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Review

A 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 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) with a time frame from January 1, 2010 to March 11, 2019. We retrieved evidence on treatment-related grade III/IV 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 and seventeen treatments were included in the effectiveness and safety NMA, respectively. 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

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Dacarbazine

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 provided 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.

1. Introduction

The incidence of cutaneous melanoma has been increasing in the past decades. The World Health Organisation (WHO) estimates around 132,000 new cases worldwide each year [1]. Although most patients are diagnosed at the local stage and have a rather favourable 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 Cytotoxic T-Lymphocyte Associated Protein 4 (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 with 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 lack of comparative evidence between the different immune checkpoint inhibitors (anti–CTLA-4 and anti-programmed cell death protein 1 (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 on 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.

2. Methods

2.1. Systematic literature review

An SLR was performed, in accordance with the 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 from January 1, 2010 to March 11, 2019. The 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. The exclusion criteria were as follows: 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 articles. Reference lists of published RCTs, reviews and meta-analyses were manually screened to ensure the inclusion of all phase III RCTs on advanced melanoma.

2.2. 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 (the year of publication and first author), trial details (the national clinical trial number, follow-up duration, intervention and comparator and the number of patients), patient characteristics (age, disease status, treatment status [treatment naive {TN} versus previously treated{PT}] and type of previous treatment), safety outcomes (counts/percentages of patients experiencing at least one grade III/IV TRAE), and effectiveness outcomes (median and hazard ratios [HRs] including 95% confidence intervals [CIs] for PFS and OS). Data of the most recent citation were 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 these 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 from 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].

2.3. 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 TN or only PT with *'older'* treatments which never demonstrated efficacy [9,17,18] (i.e. dacarbazine, temozolomide, fotemustine, carboplatin, interleukin-2, sorafenib, interferon and cytokine). Therefore, 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, irrespective of receiving previous treatment (extended network and results are presented in the Online Appendix).

The NMA was conducted in WinBUGS in accordance with methods adopted by The National Institute for Health and Care Excellence [19–22] and recommended by the International Society for Pharmacoeconomics and Outcomes Research [23,24]. A random-effect model was deemed inappropriate as the number of studies was too low in comparison with 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 III/IV 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 to have 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 (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 et al. [28]. The NMA was performed using a Markov Chain Monte Carlo (MCMC) simulation process by 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 an HR has a certain value) which is in line with decision-making theory [29]. From the outcomes of the MCMC simulation process, we calculated the 95% credible interval (CrI) and 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, refer to the studies by Caldwell *et al.* [6], Mills *et al.* [31] and Kanters *et al.* [7].

3. Results

3.1. Systematic literature review

The search identified 2023 citations. After removing duplicates, 1684 citations were retrieved from the electronic databases. Title and abstract screening resulted in the exclusion of 1552 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. Fig. 1 shows the PRISMA flow diagram.

The 28 RCTs involved a total of 14,376 patients with advanced melanoma. The RCTs were conducted in TN patients (11 RCTs), PT patients (4 RCTs) and in TN and PT patients within one trial (13 RCTs). Of the trials including PT patients (17 RCTs), most included patients were 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] irrespective of the 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. The follow-up time of the RCTs was often not reported

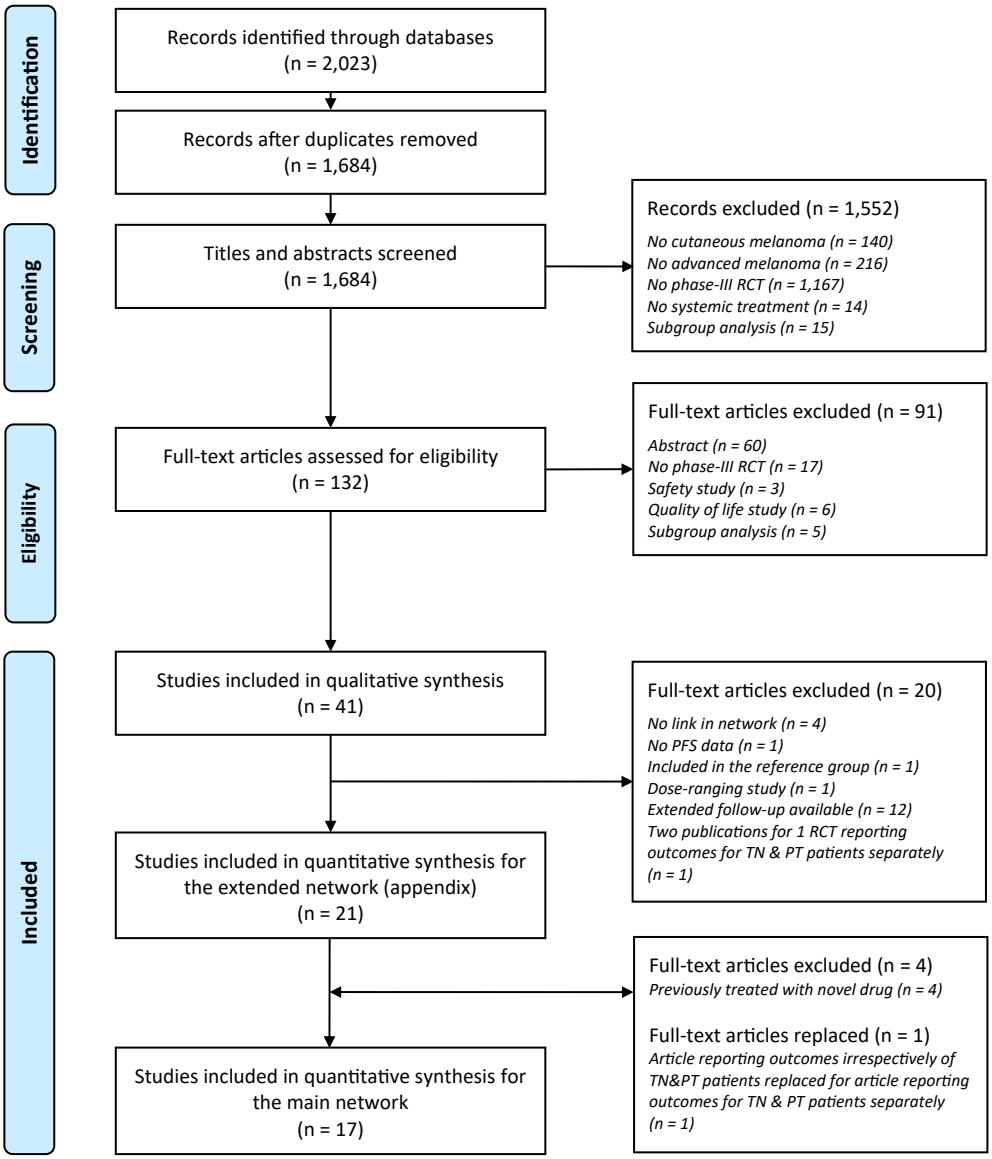

Fig. 1. PRISMA flow diagram. PFS, progression-free survival; TN, treatment naive; PT, previously treated; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

(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 III/IV TRAE (ranging from 9% in patients receiving nivolumab [26] to 84% in patients receiving interleukin-2 plus GP100 [39]). The median PFS ranged from 1.5 months for dacarbazine [34,25] and paclitaxel [25] and 14.9 months for encorafenib plus binimetinib [36]; the 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. Similarly, none of the RCTs compared head-to-head the two anti–PD-1 monotherapies, the three BRAFis or the three BRAFi plus an 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 crossover and early stop of the study due to crossing predefined boundaries (e.g. futility, efficacy or stopping boundary).

3.2. Network of treatment options

The treatment options of the RCTs were connected in a network (Fig. 2). 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 [32] could be retained within the main network as the extended follow-up published the outcomes for TN and PT patients separately [37]. Consequently, a total of 17 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 and 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.

3.3. Network meta-analysis for treatment-related grade III/IV 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). Fig. 3 presents the estimated RR for grade III/IV TRAEs ranked according to RR compared with the dacarbazine reference group. The GP100 was most favourable both in terms of RR for grade III/IV TRAE (RR TRAE: 0.58 [95% CrI: 0.25–1.16]) and PBB 0.85. Although 95% CrIs 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 III/IV TRAEs than the reference group (RR ranging from 1.08 to 2.38).

3.4. Network meta-analysis for progression-free survival

Fig. 4 presents the estimated HRs for PFS ranked according to HR for PFS compared with the dacarbazine reference group. The two BRAFi plus MEKi combination treatments were identified as the most favourable ones. 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) than 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 by 45%, 24% and 20%, respectively. All chemotherapies were less likely reducing the risk of progression, most of whose HRs were overlapping with 1.

Table 1
Results of the systematic literature review.

NCT number	First author	Year	Intervention	Comparator	Treatment status	Number of patients in ITT population		RR grade III/IV TRAEs (95% CI)	HR for PFS (95% CI)	HR for OS (95% CI)
						Int vs Comp				
00057616	Eisen[a] [40]	2010	Lenalidomide	Placebo	PT	152	154	NR	NR	1.16 (0.86–1.59)
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)
00087776	Bedikian[b] [46]	2011	Docosahexaenoic acid-paclitaxel	Dacarbazine	TN	194	199	2.13 (1.72–2.64)	NR	NR
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)
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)
00019682	Schwartzentruber[a] [39]	2011	Interleukin-2 + GP100	Interleukin-2	TN & PT	91	94	1.06 (0.92–1.23)	NR	NR
01227889	Hauschild [42]	2012	Dabrafenib	Dacarbazine	TN	187	63	NR	0.30 (0.18–0.51)	0.61 (0.25–1.48)
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)
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)
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)
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)
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)
01006252	Hamid [53]	2014	Tasisulam	Paclitaxel	PT	168	168	NR	1.30 (1.01–1.66)	1.23 (0.89–1.69)
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)
00864253	Hersh [55]	2015	*nab*-Paclitaxel	Dacarbazine	TN & PT	264	265	NR	0.79 (0.63–0.99)	0.90 (0.71–1.13)
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)
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)
01515189	Ascierto[d] [57]	2017	Ipilimumab 10 mg/kg	Ipilimumab 3 mg/kg	TN & PT	365	362	1.87 (1.44–2.43)	0.89 (0.76–1.40)	0.84 (0.70–0.99)
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)

(*continued on next page*)

Table 1 (*continued*)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Number of patients in ITT population		RR grade III/IV TRAEs (95% CI)	HR for PFS (95% CI)	HR for OS (95% CI)
						Int vs Comp				
01763164	Dummer[f] [34]	2017	Binimetinib	Dacarbazine	TN & PT	269	133	NR	0.62 (0.47–0.80)	1.00 (0.75–1.33)
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)
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)
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)
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)
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)
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)
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)
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)
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; GP100, glycoprotein 100 peptide vaccine.

[a] No link in the main network.

[b] Not included in the 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.*,[62].

[f] Only included in extended network (Appendix A.7).

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

[h] Retrieved from Dummer *et al.*,[63].

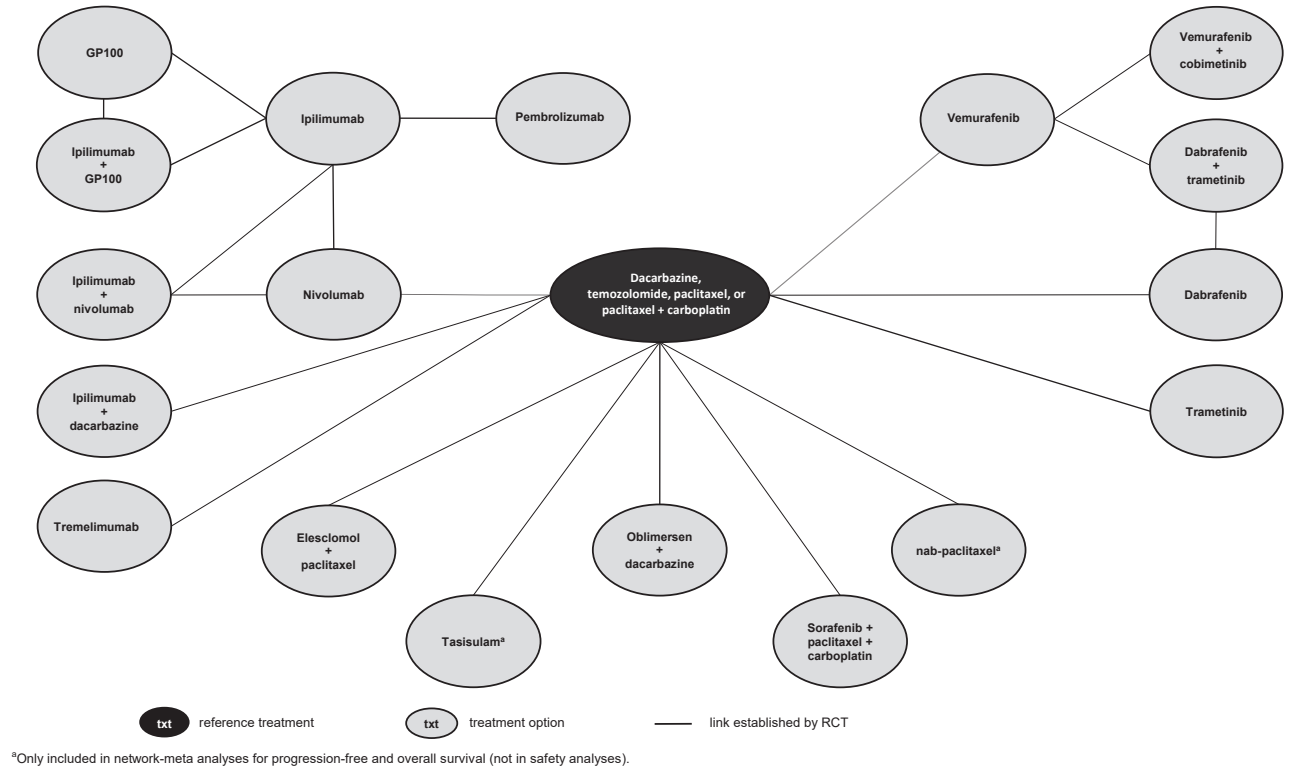

Fig. 2. Main network of treatments for advanced melanoma. GP100, glycoprotein 100 peptide vaccine; RCT, randomised controlled trial.

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]).

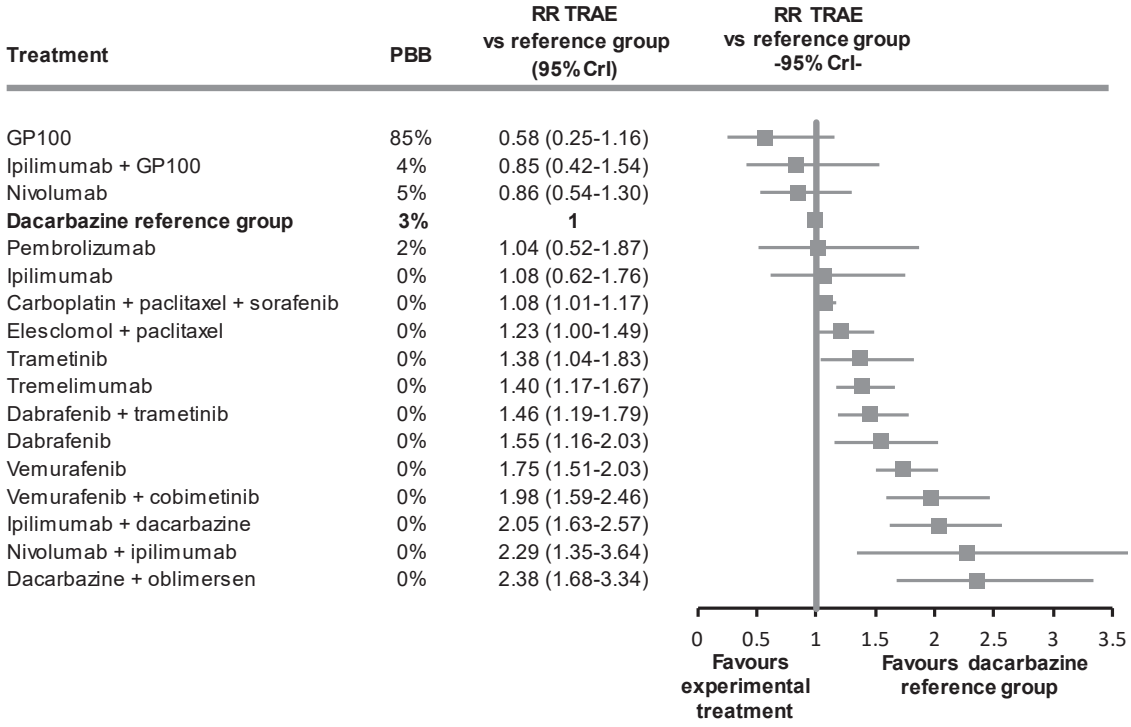

Fig. 3. Results of the network meta-analysis for adverse events. CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; RR, relative risk; TRAE, treatment-related adverse event.

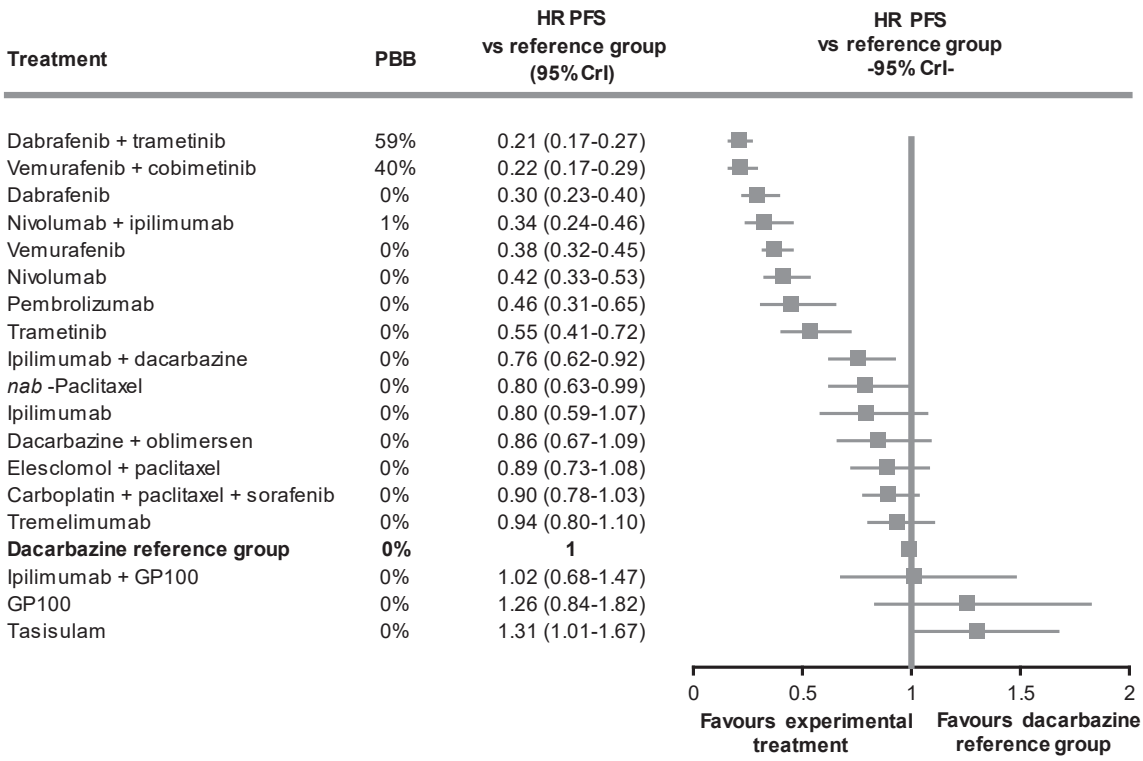

Fig. 4. Results of the network meta-analysis for progression-free survival. CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; HR, hazard ratio; PFS, progression-free survival.

3.5. Network meta-analysis for overall survival

Fig. 5 presents the estimated HRs for OS ranked according to HR for OS compared with 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% CrIs 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 both anti–PD-1 monotherapies (nivolumab: PBB: 0.05 [95% CrI: 0.36–0.59]; pembrolizumab: PBB: 0.06 [95% CrI: 0.33–0.73]).

4. Discussion

A myriad of novel treatments entered the treatment paradigm for advanced melanoma in 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 checkpoint 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.

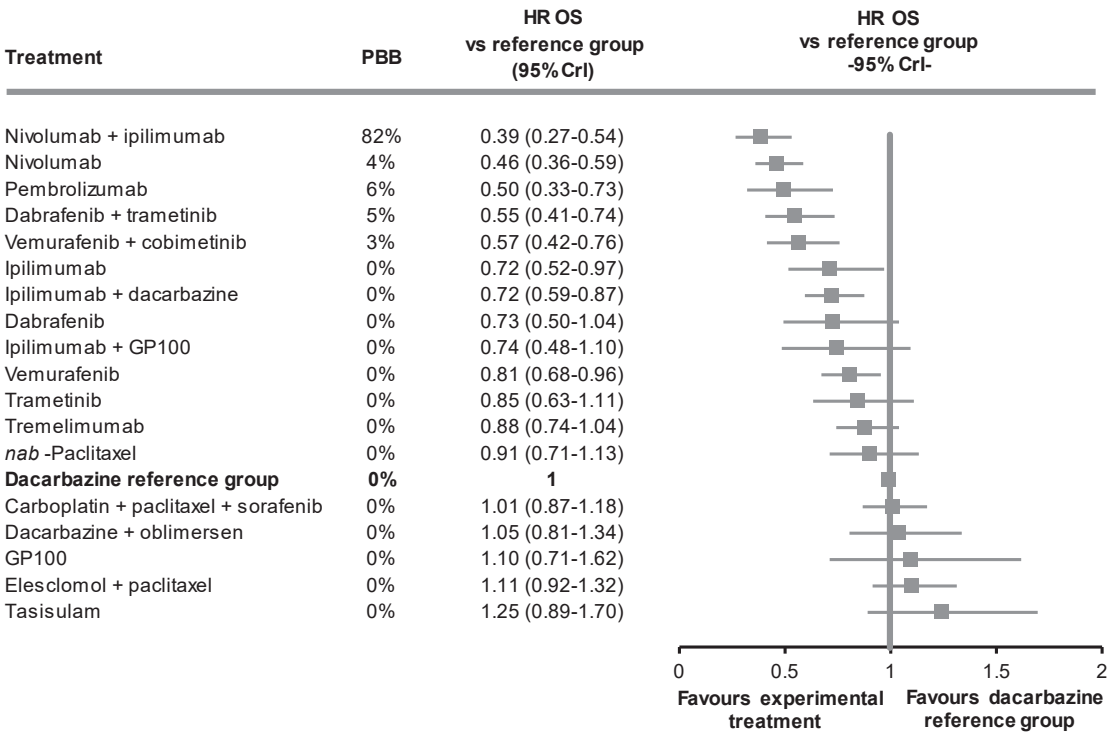

Fig. 5. Results of the network meta-analysis for overall survival. CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; HR, hazard ratio; OS, overall survival.

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 (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 an HR for OS in the first publication. In one RCT (comparing vemurafenib with 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 HRs 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 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 (Appendix A.6), the link between the dacarbazine reference group and dabrafenib was computed not only using direct evidence from the RCT by Hauschild *et al.* [42] (HR OS: 0.61) but also from indirect evidence from three other studies [43, 58, 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 with 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 a 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 CI included an 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 is comparable across the RCTs within the network. As long as prognostic factors have no influence on the treatment effect, this assumption is not violated irrespective 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 TN and PT patients. We also assumed that patients 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 a consequence, we excluded four RCTs [33–36] in our main network in which a percentage of patients were previously treated with a *'new'* (effective) treatment (i.e. BRAFi, MEKi, anti–CLTLA-4 and 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 for both TN (HR PFS: 0.57 [95% CI: 0.46–0.70] and HR OS: 0.69 [95% CI: 0.54–0.89]) and 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 differentiate between TN and PT patients in our NMA.

The Online appendix shows the impact of including all identified RCTs, irrespective of (type of) previous treatment (Appendix A.7). The extended network expands with several novel treatment options such as binimetinib, encorafenib and 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. Similarly 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 TN patients in the RCT by Ascierto *et al.* [60] (HR PFS: 0.42 and HR OS: 0.46) than in PT patients in the RCT by Larkin *et al.* [33] (HR PFS: 1.00 and HR OS: 0.95), even the 95% CIs were not overlapping. Therefore, the inclusion of the study by Larkin *et al.* [33] (in the extended network including RCTs with PT patients) resulted in less favourable outcomes for nivolumab compared with 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 with 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 HRs 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% CrIs 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-1 monotherapies 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 because of the time in which their study was conducted.

To conclude, our study identified the most effective treatment options for advanced melanoma and provided 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 optimise treatment and outcomes of patients with advanced melanoma 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 patients with BRAF-mutant advanced melanoma. In contrast to PFS, however, anti–PD-1 plus anti–CTLA-4 and both anti–PD-1 monotherapies were identified as the 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 have a conflict of interest to report for the submitted work. M.F. reports receiving grants from Roche Nederland B.V., Daiichi Sankyo, Abbvie, PamGene, Gilead Sciences Netherlands BV and Astellas Pharma BV, outside the submitted work. B.L. has nothing to disclose. M.G. is currently employed by Sanofi but conducted the submitted work outside the employment relationship with Sanofi. C.U.d.G. reports receiving grants from Boehringer Ingelheim, Astellas, Celgene, Sanofi, Janssen-Cilag, Bayer, Amgen, Genzyme, Merck, Glycostem Therapeutics, AstraZeneca, Roche and Merck, outside the submitted work. J.H. reports receiving grants and other from BMS, MSD, Novartis and NEON Therapeutics and other from Roche/Genentech, Pfizer, Astra Zeneca/Medimmune, Bayer, Ipsen, Immunocore, Gadeta, Seattle Genetics and Celsius Therapeutics, outside the submitted work. P.v.B. has nothing to disclose.

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Appendix A. Supplementary data

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