group; these HRs for OS ranged between 0.72 and 0.91. Five treatments were less favourable than the dacarbazine reference group, but the 95%CrI were overlapping with 1.

In BRAF wild-type patients, nivolumab plus ipilimumab ranked best (PBB: 0.88; HR OS: 0.39 [95%CrI: 0.27-0.54]), followed by bothanti-PD-1s monotherapies (nivolumab: PBB: 0.05 [95%CrI: 0.36-0.59]; pembrolizumab: PBB: 0.06 [95%CrI: 0.33-0.73]).

FIGURE 5. RESULTS OF THE NETWORK META-ANALYSIS FOR OVERALL SURVIVAL

Treatment	PBB	HR OS vs reference group (95% CrI)
Nivolumab + ipilimumab	82%	0.39 (0.27-0.54)
Nivolumab	4%	0.46 (0.36-0.59)
Pembrolizumab	6%	0.50 (0.33-0.73)
Dabrafenib + trametinib	5%	0.55 (0.41-0.74)
Vemurafenib + cobimetinib	3%	0.57 (0.42-0.76)
Ipilimumab	0%	0.72 (0.52-0.97)
Ipilimumab + dacarbazine	0%	0.72 (0.59-0.87)
Dabrafenib	0%	0.73 (0.50-1.04)
Ipilimumab + GP100	0%	0.74 (0.48-1.10)
Vemurafenib	0%	0.81 (0.68-0.96)
Trametinib	0%	0.85 (0.63-1.11)
Tremelimumab	0%	0.88 (0.74-1.04)
nab -Paclitaxel	0%	0.91 (0.71-1.13)
Dacarbazine reference group	**0%**	**1**
Carboplatin + paclitaxel + sorafenib	0%	1.01 (0.87-1.18)
Dacarbazine + oblimersen	0%	1.05 (0.81-1.34)
GP100	0%	1.10 (0.71-1.62)
Elesclomol + paclitaxel	0%	1.11 (0.92-1.32)
Tasisulam	0%	1.25 (0.89-1.70)



DISCUSSION

A myriad of novel treatments entered the treatment paradigm for advanced melanoma the last eight years. There is, however, a lack of head-to-head evidence. We conducted an SLR and synthesised all available phase-III RCT evidence to assess the relative safety and relative effectiveness of each novel treatment. As there is a low incentive for comparing treatments with market approval head-to-head in an RCT, we believe that evidence from NMAs will become increasingly important to inform evidence-based guideline development and support medical decision making in everyday practice, and to facilitate economic analysis [4,5,7]. There is, for example, no evidence from RCTs regarding the comparative effectiveness of immune check-point inhibitors versus mitogen-activated protein kinase pathway inhibitors. Our NMA results showed that for PFS both dabrafenib plus trametinib and vemurafenib plus cobimetinib (both a BRAFi plus MEKi combination treatment) were the most favourable treatment options. Both had, however, less favourable safety profiles. A group of five other treatments closely followed (dabrafenib, nivolumab plus ipilimumab, vemurafenib, nivolumab, and pembrolizumab, respectively). As these five treatments had considerable overlap in 95%CrIs, all five can be considered as valuable treatment options for clinical practice guided by disease and patient characteristics.

In contrast to PFS results, however, our NMA results show that for OS nivolumab in combination with ipilimumab, nivolumab monotherapy, and pembrolizumab ranked better than both BRAFi plus MEKi combination treatments, albeit with a considerable overlap of the 95%CrIs. This trend is in line with the expectation of clinical experts who generally confirmed that targeted therapies reduce the risk for progression but that immunotherapies have better overall survival outcomes than targeted therapies. Nevertheless, the estimated OS outcomes should be interpreted with caution. Many RCTs had a relatively short follow-up and could be considered rather immature regarding OS (see appendix A.2). Moreover, patients often receive further lines of treatment which also have an impact on survival. It is, however, not feasible to make a distinction between the effect on OS from the first and subsequent treatments. In the SLR, we identified nine RCTs with at least one extended follow-up publication. These publications illustrate that the HRs for OS were lower for all six that published a HR for OS in the first publication. In one RCT (comparing vemurafenib to dacarbazine), the 95%CIs for the HRs for OS were not even overlapping (first published HR OS: 0.37 [95%CI: 0.26-0.55] [64] versus extended follow-up HR OS: 0.81 [95%CI: 0.70-1.00] [62]). This was not the case for PFS; although the HR for PFS were most often somewhat lower in the extended follow-up publications, 95%CIs were largely overlapping. There is, however, no consensus to what extent PFS captures the effectiveness of a treatment in specific for immunotherapies. More importantly, there is no established evidence on the actual relationship between PFS and OS. Most studies (19 out of 28 RCTs) did not (yet) report extended follow-up. It is a concern whether less favourable extended follow-up outcomes will get published [4,65]. For all types of evidence, a longer follow-up always provides more solid evidence.

As NMAs combine direct and indirect evidence of RCTS, the outcomes of an NMA can be considered more solid than outcomes of one single RCT [8,65]. It also implies that indirect evidence can alter the HRs from the RCT. For example (see appendix A.6), the link between the dacarbazine reference group and dabrafenib was not

only computed using direct evidence from the RCT by Hauschild et al. [42] (HR OS: 0.61), but also from indirect evidence from three other studies (Chapman et al. [58], Robert et al. [43], and Long et al. [59]). Combining direct and indirect evidence resulted in a somewhat less favourable estimated HR for OS for dabrafenib versus the dacarbazine reference group (estimated HR OS: 0.73 in the NMA compared to the observed HR OS: 0.61 in the RCT).

To establish the network and conduct the NMA, we had to make assumptions which may have introduced some level of uncertainty. First, we pooled dacarbazine in a reference group with temozolomide, paclitaxel, and paclitaxel in combination with carboplatin. This assumption was based on three RCTs [25-27] in which a novel treatment was compared with the investigator's choice of chemotherapy consisting of drugs in our pooled reference group. Clinical experts confirmed the validity of this assumption. As consequence, however, our network could not include the RCT published by Patel et al. [47] comparing the effectiveness of temozolomide with dacarbazine (HR PFS: 0.92). As the confidence interval included a HR of 1, we believe, however, that this had a negligible impact on our results.

Second, a crucial assumption of an NMA is that the distribution of effect modifiers are comparable across the RCTs within the network. As long as prognostic factors have no influence on the treatment effect, this assumption is not violated irrespectively of the (differences in) prognostic factors of the study populations in the RCTs. However, to increase homogeneity of the study populations of the included RCTs, we made a distinction between treatment naive patients and previously treated patients. We also assumed that previously receiving an *'older'* treatment had no impact on the results. We believe that this assumption is valid as these *'older'* treatments never demonstrated efficacy [9,17,18]. As consequence, we excluded four RCTs [33-36] in our main network in which a percentage of patients was previously treated with a *'new'* (effective) treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, anti-PD-1). This further increased, however, the homogeneity of the study populations of our included RCTs. Carlino et al. [37] reported, for example, outcomes of pembrolizumab both for TN (HR PFS: 0.57 [95%CI: 0.46-0.70] and HR OS: 0.69 [95%CI: 0.54-0.89]) and for PT patients (HR PFS: 0.71 [95%CI: 0.53-0.94] and HR OS: 0.71 [95%CI: 0.51-0.99]). This suggests that TN and PT patients may have different outcomes, in specific for PFS, and it underpins our assumption to distinct between TN and PT patients in our NMA.

The online appendix shows the impact of including all identified RCTs, irrespectively of (type of) previous treatment (appendix A.7). The extended network expands with several novel treatment options such as binimetinib, encorafenib, encorafenib plus binimetinib. For PFS, encorafenib plus binimetinib was most favourable (PBB: 63%), however, with largely overlapping 95%CrIs with both other BRAFi plus MEKi treatments. Similar for OS, encorafenib plus binimetinib was most favourable (PBB: 41%) but with largely overlapping 95%CrIs with nivolumab plus ipilimumab, both other BRAFi plus MEKi treatments, and both anti-PD-1 monotherapies. The greatest impact of the inclusion of RCTs with patients previously treated with a novel drug is, however, related to the inclusion of the study by Larkin et al. [33] This RCT investigated nivolumab versus paclitaxel plus carboplatin or dacarbazine. This is the crucial link in the network for any comparison

between immunotherapies and targeted therapies. In the main network this link was only based on Ascierto et al. [60]. The HR for PFS and OS were much more favourable in treatment naïve patients in the RCT by Ascierto et al. [60] (HR PFS: 0.42 and HR OS: 0.46) compared to previously treated patients in the RCT by Larkin et al. [33] (HR PFS: 1.00 and HR OS: 0.95), even the 95%CI were not overlapping. Therefore, the inclusion of the study by Larkin et al. [33] (in the extended network including RCTs with previously treated patients) resulted in less favourable outcomes for nivolumab compared to the dacarbazine reference group (HR PFS: 0.42 in the main network versus 0.58 in the extended network; HR OS: 0.46 in the main network versus 0.62 in the extended network). More crucially however, all immunotherapies became less favourable in comparison to all targeted therapies owing to this link in the network (i.e., lower rank and less favourable estimated HR for PFS and OS).

To our knowledge, our study is the first study that investigated treatment specific safety and effectiveness outcomes in advanced melanoma. Two recent NMAs [12,13] only compared outcomes across classes of immunotherapies and targeted therapies. Our study shows that the estimated HR for PFS and OS are not identical for treatments within classes (e.g. within the BRAFi class: vemurafenib HR PFS: 0.38 and HR OS: 0.81 and dabrafenib HR PFS: 0.30 and HR OS: 0.73). The 95%CrI were, however, largely overlapping for treatments within a class. Both previous NMAs were conducted earlier in time than our study. Therefore, we could include more recent phase-III RCT evidence and information from extended follow-up publications. More importantly however, both Lima et al. [12] and Devji et al. [13] included phase-III as well as phase-II studies and full publications as well as conference abstracts. This may have increased uncertainty and heterogeneity in their network. As the key underlying assumption of any NMA is exchangeability [6,20], we believe that inclusion of preliminary results of conference abstracts and phase-II studies may introduce unnecessary bias which may lead to inconsistency [22,66].

Nevertheless, both previous NMAs also found for PFS an advantage of the BRAFi plus MEKi class versus anti-PD-1 plus anti-CTLA-4 class, albeit to a varying degree. This was somewhat different for OS, both Lima et al. [12] and Devji et al. [13] found no difference in estimated effect of anti-PD-1s versus the BRAFi plus MEKi class, whereas our estimates were in favour of nivolumab (HR OS: 0.86 versus dabrafenib plus trametinib and 0.80 versus vemurafenib plus cobimetinib). This difference was, however, not statistically significant as 95%CrIs were overlapping with 1. Both previous studies could not include the anti-PD-1 plus anti-CTLA-4 class for OS due to the time in which their study was conducted.

To conclude, our study identified the most effective treatment options for advanced melanoma and provides valuable insight into each treatment's relative safety and effectiveness. NMAs provide more solid evidence than single RCTs as they combine direct and indirect evidence and NMAs provide evidence on treatment comparisons never compared head-to-head in an RCT. Such evidence is relevant for the development of evidence-based guidelines and may support medical decision making and ultimately help to optimise treatment and outcomes of advanced melanoma patients in everyday clinical practice. Clinicians not only decide between treatment classes but also need to decide which treatment within the class is best for each

individual patient. Moreover, our NMA results may facilitate economic analysis evaluating relative cost-effectiveness of all novel treatment options. Our study showed that, regarding PFS, both BRAFi plus MEKi combination treatments were identified as most effective treatment for BRAF-mutant advanced melanoma patients. In contrast to PFS, however, anti-PD-1 plus anti-CTLA-4 and both anti-PD-1 mono-therapies were identified as most favourable regarding OS, irrespective of BRAF mutation. Given current clinical practice, it would be interesting to shed more light into the effectiveness of different sequences of novel treatments. Although currently lacking, such evidence may become available in the near future from new or ongoing RCTs [67] as well as from registry data [68].

CONFLICT OF INTEREST STATEMENT

None of the authors has a conflict of interest to report for the submitted work. Maria Gheorghe is currently employed by Sanofi but conducted the submitted work outside the employment relationship with Sanofi.

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APPENDICES

A.1 Search strategy systematic literature review

A.2 Details of the systematic literature review

A.3 Risk of bias assessment

A.4 Face validity of randomised controlled trial outcomes versus network meta-analysis outcomes

A.5 Details network meta-analysis estimates

A.6 Example of direct and indirect evidence within the network

A.7 Extended network and results of including phase-III trials with previously treated patients

A.8 PRISMA checklist

A.1 SEARCH STRATEGY SYSTEMATIC LITERATURE REVIEW

EMBASE.COM

((melanoma/exp/mj AND ('advanced cancer'/de OR 'metastasis'/exp)) OR ((melano* OR naevocarcinom* OR nevocarcinom*) NEAR/3 (advanced* OR metasta*)):ti) AND (therapy/exp OR therapy:lnk OR 'antineoplastic agent'/exp OR 'treatment outcome'/exp OR 'B Raf kinase inhibitor'/exp OR 'mitogen activated protein kinase inhibitor'/exp OR (therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR anti-ctla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* NEAR/3 virus*)):ab,ti) AND ('clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR randomization/exp OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) AND ('clinical effectiveness'/exp OR 'survival'/exp OR 'treatment response'/de OR adverse drug reaction/exp OR (effective* OR surviv* OR (treatment NEAR/3 response*) OR adverse*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

MEDLINE OVID

((exp * melanoma/ AND ("Neoplasm Metastasis"/)) OR ((melano* OR naevocarcinom* OR nevocarcinom*) ADJ3 (advanced* OR metasta*)).ti.) AND (therapeutics/ OR therapy.xs. OR "Antineoplastic Agents"/ OR exp "treatment outcome"/ OR (therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR anti-ctla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* ADJ3 virus*)).ab,ti.) AND (exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) AND (exp "survival"/ OR exp "Drug-Related Side Effects and Adverse Reactions"/ OR (effective* OR surviv* OR (treatment ADJ3 response*) OR adverse*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

COCHRANE

(((melano* OR naevocarcinom* OR nevocarcinom*) NEAR/3 (advanced* OR metasta*)):ti) AND ((therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR anti-ctla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* NEAR/3 virus*)):ab,ti) AND ((effective* OR surviv* OR (treatment NEAR/3 response*) OR adverse*):ab,ti)

A.2 DETAILS OF THE SYSTEMATIC LITERATURE REVIEW

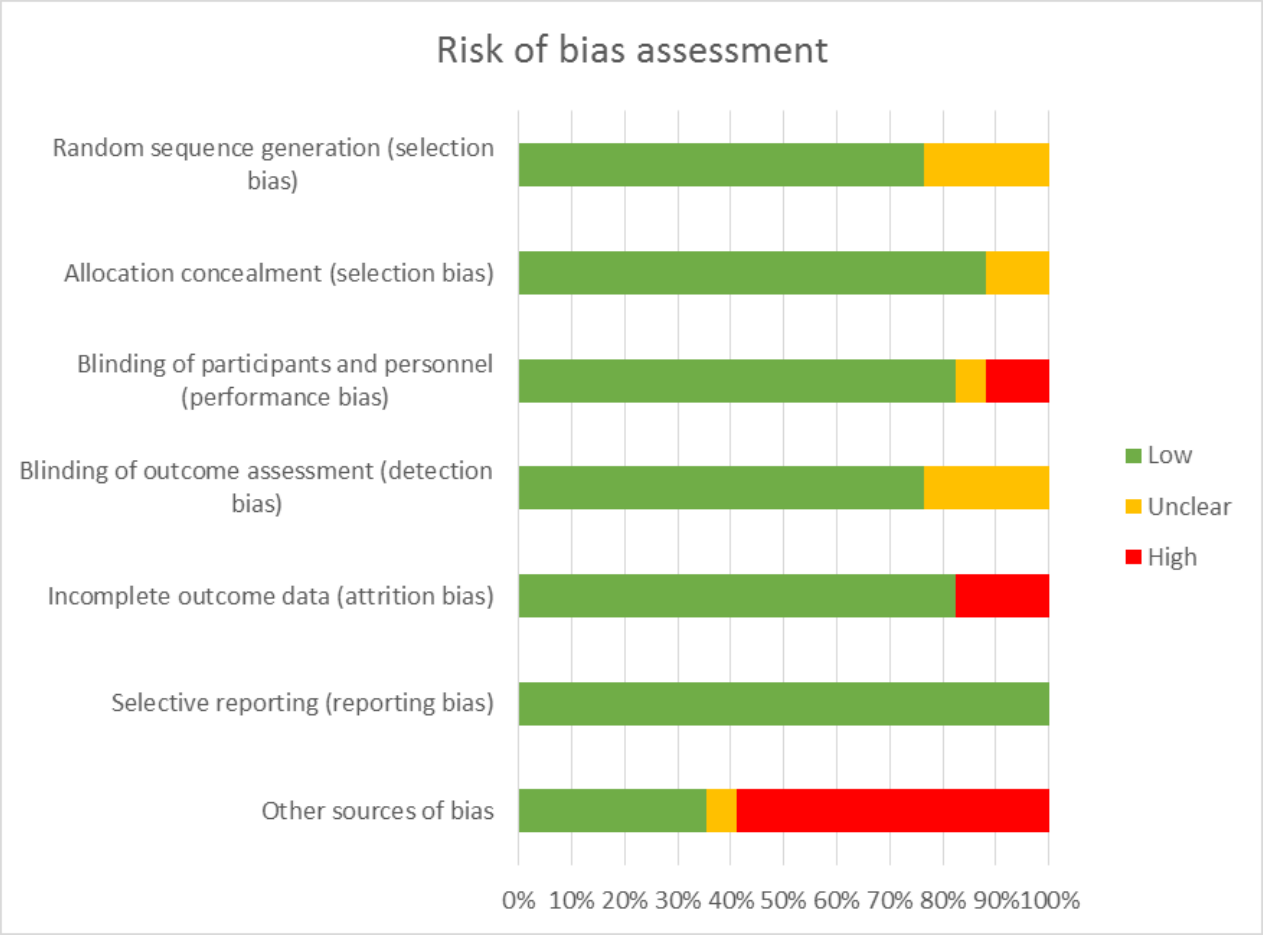
NCT number	First author	Year	Intervention	Comparator	Median FU in months (range)		Treatment status	Previous treatments	Patient population	Number of patients in ITT population		Median [mean] age		Percentage of patients with grade 3/4 TRAEs		RR grade 3/4 TRAEs (95% CI)	Median PFS in months (95% CI)		HR for PFS (95% CI)	Median OS in months (95% CI)		HR for OS (95% CI)
					Int vs Comp					*Int vs Comp*		*Int vs Comp*		*Int vs Comp*			*Int vs Comp*			*Int vs Comp*		
NCT00057616	Eisen[a] [1]	2010	Lenalidomide	Placebo	NR	NR	PT	Dacarbazine, interleukin-2, interferon-α, and/or interferon-β	Stage IV	152	154	62	56	NR	NR	NR	NR	NR	NR	5.9 (range: 5.1-7.7)	7.4 (range: 5.5-8.2)	1.16 (0.86-1.59)
NCT00094653	Hodi [2]	2010	A: Ipilimumab + GP100	C: GP100	21.0 (NR)	17.2 (NR)	PT	Dacarbazine, temozolomide, fotemustine, carboplatin, and/or interleukin-2	Unresectable stage III or IV	403	136	[56]	[57]	17%	11%	A vs B: 0.76 (0.52-1.11)	2.8 (2.7-2.8)	2.8 (2.7-2.8)	A vs B: 1.25 (1.06-1.49)	10.0 (8.5-11.5)	6.4 (5.5-8.7)	A vs B: 1.04 (0.83-1.30)
			B: Ipilimumab		27.8 (NR)					137		[57]		23%		A vs C: 1.53 (0.90-2.58) B vs C: 2.00 (1.14-3.57)	2.9 (2.8-3.0)		A vs C: 0.81 (0.66-0.99) B vs C: 0.64 (0.50-0.82)	10.1 (8.0-13.8)		A vs C: 0.68 (0.55-0.85) B vs C: 0.66 (0.51-0.87)
NCT00087776	Bedikian[a] [3]	2011	Docosahexaenoic acid-paclitaxel	Dacarbazine	NR	NR	TN	NA	Stage IV	194	199	61	62	72%	34%	2.13 (1.72-2.64)	1.6 (1.4-2.5)[c]	1.6 (1.4-2.0)[c]	NR	8.8 (7.2-9.8)	7.4 (6.3-8.7)	NR
NCT01006980	Chapman[a] [4]	2011	Vemurafenib	Dacarbazine	3.8 (NR)	2.3 (NR)	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	337	338	56	52	NR	NR	NR	5.3 (NR)	1.6 (NR)	0.26 (0.20-0.33)	7.2 (NR)[e]	9.2 (NR)[e]	0.37 (0.26-0.55)
NCT00009852	Patel [5]	2011	Temozolomide	Dacarbazine	19 (NR)		TN & PT	Vaccine therapy (except for cytokine)	Stage IV	429	430	NR	NR	35%[d]	29%[d]	1.21 (0.99-1.47)	2.3 (NR)	2.2 (NR)	0.92 (0.80-1.06)	9.1 (NR)	9.4 (NR)	1.00 (0.86-1.17)
NCT00324155	Robert [6]	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	NR	NR	TN	NA	Unresectable stage III or IV	250	252	[56]	[56]	56%[d]	27%[d]	2.05 (1.63-2.57)	NR	NR	0.76 (0.63-0.93)	11.2 (9.4-13.6)	9.1 (7.8-10.5)	0.72 (0.59-0.87)
NCT00019682	Schwartzentruber[a] [7]	2011	Interleukin-2 + GP100	Interleukin-2	41.5 (NR)		TN & PT	Chemotherapy, interferon-α, and/or low-dose interleukin-2	Locally advanced stage III or IV	91	94	[47]	[50]	84%[d]	78%[d]	1.06 (0.92-1.23)	2.2 (1.7-3.9)	1.6 (1.5-1.8)	NR	17.8 (11.9-25.8)	11.1 (8.7-16.3)	NR
NCT01245062	Flaherty[a] [8]	2012	Trametinib	Dacarbazine or paclitaxel	NR	NR	TN & PT	Chemotherapy, immunotherapy (other than ipilimumab), and/or sorafenib	Unresectable stage IIIC or IV BRAF mutated	214	108	55	54	NR	NR	NR	4.8 (NR)	1.5 (NR)	0.45 (0.33-0.63)	Not reached	Not reached	0.54 (0.32-0.92)
NCT01227889	Hauschild [9]	2012	Dabrafenib	Dacarbazine	4.9 (0-9.9)		TN	NA	Unresectable stage III or IV BRAF mutated	187	63	53	50	NR	NR	NR	5.1 (NR)	2.7 (NR)	0.30 (0.18-0.51)	Not reached	Not reached	0.61 (0.25-1.46)
NCT01359956	Dapunte[a] [10]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	NR	NR	TN	NA	Stage IV	64	70	[54]	[59]	NR	NR	A+B vs C+D: NR	A+B: 2.7 (2.4-3.8)	C+D: 2.5 (2.3-3.7)	A+B vs C+D: 0.93 (0.72-1.21)	A+B: 7.9 (6.6-10.2)	C+D: 8.6 (6.3-10.4)	A+B vs C+D: 0.93 (0.71-1.21)
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	NR	NR				68	58	[50]	[56]	NR	NR	B+D vs A+C: NR	B+D: 2.8 (2.4-3.9)	A+C: 2.5 (2.3-2.9)	B+D vs A+C: 0.96 (0.73-1.25)	B+D: 9.1 (8.3-11.1)	A+C: 7.7 (6.3-9.7)	B+D vs A+C: 0.92 (0.70-1.20)
NCT00110019	Flaherty [11]	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	NR		TN & PT	Interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor, and/or vaccine	Unresectable stage III or IV	410	413	61	59	82%[d]	76%[d]	1.06 (1.01-1.17)	4.9 (4.5-5.6)	4.2 (3.4-4.7)	0.90 (0.78-1.03)	11.1 (10.3-12.3)	11.3 (9.8-12.2)	1.01 (0.87-1.18)
NCT00522834	O'Day [12]	2013	Elesclomol + paclitaxel	Paclitaxel	NR		TN & PT	Kinase inhibitor, immunotherapy, biologic therapy, and/or vaccine	Stage IV	325	326	60	60	41%	34%	1.23 (1.00-1.50)	3.4 (2.3-3.5)	1.9 (1.9-2.9)	0.89 (0.73-1.08)	10.6 (9.3-12.2)	11.4 (10.2-13.6)	1.10 (0.92-1.32)
NCT00257205	Ribas [13]	2013	Tremelimumab	Temozolomide or dacarbazine	NR		TN	NA	Unresectable stage IIIC or IV	328	327	[57]	[56]	52%	37%	1.40 (1.18-1.67)	NR	NR	0.94 (0.81-1.11)	12.6 (10.8-14.3)	10.7 (9.4-12.0)	0.88 (0.74-1.04)
NCT00518895	Bedikian [14]	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	NR		TN & PT	Immunotherapy, cytokine, biologic therapy, and/or vaccine	Unresectable stage III or IV	157	157	58	60	49%	21%	2.38 (1.68-3.36)	2.8 (NR)	2.7 (NR)	0.85 (0.67-1.09)	13.5 (NR)	13.1 (NR)	1.04 (0.81-1.34)
NCT01006252	Hamid [15]	2014	Tasisulam	Paclitaxel	5.3 (NR)		PT	Dacarbazine or temozolomide	Stage IV	168	168	60	60	NR	NR	NR	1.9 (1.9-2.0)	2.1 (1.9-3.0)	1.30 (1.01-1.66)	8.8 (5.9-8.3)	9.4 (6.9-NR)	1.23 (0.89-1.69)
NCT01689519	Larkin[a] [16]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	7.3 (0.5-16.5)		TN	NA	Unresectable stage IIIC or IV BRAF-mutated	247	248	56	55	63%[d]	58%[d]	1.08 (0.93-1.24)	9.9 (9.0-not reached)	6.2 (5.6-7.4)	0.51 (0.39-0.68)	Not reached	Not reached	0.65 (0.42-1.00)
NCT01584648	Long[a] [17]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	9 (0-16)		TN	NA	Unresectable stage IIIC or IV BRAF-mutated	211	212	55	57	35%[d]	37%[d]	0.93 (0.72-1.20)	9.3 (NR)	8.8 (NR)	0.75 (0.57-0.99)	Not reached	Not reached	0.63 (0.42-0.94)
NCT01006980	McArthur[a] [18]	2014	Vemurafenib	Dacarbazine	12.5 (7.7-16.0)	9.5 (3.1-14.7)	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	337	338	56	53	71%[c]	41%[c]	1.73 (1.49-2.02)	6.9 (6.1-7.0)	1.6 (1.6-2.1)	0.38 (0.32-0.46)	13.6 (12.0-15.2)	9.7 (7.9-12.8)	0.70 (0.57-0.87)
NCT00769704	Andtbacka[a] [19]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	44.4 (32.4-58.7)		TN & PT	Unknown	Unresectable stage IIIB or IV	295	141	63	64	11%	5%	2.32 (0.99-5.41)	NR	NR	NR	23.3 (19.5-29.8)	18.9 (16.0-23.7)	0.79 (0.62-1.00)
NCT00866253	Hersh [20]	2015	nab- Paclitaxel	Dacarbazine	NR	NR	TN & PT	Kinase inhibitor and/or cytokine	Stage IV	264	265	62	64	NR	NR	NR	4.8 (3.7-5.5)	2.5 (2.0-3.6)	0.79 (0.63-0.99)	12.6 (11.1-14.2)	10.5 (9.5-12.4)	0.90 (0.71-1.13)
NCT01844505	Larkin[a] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab	12.2-12.5 (NR)		TN	NA	Unresectable stage III or IV	314	316	[59]	[59]	55%	16%	A vs B: 3.37 (2.57-4.42)	11.5 (8.9-16.7)	B: 6.9 (4.3-9.5)	A vs B: 0.74 (0.60-0.92)	NR	NR	NR
			C: Ipilimumab								315		[61]		27%	A vs C: 2.01 (1.63-2.47) B vs C: 0.60 (0.44-0.81)		C: 2.9 (2.8-3.4)	A vs C: 0.42 (0.34-0.52) B vs C: 0.57 (0.46-0.67)		NR	
NCT01584648	Long[a] [22]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	20 (0-30)	16 (0-32)	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	211	212	55	57	32%	31%	1.02 (0.77-1.36)	11.0 (8.0-13.9)	8.8 (5.9-9.3)	0.67 (0.53-0.84)	25.1 (18.2-not reached)	18.7 (15.2-23.7)	0.71 (0.55-0.92)
NCT01597908	Robert [23]	2015a	Dabrafenib + trametinib	Vemurafenib	11 (NR)	10 (NR)	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	352	352	55	54	52%[d]	63%[d]	0.82 (0.73-0.94)	11.4 (NR)	7.3 (NR)	0.56 (0.49-0.69)	Not reached	17.2 (NR)	0.69 (0.53-0.89)
NCT01866319	Robert[a] [24]	2015b	A: Pembrolizumab 2-weekly	C: Ipilimumab	7.9 (6.1-11.5)		TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	279	278	61	62	13%	20%	A vs C: 0.68 (0.46-1.01)	5.5 (3.4-6.9)	2.8 (2.8-2.9)	A vs C: 0.58 (0.46-0.72)	Not reached	Not reached	A vs C: 0.63 (0.47-0.83)
			B: Pembrolizumab 3-weekly							277		63		10%		B vs C: 0.52 (0.34-0.80)	4.1 (2.9-6.9)		B vs C: 0.58 (0.47-0.72)	Not reached		B vs C: 0.69 (0.52-0.90)
NCT01721772	Robert[a] [25]	2015c	Nivolumab	Dacarbazine	8.9 (NR)	6.8 (NR)	TN	NA	Unresectable stage III or IV BRAF wildtype	210	208	64	66	12%	18%	0.66 (0.41-1.07)	5.1 (3.5-10.8)	2.2 (2.1-2.4)	0.43 (0.34-0.56)	Not reached	10.8 (9.3-12.1)	0.42 (0.29-0.61)
NCT01721746	Weber[a] [26]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	8.4 (7.0-9.8)		PT	Ipilimumab and/or BRAF inhibitor	Unresectable stage IIIC or IV	272	133	59	62	9%	31%	0.29 (0.18-0.46)	4.7 (2.3-6.5)	4.2 (2.1-6.3)	0.82 (0.51-1.31)	NR	NR	NR
NCT01689519	Ascierto[a] [27]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	PFS: 14.2 (8.5-17.3) OS: 18.5 (8.5-23.5)		TN	NA	Unresectable stage IIIC or IV BRAF-mutated	247	248	56	55	57%	51%	1.13 (0.96-1.33)	12.3 (9.5-13.4)	7.2 (5.6-7.5)	0.58 (0.46-0.72)	22.3 (20.3-not estimable)	17.4 (15.0-19.8)	0.70 (0.55-0.90)
NCT01515189	Ascierto[a] [28]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	OS: 14.5 (4.6-42.3)	OS: 11.2 (4.9-29.6)	TN & PT	Any treatment (except for BRAF inhibitors, CTLA-4 or PD-1 antagonists, and PD-L1 or CD137 agonists)	Unresectable stage III or IV	365	362	62	62	34%	18%	1.87 (1.44-2.43)	2.8 (2.8-3.0)	2.8 (2.8-2.8)	0.89 (0.76-1.40)	15.7 (11.6-17.8)	11.5 (9.9-13.3)	0.84 (0.70-0.99)
NCT01006980	Chapman[a] [29]	2017	Vemurafenib	Dacarbazine	13.4 (0.4-59.6)	9.2 (0-56.2)	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	337	338	56	52	75%[c]	43%[c]	1.75 (1.51-2.03)	NR	NR	NR	13.6 (12.0-15.4)	9.7 (7.9-12.8)	0.81 (0.70-1.00)
NCT01763164	Dummer[a] [30]	2017	Binimetinib	Dacarbazine	PFS: 1.7 (1.4-4.1) OS: 9.2 (4.8-13.9)		TN & PT	Immunotherapy	Unresectable stage IIIC or IV NRAS mutated	269	133	65	62	NR	NR	NR	2.8 (2.8-3.6)	1.5 (1.5-1.7)	0.62 (0.47-0.80)	11.0 (8.9-13.6)	10.1 (7.0-16.5)	1.00 (0.75-1.33)
NCT01721746	Larkin[a] [31]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	NR	NR	PT	Ipilimumab and/or BRAF inhibitor	Unresectable stage IIIC or IV	272	133	59	62	14%	34%	0.41 (0.28-0.62)	3.1 (2.3-3.5)	3.7 (2.3-5.3)	1.00 (0.78-1.44)	15.7 (12.9-19.8)	14.4 (11.7-18.2)	0.95 (0.70-1.29)
NCT01584648	Long[a] [32]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	NR	NR	TN	NA	Unresectable stage IIIC or IV BRAF-mutated	211	212	55	57	48%[d]	50%[d]	0.95 (0.79-1.16)	NR	NR	0.71 (0.57-0.88)	NR	NR	0.75 (0.58-0.96)
NCT01866319	Schachter[a,f] [33]	2017	A: Pembrolizumab 2-weekly	C: Ipilimumab	22.9 (NR)		TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	279	278	61	62	17%	20%	A vs C: 0.87 (0.60-1.24)	5.6 (3.4-8.2)	2.8 (2.8-2.9)	A vs C: 0.61 (0.50-0.75)	Not reached (22.1-not reached)	16.0 (13.5-22.0)	A vs C: 0.68 (0.53-0.87)
			B: Pembrolizumab 3-weekly							277		63		17%		B vs C: 0.85 (0.59-1.22)	4.1 (2.9-7.2)		B vs C: 0.61 (0.50-0.75)	Not reached (23.5-not reached)		B vs C: 0.68 (0.53-0.86)
NCT00779714	Ugurel[a] [34]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cyclarabine	Dacarbazine	26.4 (NR)		TN & PT	Immunotherapy or targeted therapy	Stage IV	141	133	NR	NR	40%	12%	3.27 (1.84-5.50)	2.5 (2.3-2.6)	2.3 (2.3-2.5)	0.91 (0.70-1.18)	9.2 (8.0-12.1)	9.0 (7.3-11.6)	1.08 (0.80-1.45)
NCT01844505	Wolchok[a,f] [35]	2017	A: Nivolumab + ipilimumab	B: Nivolumab	38 (NR)	35.7 (NR)	TN	NA	Unresectable stage III or IV	314	316	[59]	[58]	59%	21%	A vs B: 2.75 (2.18-3.46)	11.5 (8.7-19.3)	6.9 (5.1-9.7)	A vs B: 0.78 (0.64-0.96)	Not reached (38.2-not reached)	37.6 (29.1-not reached)	A vs B: 0.85 (0.68-1.07)
			C: Ipilimumab			18.6 (NR)					315		[61]		28%	A vs C: 2.13 (1.74-2.60) B vs C: 0.77 (0.59-1.02)		2.9 (2.8-3.2)	A vs C: 0.43 (0.35-0.52) B vs C: 0.55 (0.45-0.66)		19.9 (16.9-24.6)	A vs C: 0.55 (0.45-0.69) B vs C: 0.65 (0.53-0.80)
NCT01866319	Carlino[a] [36]	2018	Pembrolizumab	Ipilimumab	33.9 (NR)		TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	TN: 368 PT: 187	TN: 181 PT: 97	TN: 65 PT: 59	TN: 63 PT: 58	TN: 19% PT: 13%	TN: 20% PT: 18%	TN: 0.95 (0.66-1.37) PT: 0.74 (0.42-1.31)	TN: 6.6 (4.4-9.8) PT: 2.9 (2.8-4.1)	TN: 2.8 (2.8-3.0) PT: 2.8 (2.8-3.0)	TN: 0.57 (0.46-0.70) PT: 0.71 (0.53-0.94)	TN: Not reached (27.3-not reached) PT: 23.5 (16.8-33.6)	TN: 17.1 (13.8-26.2) PT: 13.6 (10.7-22.0)	TN: 0.69 (0.54-0.89) PT: 0.71 (0.51-0.99)
NCT01909453	Dummer[a,f] [37]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	PFS: 16.7 (16.3-18.4)	PFS: 16.6 (14.8-18.1)	TN & PT	First-line immunotherapy	Unresectable stage IIIB/IIIC or IV BRAF-mutated	192	194	57	54	58%[c]	66%[c]	A vs B: 0.87 (0.75-1.02)	14.9 (11.0-18.5)	9.6 (7.5-14.8)	A vs B: 0.75 (0.56-1.00)	NR	NR	A vs B: NR
			C: Vemurafenib			PFS: 14.4 (10.1-16.6)					191		56		63%[c]	A vs C: 0.91 (0.77-1.07)		7.3 (5.6-8.2)	A vs C: 0.54 (0.41-0.71)		NR	A vs C: NR
NCT01909453	Dummer[a,f] [38]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	PFS: 32.3 (31.7-34.9) OS: 37.2 (36.1-38.5)	PFS: 32.0 (24.0-34.9) OS: 36.3 (34.8-37.2)	TN & PT	First-line immunotherapy	Unresectable stage IIIB/IIIC or IV BRAF-mutated	192	194	57	54	NR	NR	NR	14.9 (11.0-20.2)	9.6 (7.4-14.8)	A vs B: 0.77 (0.59-1.00)	33.6 (24.4-39.2)	23.5 (19.6-33.6)	A vs B: 0.81 (0.61-1.06)
			C: Vemurafenib			PFS: 22.2 (11.0-32.3) OS: 25.9 (14.9-38.0)					191		56		NR	NR		7.3 (5.6-7.9)	A vs C: 0.51 (0.39-0.67) B vs C: 0.68 (0.52-0.88)		16.9 (14.0-24.5)	A vs C: 0.61 (0.47-0.79) B vs C: 0.76 (0.58-0.99)
NCT01844505	Hodi[a] [39]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	46.9 (10.9-51.8)	36.0 (10.5-51.4)	TN	NA	Unresectable stage III or IV	314	316	61	60	59%	22%	A vs B: 2.64 (2.11-3.31)	11.5 (8.7-19.3)	6.9 (5.1-10.2)	A vs B: 0.79 (0.65-0.97)	Not reached (38.2-not reached)	36.9 (28.3-not reached)	A vs B: 0.84 (0.67-1.05)
			C: Ipilimumab			18.6 (7.6-49.5)					315		62		28%	A vs C: 2.14 (1.75-2.62) B vs C: 0.81 (0.62-1.06)		2.9 (2.8-3.2)	A vs C: 0.42 (0.35-0.51) B vs C: 0.53 (0.44-0.64)		19.9 (16.9-24.6)	A vs C: 0.54 (0.44-0.67) B vs C: 0.65 (0.53-0.79)
NCT01721772	Ascierto[a] [40]	2019	Nivolumab	Dacarbazine	38.4 (NR)	38.5 (NR)	TN	NA	Unresectable stage III or IV BRAF wildtype	210	208	64	66	15%	18%	0.86 (0.55-1.33)	5.1 (3.5-12.2)	2.2 (2.1-2.5)	0.42 (0.33-0.53)	37.5 (25.5-not reached)	11.3 (9.6-13.0)	0.46 (0.36-0.59)
NCT01245062	Robert[a] [41]	2019	Trametinib	Dacarbazine or paclitaxel	14.7 (0-70)	8.7 (0-70)	TN & PT	Chemotherapy, immunotherapy (other than ipilimumab), and/or sorafenib	Unresectable stage IIIC or IV BRAF mutated	214	108	55	54	53%[d]	38%[d]	1.37 (1.04-1.81)	4.9 (NR)	1.5 (NR)	0.54 (0.41-0.73)	15.6 (NR)	11.3 (NR)	0.84 (0.63-1.11)

CI, confidence interval; Comp, comparator; FU, follow-up; HR, hazard ratio; Int, intervention; ITT, intention-to-treat; kg, kilogram; mg, milligram; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; PT, previously treated; RR, relative risk; TN, treatment naive; TRAEs, treatment-related adverse events.

[a]No link in main network.
[b]Not included in main network because data on progression-free survival was not presented.
[c]Time to progression instead of progression-free survival.
[d]Extended follow-up available.
[e]Derived from the Kaplan-Meier curves.
[f]Temozolomide is pooled within the dacarbazine reference group.
[g]Number of patients with grade 3 or 4 adverse events, irrespective of causality.
[h]Extended follow-up.
[i]Sum of patients with at least one grade 3 adverse event and patients with at least one grade 4 adverse event, irrespective of causality.
[j]Dose-ranging study.
[k]Only included in extended network (see appendix A.7).
[l]Treatment line specific outcomes of Schachter *et al.* 2017 (only included in main network).

A.3 RISK OF BIAS ASSESSMENT

A.3.1 FIGURE OVERVIEW RISK OF BIAS ASSESSMENT



A.3.2 TABLE DETAILS RISK OF BIAS ASSESSMENT

First author	Year	Intervention	Comparator	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
				Random sequence generation	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other sources of bias*
Hodi	2010	A: Ipilimumab + GP100 B: Ipilimumab	C: GP100	Low	Low	Low	Low	Low	Low	Low
Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	Low	Low	Low	Low	Low	Low	Low
Hauschild	2012	Dabrafenib	Dacarbazine	Low	Low	Low[a]	Low	Low	Low	High[b]
Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	Unclear	Unclear	Low	Low	Low	Low	High[c]
O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	Low	Low	Low	Low	High[d]	Low	Low
Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	Low	Low	Low[a]	Unclear	Low	Low	High[b]
Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	Unclear	Low	Low	Low	Low	Low	High[c]
Hamid	2014	Tasisulam	Paclitaxel	Unclear	Unclear	Unclear[a]	Unclear	High[d]	Low	High[c]
Hersh	2015	*nab*-Paclitaxel	Dacarbazine	Unclear	Low	Low[a]	Low	Low	Low	High[c]
Robert	2015	Dabrafenib + trametinib	Vemurafenib	Low	Low	Low[a]	Unclear	Low	Low	Low
Ascierto	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	Low	Low	Low	Low	Low	Low	Low
Chapman	2017	Vemurafenib	Dacarbazine	Low	Low	High[a]	Unclear	Low	Low	Low[b]
Long	2017	Dabrafenib + trametinib	Dabrafenib + placebo	Low	Low	Low	Low	Low	Low	High[b]
Ascierto	2018	Nivolumab	Dacarbazine	Low	Low	Low	Low	Low	Low	High[b]
Carlino	2018	Pembrolizumab	Ipilimumab	Low	Low	High[a]	Low	High	Low	Unclear[b]
Hodi	2018	A: Nivolumab + ipilimumab	B: Nivolumab C: Ipilimumab	Low	Low	Low	Low	Low	Low	High[c]
Robert	2019	Trametinib	Dacarbazine or paclitaxel	Low	Low	Low[a]	Low	Low	Low	High[b,c]

Abbreviations: high, high risk of bias; low, low risk of bias; unclear, unclear risk of bias.

[a]Open-label study.

[b]Treatment cross-over permitted.

[c]Proportional hazard assumption violated.

[d]Study stopped earlier.

A.4 FACE VALIDITY OF RANDOMISED CONTROLLED TRIAL OUTCOMES VERSUS NETWORK META-ANALYSIS OUTCOMES

TABLE A.4 FACE VALIDITY OF RANDOMISED CONTROLLED TRIAL OUTCOMES VERSUS NETWORK META-ANALYSIS OUTCOMES

NCT number	First author	Year	Intervention	Comparator	RR grade 3/4 TRAEs (95% CI/CrI)		HR for PFS (95% CI)		HR for OS (95% CI)	
					RCT	NMA	RCT	NMA	RCT	NMA
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	A vs B: 0.76 (0.52-1.11)	A vs B: 0.78 (0.53-1.14)	A vs B: 1.25 (1.06-1.49)	A vs B: 1.28 (0.99-1.61)	A vs B: 1.04 (0.83-1.30)	A vs B: 1.04 (0.79-1.34)
			B: Ipilimumab		A vs C: 1.53 (0.90-2.58)	A vs C: 1.54 (0.91-2.56)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.68 (0.55-0.85)	A vs C: 0.68 (0.55-0.84)
					B vs C: 2.02 (1.14-3.57)	B vs C: 1.86 (1.11-3.48)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.66 (0.51-0.87)	B vs C: 0.65 (0.51-0.86)
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	2.05 (1.63-2.57)	2.05 (1.63-2.57)	0.76 (0.63-0.93)	0.76 (0.62-0.92)	0.72 (0.59-0.87)	0.72 (0.59-0.87)
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	NR	NR	0.30 (0.18-0.51)	0.30 (0.23-0.40)	0.61 (0.25-1.48)	0.73 (0.50-1.04)
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	1.08 (1.01-1.17)	1.08 (1.01-1.17)	0.90 (0.78-1.03)	0.90 (0.78-1.03)	1.01 (0.87-1.18)	1.01 (0.87-1.18)
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	1.23 (1.00-1.50)	1.23 (1.00-1.49)	0.89 (0.73-1.08)	0.89 (0.73-1.08)	1.10 (0.92-1.32)	1.11 (0.92-1.32)
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	1.40 (1.18-1.67)	1.40 (1.17-1.67)	0.94 (0.81-1.11)	0.94 (0.80-1.10)	0.88 (0.74-1.04)	0.88 (0.74-1.04)
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	2.38 (1.68-3.36)	2.38 (1.68-3.34)	0.85 (0.67-1.09)	0.86 (0.67-1.09)	1.04 (0.81-1.34)	1.05 (0.81-1.34)
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	NR	NR	1.30 (1.01-1.66)	1.31 (1.01-1.67)	1.23 (0.89-1.69)	1.25 (0.89-1.70)
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	NR	NR	0.79 (0.63-0.99)	0.80 (0.63-0.99)	0.90 (0.71-1.13)	0.91 (0.71-1.13)
NCT01597908	Robert	2015	Dabrafenib + trametinib	Vemurafenib	0.82 (0.73-0.94)	0.84 (0.72-0.96)	0.56 (0.49-0.69)	0.56 (0.47-0.66)	0.69 (0.53-0.89)	0.69 (0.53-0.87)
NCT01689519	Ascierto	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	1.13 (0.96-1.33)	1.13 (0.96-1.33)	0.58 (0.46-0.72)	0.58 (0.46-0.73)	0.70 (0.55-0.90)	0.71 (0.55-0.89)
NCT01006980	Chapman	2017	Vemurafenib	Dacarbazine	1.75 (1.51-2.03)	1.75 (1.51-2.03)	0.38 (0.32-0.46)[a]	0.38 (0.32-0.45)	0.81 (0.70-1.00)	0.81 (0.68-0.96)
NCT01584648	Long	2017	Dabrafenib + trametinib	Dabrafenib + placebo	0.95 (0.78-1.16)	0.95 (0.78-1.15)	0.71 (0.57-0.88)	0.71 (0.58-0.87)	0.75 (0.58-0.96)	0.77 (0.60-0.97)
NCT01721772	Ascierto	2018	Nivolumab	Dacarbazine	0.86 (0.55-1.33)	0.86 (0.54-1.30)	0.42 (0.33-0.53)	0.42 (0.33-0.53)	0.46 (0.36-0.59)	0.46 (0.36-0.59)
NCT01866319	Carlino[b]	2018	Pembrolizumab	Ipilimumab	0.95 (0.66-1.37)	0.96 (0.66-1.37)	0.57 (0.46-0.70)	0.57 (0.46-0.70)	0.69 (0.54-0.89)	0.70 (0.54-0.89)
NCT01844505	Hodi	2018	A: Nivolumab + ipilimumab	B: Nivolumab	A vs B: 2.64 (2.11-3.31)	A vs B: 2.67 (2.13-3.35)	A vs B: 0.79 (0.65-0.97)	A vs B: 0.80 (0.64-0.98)	A vs B: 0.84 (0.67-1.05)	A vs B: 0.84 (0.66-1.05)
				C: Ipilimumab	A vs C: 2.14 (1.75-2.62)	A vs C: 2.14 (1.75-2.61)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.54 (0.44-0.67)	A vs C: 0.54 (0.44-0.67)
					B vs C: 0.81 (0.62-1.06)	B vs C: 0.79 (0.61-1.05)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.65 (0.53-0.79)	B vs C: 0.65 (0.53-0.79)
NCT01245062	Robert	2019	Trametinib	Dacarbazine or paclitaxel	1.37 (1.04-1.81)	1.38 (1.04-1.83)	0.54 (0.41-0.73)	0.55 (0.41-0.72)	0.84 (0.63-1.11)	0.85 (0.63-1.11)

CI, confidence interval; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; NR, not reported; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RR, relative risk; TRAEs, treatment-related adverse events.
[a]Retrieved from McArthur *et al.* 2014.
[b]Outcomes of treatment naive patients.

A.5 DETAILS NETWORK META-ANALYSIS ESTIMATES

TABLE A.5.1 ESTIMATED RELATIVE RISK FOR A GRADE 3/4 TREATMENT-RELATED ADVERSE EVENT

Intervention / **Comparator**	Carboplatin + paclitaxel + sorafenib	Dabrafenib	Dabrafenib + trametinib	Dacarbazine + oblimersen	Dacarbazine reference group	Elesclomol + paclitaxel	GP100	Ipilimumab	Ipilimumab + dacarbazine	Ipilimumab + GP100	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Trametinib	Tremelimumab	Vemurafenib	Vemurafenib + cobimetinib
Carboplatin + paclitaxel + sorafenib	1																
Dabrafenib	1.43 (1.06-1.89)	1															
Dabrafenib + trametinib	1.35 (1.08-1.67)	0.95 (0.78-1.15)	1														
Dacarbazine + oblimersen	2.20 (1.53-3.11)	1.49 (0.98-2.40)	1.58 (1.09-2.42)	1													
Dacarbazine reference group	0.92 (0.86-0.99)	0.65 (0.49-0.86)	0.68 (0.56-0.84)	0.42 (0.30-0.60)	1												
Elesclomol + paclitaxel	1.13 (0.91-1.40)	0.78 (0.56-1.12)	0.83 (0.63-1.12)	0.51 (0.35-0.77)	1.23 (1.00-1.49)	1											
GP100	0.54 (0.23-1.07)	0.38 (0.15-0.79)	0.40 (0.17-0.81)	0.25 (0.10-0.53)	0.58 (0.25-1.16)	0.48 (0.20-0.97)	1										
Ipilimumab	1.00 (0.57-1.63)	0.71 (0.38-1.23)	0.75 (0.41-1.25)	0.47 (0.24-0.83)	1.08 (0.62-1.76)	0.89 (0.49-1.49)	1.86 (1.11-3.48)	1									
Ipilimumab + dacarbazine	1.86 (1.48-2.40)	1.30 (0.92-1.90)	1.38 (1.03-1.90)	0.85 (0.57-1.30)	2.05 (1.63-2.57)	1.64 (1.23-2.26)	3.47 (1.70-8.47)	1.87 (1.10-3.44)	1								
Ipilimumab + GP100	0.78 (0.38-1.42)	0.56 (0.26-1.07)	0.58 (0.28-1.09)	0.37 (0.16-0.72)	0.85 (0.42-1.54)	0.70 (0.33-1.30)	1.54 (0.91-2.56)	0.78 (0.53-1.14)	0.42 (0.20-0.79)	1							
Nivolumab	0.79 (0.49-1.20)	0.56 (0.32-0.92)	0.59 (0.35-0.93)	0.37 (0.20-0.62)	0.86 (0.54-1.30)	0.71 (0.42-1.11)	1.47 (0.83-2.94)	0.79 (0.61-1.05)	0.42 (0.25-0.67)	1.01 (0.65-1.67)	1						
Nivolumab + ipilimumab	2.12 (1.24-3.38)	1.51 (0.81-2.55)	1.58 (0.89-2.61)	0.99 (0.51-1.73)	2.29 (1.35-3.64)	1.89 (1.07-3.11)	4.31 (2.29-7.63)	2.14 (1.75-2.61)	1.13 (0.63-1.88)	2.84 (1.78-4.26)	2.67 (2.13-3.35)	1					
Pembrolizumab	0.96 (0.48-1.73)	0.68 (0.32-1.29)	0.72 (0.35-1.33)	0.45 (0.20-0.87)	1.04 (0.52-1.87)	0.85 (0.41-1.57)	1.72 (0.94-3.65)	0.96 (0.66-1.37)	0.51 (0.25-0.95)	1.18 (0.72-2.08)	1.21 (0.75-1.87)	0.43 (0.29-0.68)	1				
Trametinib	1.27 (0.95-1.70)	0.91 (0.60-1.33)	0.95 (0.67-1.34)	0.60 (0.37-0.91)	1.38 (1.04-1.83)	1.13 (0.80-1.59)	2.32 (1.12-5.97)	1.37 (0.73-2.36)	0.68 (0.47-0.97)	1.60 (0.84-3.44)	1.69 (0.97-2.76)	0.59 (0.35-1.09)	1.48 (0.69-2.77)	1			
Tremelimumab	1.30 (1.07-1.56)	0.90 (0.65-1.27)	0.95 (0.73-1.26)	0.59 (0.40-0.87)	1.40 (1.17-1.67)	1.16 (0.88-1.50)	2.39 (1.19-5.76)	1.29 (0.77-2.32)	0.69 (0.52-0.91)	1.65 (0.89-3.42)	1.62 (1.04-2.70)	0.61 (0.37-1.07)	1.34 (0.73-2.74)	1.01 (0.73-1.42)	1		
Vemurafenib	1.62 (1.37-1.91)	1.13 (0.90-1.44)	1.20 (1.04-1.38)	0.76 (0.51-1.08)	1.75 (1.51-2.03)	1.44 (1.12-1.84)	2.99 (1.49-7.15)	1.61 (0.97-2.86)	0.87 (0.65-1.12)	2.06 (1.12-4.24)	2.03 (1.31-3.34)	0.76 (0.47-1.32)	1.68 (0.92-3.39)	1.26 (0.92-1.75)	1.26 (0.99-1.58)	1	
Vemurafenib + cobimetinib	1.83 (1.45-2.30)	1.30 (0.96-1.72)	1.36 (1.09-1.68)	0.86 (0.55-1.26)	1.98 (1.59-2.46)	1.63 (1.20-2.18)	3.36 (1.65-8.20)	1.81 (1.07-3.31)	0.98 (0.70-1.33)	2.31 (1.23-4.88)	2.43 (1.45-3.86)	0.85 (0.52-1.52)	1.89 (1.02-3.91)	1.42 (1.00-2.05)	1.42 (1.07-1.87)	1.13 (0.96-1.33)	1

Estimated mean relative risk for grade 3/4 adverse event *(95% credible interval)*

TABLE A.5.2 ESTIMATED MEAN HAZARD RATIO FOR PROGRESSION-FREE SURVIVAL

Intervention / Comparator	Carboplatin + paclitaxel + sorafenib	Dabrafenib	Dabrafenib + trametinib	Dacarbazine + oblimersen	Dacarbazine reference group	Elesclomol + paclitaxel	GP100	Ipilimumab	Ipilimumab + dacarbazine	Ipilimumab + GP100	*nab* -paclitaxel	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Tasisulam	Tremelimumab	Trametinib	Vemurafenib	Vemurafenib + cobimetinib
Carboplatin + paclitaxel + sorafenib	1																		
Dabrafenib	0.33 (0.24-0.45)	1																	
Dabrafenib + trametinib	0.24 (0.18-0.31)	0.71 (0.58-0.87)	1																
Dacarbazine + oblimersen	0.95 (0.71-1.25	2.89 (1.96-4.11)	4.00 (2.86-5.56)	1															
Dacarbazine reference group	1.11 (0.97-1.28)	3.33 (2.50-4.35)	4.76 (3.70-5.88)	1.16 (0.92-1.49)	1														
Elesclomol + paclitaxel	1.00 (0.78-1.26)	3.02 (2.11-4.18)	4.17 (3.13-5.56)	1.03 (0.77-1.43)	0.89 (0.73-1.08)	1													
GP100	1.41 (0.91-2.08)	4.26 (2.56-6.68)	5.98 (3.72-9.14)	1.50 (0.92-2.31)	1.26 (0.84-1.82)	1.42 (0.90-2.14)	1												
Ipilimumab	0.89 (0.63-1.23)	2.71 (1.76-4.01)	3.80 (2.56-5.46)	0.95 (0.63-1.37)	0.80 (0.59-1.07)	0.90 (0.62-1.28)	0.64 (0.50-0.82)	1											
Ipilimumab + dacarbazine	0.84 (0.67-1.06)	2.50 (1.82-3.57)	3.57 (2.63-4.76)	0.88 (0.65-1.22)	0.76 (0.62-0.92)	0.85 (0.65-1.12)	0.60 (0.40-0.94)	0.94 (0.67-1.37)	1										
Ipilimumab + GP100	1.14 (0.74-1.68)	3.45 (2.08-5.40)	4.84 (3.01-7.41)	1.21 (0.75-1.87)	1.02 (0.68-1.47)	1.15 (0.73-1.74)	0.81 (0.66-0.99)	1.28 (0.99-1.61)	1.35 (0.86-2.04)	1									
nab -paclitaxel	0.89 (0.67-1.14)	2.68 (1.84-3.77)	3.70 (2.70-5.00)	0.94 (0.67-1.29)	0.80 (0.63-0.99)	0.90 (0.66-1.20)	0.62 (0.41-1.00)	0.98 (0.68-1.45)	1.05 (0.77-1.40)	0.77 (0.50-1.22)	1								
Nivolumab	0.47 (0.35-0.61)	1.43 (0.98-2.02)	2.00 (1.43-2.75)	0.50 (0.35-0.69)	0.42 (0.33-0.53)	0.48 (0.35-0.64)	0.34 (0.25-0.46)	0.53 (0.44-0.64)	0.56 (0.41-0.75)	0.41 (0.31-0.57)	0.54 (0.38-0.74)	1							
Nivolumab + ipilimumab	0.38 (0.26-0.52)	1.14 (0.73-1.70)	1.60 (1.06-2.32)	0.40 (0.26-0.58)	0.34 (0.24-0.46)	0.38 (0.26-0.54)	0.27 (0.20-0.37)	0.42 (0.35-0.51)	0.45 (0.30-0.64)	0.34 (0.24-0.45)	0.43 (0.29-0.62)	0.80 (0.64-0.98)	1						
Pembrolizumab	0.51 (0.34-0.74)	1.55 (0.95-2.40)	2.18 (1.38-3.28)	0.54 (0.34-0.83)	0.46 (0.31-0.65)	0.52 (0.33-0.77)	0.36 (0.26-0.51)	0.57 (0.46-0.70)	0.61 (0.39-0.90)	0.44 (0.33-0.62)	0.59 (0.37-0.88)	1.09 (0.81-1.42)	1.35 (1.02-1.79)	1					
Tasisulam	1.46 (1.09-1.92)	4.42 (2.99-6.32)	5.88 (4.35-8.33)	1.55 (1.08-2.17)	1.31 (1.01-1.67)	1.48 (1.06-2.00)	1.02 (0.66-1.67)	1.61 (1.11-2.44)	1.73 (1.25-2.34)	1.27 (0.82-2.04)	1.61 (1.18-2.33)	3.03 (2.17-4.35)	3.85 (2.63-5.88)	2.78 (1.85-4.55)	1				
Tremelimumab	1.05 (0.85-1.29)	3.18 (2.28-4.32)	4.38 (3.36-5.83)	1.10 (0.83-1.47)	0.94 (0.80-1.10)	1.06 (0.82-1.36)	0.74 (0.50-1.15)	1.16 (0.85-1.67)	1.25 (0.96-1.59)	0.92 (0.62-1.42)	1.18 (0.90-1.57)	2.22 (1.69-2.94)	2.78 (1.96-4.00)	2.04 (1.39-3.13)	0.71 (0.54-0.97)	1			
Trametinib	0.59 (0.44-0.83)	1.75 (1.20-2.70)	2.50 (1.75-3.70)	0.63 (0.43-0.93)	0.55 (0.41-0.72)	0.60 (0.43-0.85)	0.42 (0.27-0.71)	0.67 (0.45-1.03)	0.72 (0.50-1.01)	0.52 (0.33-0.87)	0.67 (0.47-0.99)	1.27 (0.88-1.85)	1.59 (1.05-2.50)	1.16 (0.75-1.92)	0.41 (0.28-0.61)	0.56 (0.41-0.80)	1		
Vemurafenib	0.42 (0.34-0.53)	1.28 (0.99-1.63)	1.79 (1.52-2.13)	0.45 (0.33-0.60)	0.38 (0.32-0.45)	0.43 (0.33-0.55)	0.30 (0.20-0.47)	0.47 (0.34-0.68)	0.50 (0.39-0.65)	0.37 (0.25-0.58)	0.48 (0.36-0.64)	0.89 (0.68-1.20)	1.12 (0.79-1.64)	0.83 (0.56-1.27)	0.30 (0.22-0.40)	0.41 (0.32-0.51)	0.71 (0.50-0.98)	1	
Vemurafenib + cobimetinib	0.25 (0.18-0.34)	0.75 (0.53-1.03)	1.05 (0.78-1.37)	0.26 (0.18-0.38)	0.22 (0.17-0.29)	0.25 (0.18-0.35)	0.17 (0.11-0.29)	0.27 (0.18-0.42)	0.29 (0.21-0.41)	0.21 (0.14-0.35)	0.28 (0.19-0.40)	0.53 (0.36-0.76)	0.65 (0.43-1.02)	0.47 (0.31-0.78)	0.17 (0.12-0.25)	0.24 (0.17-0.32)	0.42 (0.27-0.61)	0.58 (0.46-0.73)	1

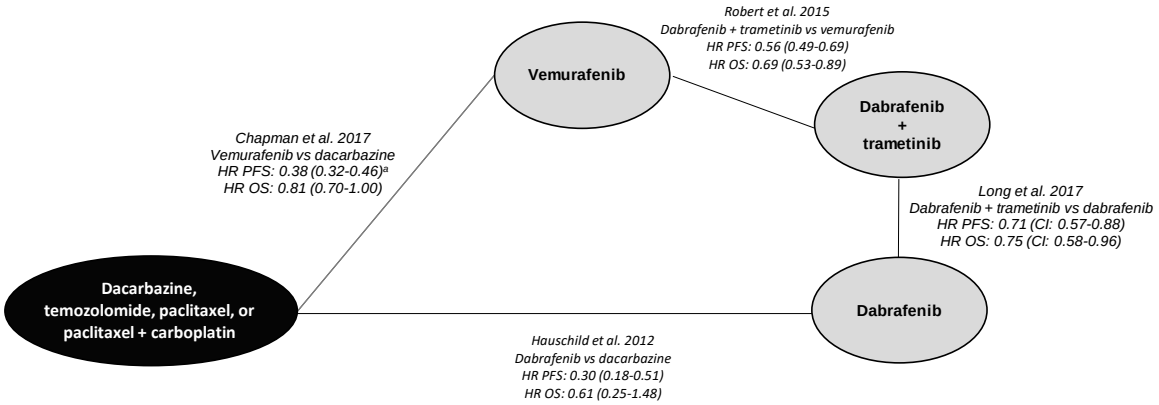
Estimated mean hazard ratio for progression-free survival (95% credible interval)

TABLE A.5.3 ESTIMATED MEAN HAZARD RATIO FOR OVERALL SURVIVAL

Intervention / Comparator	Carboplatin + paclitaxel + sorafenib	Dabrafenib	Dabrafenib + trametinib	Dacarbazine + oblimersen	Dacarbazine reference group	Elesclomol + paclitaxel	GP100	Ipilimumab	Ipilimumab + dacarbazine	Ipilimumab + GP100	*nab*-paclitaxel	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Tasisulam	Tremelimumab	Trametinib	Vemurafenib	Vemurafenib + cobimetinib
Carboplatin + paclitaxel + sorafenib	1																		
Dabrafenib	0.70 (0.48-1.06)	1																	
Dabrafenib + trametinib	0.55 (0.39-0.75)	0.77 (0.60-0.97)	1																
Dacarbazine + oblimersen	1.04 (0.77-1.38)	1.48 (0.93-2.26)	1.87 (1.29-2.80)	1															
Dacarbazine reference group	0.99 (0.85-1.15)	1.37 (0.96-2.01)	1.81 (1.36-2.46)	0.95 (0.75-1.24)	1														
Elesclomol + paclitaxel	1.10 (0.86-1.38)	1.57 (1.02-2.30)	1.98 (1.42-2.85)	1.05 (0.78-1.44)	1.11 (0.92-1.32)	1													
GP100	1.09 (0.68-1.65)	1.55 (0.86-2.60)	2.03 (1.18-3.27)	1.06 (0.63-1.68)	1.10 (0.71-1.62)	1.00 (0.62-1.53)	1												
Ipilimumab	0.71 (0.49-1.00)	1.02 (0.61-1.61)	1.33 (0.84-2.01)	0.70 (0.45-1.02)	0.72 (0.52-0.97)	0.65 (0.45-0.93)	0.65 (0.51-0.86)	1											
Ipilimumab + dacarbazine	0.71 (0.56-0.91)	0.98 (0.66-1.52)	1.30 (0.92-1.88)	0.68 (0.50-0.95)	0.72 (0.59-0.87)	0.65 (0.50-0.85)	0.65 (0.43-1.06)	1.00 (0.70-1.47)	1										
Ipilimumab + GP100	0.74 (0.47-1.12)	1.06 (0.59-1.76)	1.38 (0.80-2.22)	0.72 (0.43-1.14)	0.74 (0.48-1.10)	0.68 (0.42-1.04)	0.68 (0.55-0.84)	1.04 (0.79-1.34)	1.04 (0.64-1.60)	1									
nab-paclitaxel	0.90 (0.67-1.18)	1.28 (0.81-1.93)	1.62 (1.13-2.39)	0.88 (0.61-1.22)	0.91 (0.71-1.13)	0.83 (0.61-1.10)	0.82 (0.52-1.34)	1.25 (0.86-1.88)	1.27 (0.92-1.70)	1.20 (0.77-1.97)	1								
Nivolumab	0.46 (0.34-0.61)	0.66 (0.41-0.99)	0.86 (0.57-1.24)	0.45 (0.31-0.63)	0.46 (0.36-0.59)	0.42 (0.31-0.57)	0.42 (0.31-0.60)	0.65 (0.53-0.79)	0.65 (0.47-0.88)	0.62 (0.45-0.88)	0.52 (0.37-0.72)	1							
Nivolumab + ipilimumab	0.39 (0.26-0.55)	0.55 (0.32-0.88)	0.72 (0.44-1.10)	0.38 (0.24-0.56)	0.39 (0.27-0.54)	0.35 (0.24-0.51)	0.36 (0.25-0.50)	0.54 (0.44-0.67)	0.54 (0.36-0.79)	0.53 (0.38-0.73)	0.43 (0.28-0.64)	0.84 (0.66-1.05)	1						
Pembrolizumab	0.50 (0.31-0.74)	0.71 (0.39-1.18)	0.92 (0.54-1.48)	0.48 (0.29-0.76)	0.50 (0.33-0.73)	0.46 (0.28-0.69)	0.45 (0.32-0.66)	0.70 (0.54-0.89)	0.70 (0.43-1.06)	0.66 (0.47-0.96)	0.56 (0.34-0.86)	1.08 (0.77-1.46)	1.26 (0.92-1.77)	1					
Tasisulam	1.24 (0.85-1.74)	1.77 (1.06-2.79)	2.20 (1.45-3.49)	1.21 (0.79-1.78)	1.25 (0.89-1.70)	1.14 (0.77-1.62)	1.11 (0.68-1.94)	1.69 (1.10-2.73)	1.74 (1.17-2.49)	1.63 (1.00-2.85)	1.34 (0.92-2.04)	2.62 (1.78-4.02)	3.13 (2.01-5.15)	2.43 (1.50-4.22)	1				
Tremelimumab	0.88 (0.69-1.10)	1.25 (0.82-1.83)	1.59 (1.14-2.27)	0.84 (0.62-1.15)	0.88 (0.74-1.04)	0.81 (0.62-1.02)	0.80 (0.53-1.28)	1.22 (0.87-1.78)	1.23 (0.94-1.58)	1.18 (0.78-1.88)	0.97 (0.73-1.30)	1.89 (1.42-2.58)	2.26 (1.58-3.37)	1.76 (1.16-2.80)	0.70 (0.50-1.03)	1			
Trametinib	0.82 (0.60-1.15)	1.14 (0.74-1.86)	1.50 (1.02-2.32)	0.79 (0.55-1.18)	0.85 (0.63-1.11)	0.75 (0.55-1.07)	0.76 (0.48-1.29)	1.16 (0.77-1.81)	1.19 (0.83-1.65)	1.12 (0.70-1.90)	0.92 (0.65-1.35)	1.79 (1.26-2.66)	2.14 (1.41-3.43)	1.67 (1.05-2.82)	0.67 (0.45-1.05)	0.94 (0.69-1.33)	1		
Vemurafenib	0.80 (0.63-1.00)	1.14 (0.80-1.57)	1.46 (1.15-1.89)	0.78 (0.57-1.05)	0.81 (0.68-0.96)	0.74 (0.57-0.94)	0.73 (0.48-1.17)	1.12 (0.79-1.63)	1.13 (0.86-1.45)	1.08 (0.71-1.72)	0.88 (0.67-1.20)	1.73 (1.29-2.36)	2.06 (1.43-3.09)	1.61 (1.06-2.56)	0.67 (0.45-0.94)	0.92 (0.71-1.17)	0.97 (0.69-1.33)	1	
Vemurafenib + cobimetinib	0.57 (0.40-0.78)	0.80 (0.51-1.19)	1.05 (0.72-1.47)	0.55 (0.36-0.80)	0.57 (0.42-0.76)	0.52 (0.36-0.73)	0.51 (0.31-0.87)	0.78 (0.51-1.23)	0.80 (0.55-1.12)	0.75 (0.46-1.28)	0.64 (0.43-0.92)	1.25 (0.83-1.81)	1.43 (0.93-2.32)	1.12 (0.69-1.91)	0.47 (0.29-0.71)	0.65 (0.45-0.91)	0.69 (0.44-1.01)	0.71 (0.55-0.89)	1

Estimated mean hazard ratio for overall survival (95% credible interval)

A.6 EXAMPLE OF DIRECT AND INDIRECT EVIDENCE WITHIN THE NETWORK

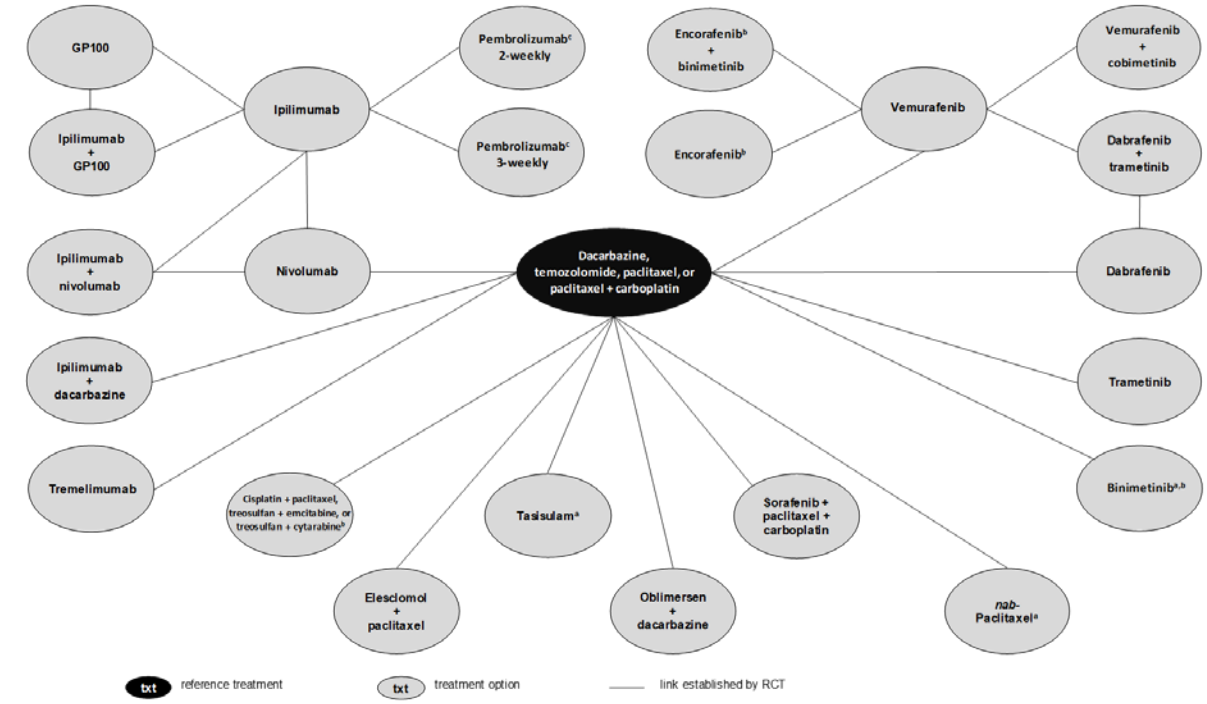


CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; vs, versus.
[a]Retrieved from McArthur *et al.* 2017.

	RCT		NMA	
Progression-free survival	**HR**	**CI**	**HR**	**CrI**
Dabrafenib versus dacarbazine reference group	0,30	(0.18-0.51)	0,30	(0.23-0.40)
Dabrafenib + trametinib versus dacarbazine reference group	n/a		0,21	(0.17-0.27)
Vemurafenib versus dacarbazine reference group	0,38	(0.32-0.46)	0,38	(0.32-0.45)
Overall survival				
Dabrafenib versus dacarbazine reference group	0,61	(0.25-1.48)	0,73	(0.50-1.04)
Dabrafenib + trametinib versus dacarbazine reference group	n/a		0,55	(0.41-0.74)
Vemurafenib versus dacarbazine reference group	0,81	(0.70-1.00)	0,81	(0.68-0.96)

A.7 EXTENDED NETWORK AND RESULTS OF INCLUDING PHASE-III TRIALS WITH PREVIOUSLY TREATED PATIENTS

FIGURE A.7.1 EXTENDED NETWORK: NETWORK OF TREATMENT FOR ADVANCED MELANOMA INCLUDING PHASE-III TRIALS WITH PREVIOUSLY TREATED PATIENTS



[a]Only included in network-meta analyses for progression-free and overall survival (not in safety analyses);
[b]Only included in extended network;
[c]In extended network Schachter et al 2017 including treatment naive and previously treated patients.

FIGURE A.7.2 EXTENDED NETWORK: RESULTS OF THE NETWORK META-ANALYSIS FOR TREATMENT RELATED ADVERSE EVENTS

Treatment	PBB	RR TRAE vs reference group (95% CrI)
GP100	83%	0.38 (0.18-0.72)
Ipilimumab + GP100	4%	0.55 (0.30-0.93)
Nivolumab	5%	0.56 (0.41-0.75)
Pembrolizumab (every 3 wk)	5%	0.60 (0.33-1.00)
Pembrolizumab (every 2 wk)	4%	0.61 (0.34-1.02)
Ipilimumab	0%	0.71 (0.46-1.04)
Dacarbazine reference group	**0%**	**1**
Carboplatin + paclitaxel + sorafenib	0%	1.08 (1.01-1.17)
Elesclomol + paclitaxel	0%	1.23 (1.00-1.50)
Trametinib	0%	1.38 (1.05-1.82)
Tremelimumab	0%	1.40 (1.17-1.67)
Dabrafenib + trametinib	0%	1.46 (1.19-1.78)
Nivolumab + ipilimumab	0%	1.50 (1.01-2.16)
Dabrafenib	0%	1.55 (1.16-2.04)
Encorafenib + binimetinib	0%	1.60 (1.27-1.98)
Vemurafenib	0%	1.75 (1.51-2.03)
Encorafenib	0%	1.83 (1.47-2.24)
Vemurafenib + cobimetinib	0%	1.98 (1.58-2.46)
Ipilimumab + dacarbazine	0%	2.05 (1.63-2.57)
Dacarbazine + oblimersen	0%	2.38 (1.67-3.35)
Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan +	0%	3.27 (1.93-5.41)

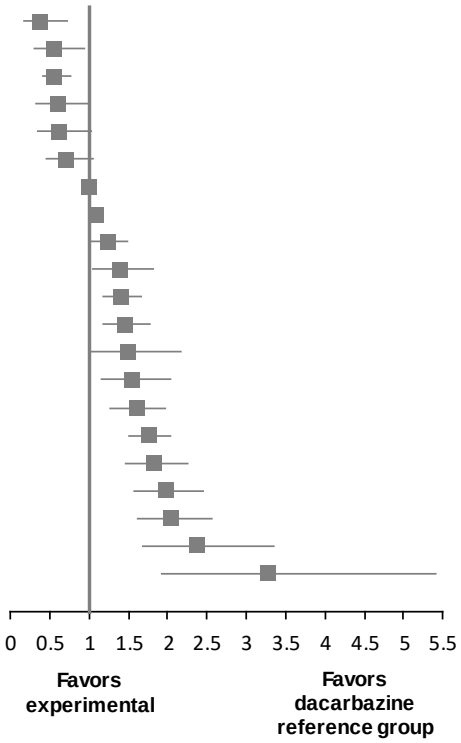
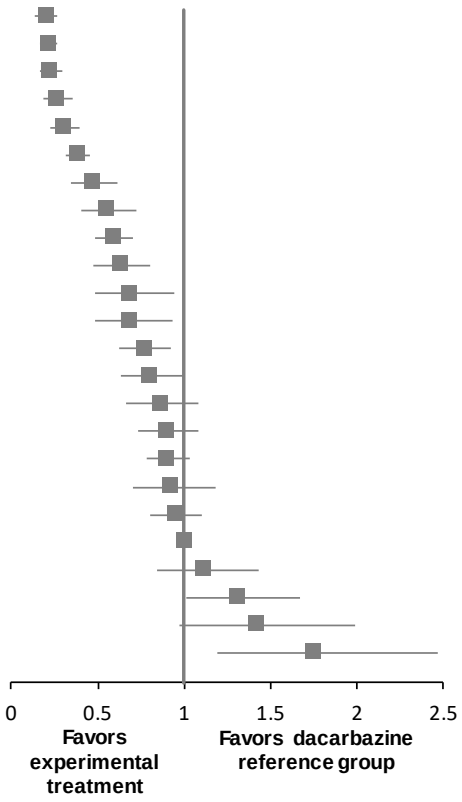


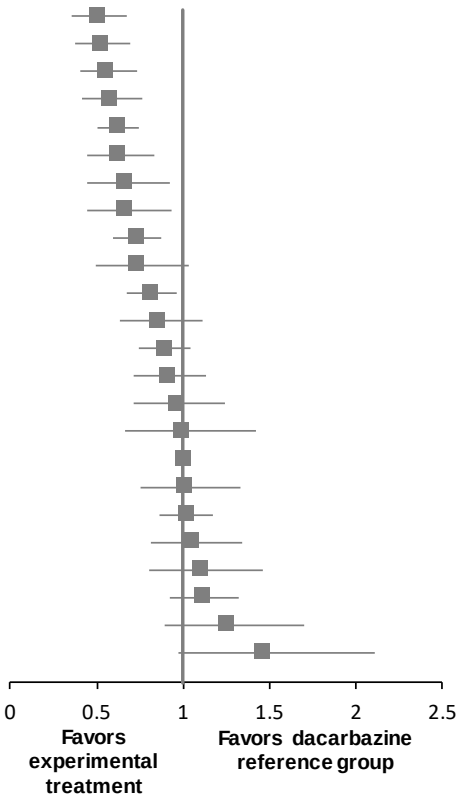
FIGURE A.7.3 EXTENDED NETWORK: RESULTS OF THE NETWORK META-ANALYSIS FOR PROGRESSION-FREE SURVIVAL

Treatment	PBB	HR PFS vs reference group (95% CrI)
Encorafenib + binimetinib	63%	0.20 (0.14-0.27)
Dabrafenib + trametinib	20%	0.21 (0.17-0.27)
Vemurafenib + cobimetinib	16%	0.22 (0.17-0.29)
Encorafenib	1%	0.26 (0.19-0.35)
Dabrafenib	0%	0.30 (0.23-0.40)
Vemurafenib	0%	0.38 (0.32-0.45)
Nivolumab + ipilimumab	0%	0.47 (0.35-0.61)
Trametinib	0%	0.55 (0.40-0.72)
Nivolumab	0%	0.58 (0.48-0.70)
Binimetinib	0%	0.63 (0.48-0.81)
Pembrolizumab (every 2 wk)	0%	0.68 (0.48-0.94)
Pembrolizumab (every 3 wk)	0%	0.68 (0.48-0.94)
Ipilimumab + dacarbazine	0%	0.76 (0.63-0.92)
nab -Paclitaxel	0%	0.80 (0.63-0.99)
Dacarbazine + oblimersen	0%	0.86 (0.67-1.09)
Elesclomol + paclitaxel	0%	0.89 (0.73-1.08)
Carboplatin + paclitaxel + sorafenib	0%	0.90 (0.78-1.03)
Cisplatin + paclitaxel, treosulfan + gen	0%	0.92 (0.70-1.18)
Tremelimumab	0%	0.94 (0.80-1.10)
Dacarbazine reference group	**0%**	**1**
Ipilimumab	0%	1.11 (0.84-1.43)
Tasisulam	0%	1.31 (1.01-1.67)
Ipilimumab + GP100	0%	1.41 (0.97-1.99)
GP100	0%	1.75 (1.19-2.47)



A.7.4 EXTENDED NETWORK: RESULTS OF THE NETWORK META-ANALYSIS FOR OVERALL SURVIVAL

Treatment	PBB	HR OS vs reference group (95% CrI)
Encorafenib + binimetinib	41%	0.50 (0.36-0.67)
Nivolumab + ipilimumab	31%	0.52 (0.38-0.69)
Dabrafenib + trametinib	12%	0.55 (0.40-0.74)
Vemurafenib + cobimetinib	9%	0.57 (0.42-0.76)
Nivolumab	0%	0.62 (0.51-0.74)
Encorafenib	2%	0.62 (0.45-0.84)
Pembrolizumab (every 3 wk)	2%	0.65 (0.45-0.93)
Pembrolizumab (every 2 wk)	2%	0.65 (0.44-0.94)
Ipilimumab + dacarbazine	0%	0.72 (0.59-0.88)
Dabrafenib	0%	0.73 (0.50-1.04)
Vemurafenib	0%	0.81 (0.67-0.96)
Trametinib	0%	0.85 (0.63-1.11)
Tremelimumab	0%	0.88 (0.74-1.04)
nab -Paclitaxel	0%	0.91 (0.71-1.13)
Ipilimumab	0%	0.95 (0.72-1.25)
Ipilimumab + GP100	0%	0.99 (0.67-1.43)
Dacarbazine reference group	**0%**	**1**
Binimetinib	0%	1.01 (0.75-1.33)
Carboplatin + paclitaxel + sorafenib	0%	1.01 (0.87-1.18)
Dacarbazine + oblimersen	0%	1.05 (0.81-1.34)
Cisplatin + paclitaxel, treosulfan + gen	0%	1.09 (0.80-1.46)
Elesclomol + paclitaxel	0%	1.10 (0.92-1.32)
Tasisulam	0%	1.25 (0.89-1.69)
GP100	0%	1.46 (0.97-2.10)



A.8 PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7,8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7,8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7,8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7,8,9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8,9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8,9