Cancer Treatment Reviews 74 (2019) 43–48

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Systematic or Meta-analysis Studies

Network meta-analysis of therapies for previously untreated advanced BRAF-mutated melanoma

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ARTICLE INFO

Keywords:
BRAF-mutated melanoma
Targeted therapy
Immunotherapy
Network meta-analysis

ABSTRACT

Background: The spectrum of treatment options for patients with metastatic BRAF-mutated melanoma is broad, spanning multiple treatment classes. However, there is a lack of head-to-head evidence comparing targeted and immunotherapies. The purpose of this study is to conduct a network meta-analysis (NMA) in previously untreated, BRAF-mutated melanoma patients and estimate the relative efficacy of systemic therapies for this patient population at the treatment level.

Methods: The literature review included searches of MEDLINE, EMBASE, and the Cochrane Central Registry of Controlled Trials (CENTRAL) to November 2018. Randomized controlled trials of previously untreated patients with advanced melanoma were eligible if at least one intervention was either a targeted or immune therapy. Relative treatment effects were estimated by fixed effect Bayesian NMAs on progression-free survival (PFS) and overall survival (OS), based on the hazard ratio.

Results: Combination dabrafenib with trametinib (HR 0.22 [95% CrI 0.17, 0.28] vs dacarbazine) and combination vemurafenib with cobimetinib (HR 0.22 [95% CrI 0.17, 0.29] vs dacarbazine) were likely to rank as the most favorable treatment options for PFS, while combination nivolumab with ipilimumab was likely to be the most efficacious in terms of OS (HR 0.33 [0.24, 0.47] vs dacarbazine).

Conclusions and relevance: The findings highlight the efficacy of combination PD-1 with CTLA-4 inhibitors and combination BRAF with MEK inhibitors in the treatment of advanced melanoma. However, as few trials informed each treatment comparison, research is needed to further refine our understanding of this complex and rapidly evolving treatment landscape.

Introduction

Until recently, effective treatment options for patients with advanced stage melanoma were limited. Indeed, according to a 2011 systematic review of treatment options in melanoma, patients with metastatic disease had a median survival of under one year [1]. However, recent developments in understanding molecular mechanisms of oncogenesis, including the role of the mitogen-activated protein kinase (MAPK) signaling pathway, have led to the introduction of a number of novel treatment options. Approximately 40–70% of advanced melanoma cases harbor a BRAF mutation, causing constitutive activation of the MAPK pathway [1–4].

Among recent developments in treatment options are selective BRAF and MEK inhibitors, which have improved patient outcomes with respect to progression-free survival (PFS) and overall survival (OS) compared to cytotoxic chemotherapy [5–7]. Furthermore, advancements have led to the development of immune checkpoint inhibitors, with targets including the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). These molecules play a co-regulatory role in the down-regulation of T-cell activation, and inhibition of these targets has demonstrated clinical benefit over traditional chemotherapy [8–15]. However, no head-to-head randomized controlled trial (RCT) evidence currently exists between targeted therapies, such as selective BRAF and MEK inhibitors, and immunotherapies. To address this knowledge gap, we recently undertook a systematic literature review and network meta-analysis (NMA) to evaluate the relative efficacy of treatments for patients with advanced BRAF-mutated melanoma [16]. The findings suggested that

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https://doi.org/10.1016/j.ctrv.2019.02.001
Received 22 March 2018; Received in revised form 31 January 2019; Accepted 4 February 2019

combination BRAF with MEK inhibitors and PD-1 inhibitors were statistically similar and associated with improved OS compared to most other treatment classes. Combination BRAF with MEK inhibitors were statistically superior to all other treatment classes with respect to PFS. However, as dual immune checkpoint inhibition may prove to be an important treatment option, the conclusions were cautious given the lack of long-term survival data for combination CTLA-4 with PD-1 inhibitors at the time of the analysis. Additionally, comparisons were based on treatment class due to limited evidence and, thus, it is not possible to draw conclusions regarding the relative treatment effects of individual treatments.

The purpose of this study was to update the literature search and explore the evidence base in previously untreated advanced BRAF-mutated melanoma by estimating the relative treatment effects between individual treatment options.

Methods

Identification of the evidence base

Our systematic literature review and NMA was updated to November 10, 2018. The complete search strategy, literature screening, and data extraction methods have been described previously [16]. Briefly, RCTs which reported OS or PFS in previously untreated adult patients with unresectable lymph node metastasis (American Joint Committee on Cancer [AJCC] TNM Stage IIIc) or distant metastatic (AJCC TNM stage IV) melanoma were eligible if at least one intervention was a targeted (BRAF or MEK) or an immune checkpoint (CTLA-4 or PD-1) inhibitor.

Statistical analyses

Bayesian NMAs were conducted to estimate the hazard ratios (HRs), with corresponding 95% credible interval (CrIs), for PFS and OS at both the treatment class-level and individual treatment-level. Analyses were conducted based on the reported HRs between trial arms. In the case of multi-arm trials (i.e. trials with three or more interventions), adjustments were made to reflect the correlations between relative treatment effects by converting log-HRs to log-hazards [17,18].

Both fixed effects and random effects models were fitted to the data using Markov Chain Monte Carlo (MCMC) methods. Model fit was assessed according to the deviance information criteria (DIC). A four-chain model with non-informative priors was run with an adaptation phase of 50,000 iterations followed by 400,000 model iterations. The thin ratio was set to 5. Non-convergence was assessed by the Gelman-Rubin statistic.

Inconsistency was evaluated by edge-splitting, an approach that estimates relative treatment effects based on direct evidence (i.e. pairwise comparisons between treatments nodes) and indirect evidence (i.e. relative treatment effects estimated only using indirect evidence) separately. If a model is consistent, the direction and statistical importance of effect will be maintained.

Relative treatment rankings were evaluated according to the surface under the cumulative ranking curve (SUCRA) method, which generates a value on 0–100% to indicate the probable worst and best treatment options, respectively, in the network [19].

In this Bayesian context, the interpretation of HRs from the relative treatment effect estimates is similar to the frequentist framework, where statistical importance (i.e. statistical significance in the frequentist framework) is established when the 95% CrI does not contain 1.0. Models were programmed in R v3.1.3 (www.r-project.org) using the gemtc package [20].

Results

Clinical evidence

The literature review identified 8 new publications [21–28], which were updates of previously included trials, generating an evidence base of 25 publications [5,12,14,21–43] describing 15 trials. However, two trials were only eligible for inclusion in the treatment-class level analysis due to the network structure [42,43]. From the literature update, two-year OS results from the CheckMate-069 trial, where patients were randomized to combination ipilimumab with nivolumab or ipilimumab monotherapy, were identified. The median survival had not been reached in either group. Updated PFS and recently published OS outcomes in the three-arm CheckMate-067 trial were also identified [23]. At the time of publishing, median OS had not been reached in the combination nivolumab with ipilimumab group but was 37.6 months in patients treated with nivolumab and 19.9 months in patients treated with ipilimumab. Recently published three-year efficacy outcomes, including both PFS and OS, for the COMBI-d trial [27] and CheckMate-066 [26] were also identified. Four-year survival outcomes from the CheckMate-067 trial [28], where median OS had not yet been reached in the combination nivolumab with ipilimumab group, were included. Lastly, the final protocol-specified survival analysis from the Keynote-006 trial [24] was included. No new trials were identified.

In the treatment-level analysis, the following interventions from 13 trials are included: combination vemurafenib with cobimetinib [5,22], vemurafenib monotherapy [5,22,25,30,32,40], combination dabrafenib with trametinib [27,29,32], dabrafenib monotherapy [27,29,35], combination selumetinib with dacarbazine [31], tremelimumab monotherapy (overall survival only) [36], dacarbazine monotherapy [14,25,26,30,31,33,35,36,40,41], combination ipilimumab with dacarbazine [14,41], nivolumab or pembrolizumab [23,24,26,28,33,34,38], combination nivolumab with ipilimumab [12,21,23,28,38], ipilimumab monotherapy [12,21,23,24,28,34,37,38], and combination ipilimumab with sargramostim [37]. While no head-to-head evidence is available for nivolumab and pembrolizumab, both exhibiting anti-PD-1 mechanism of action, indirect evidence suggests they perform similarly across multiple diseases [44,45]. Therefore, both monoclonal antibodies were considered clinically equivalent and included as a single treatment option in order to establish a critical connection in the evidence network. In Keynote-006 [24,34], outcomes were reported from two doses of pembrolizumab (10 mg/kg q3wk or 10 mg/kg q2wk). From this trial, we included only the '10 mg q3wk' dose of pembrolizumab. As of June 2017, pembrolizumab 2 mg/kg q3wk is the only dose currently approved by the US Food and Drug Association (FDA) or Health Canada for unresectable or metastatic melanoma [46,47]. Furthermore, phase I evidence suggests that the 2 mg/kg and 10 mg/kg doses of pembrolizumab perform similarly in melanoma patients [48]. Additional interventions were included in the treatment class-level analysis, but could not be connected in the individual treatment-level network: selumetinib (MEK) [42], selumetinib with docetaxel (MEK with chemotherapy) [43], docetaxel (chemotherapy) [43], and temozolomide (chemotherapy) [42]. However, the authors considered these interventions to be of low clinical relevance for this patient population. A summary of treatment categorization into treatment classes is presented in Table A.1.

Trial characteristics, as well as demographic and clinical characteristics of the enrolled patients, reported previously [16], were well matched across trials. The median age at enrollment was above 50 years in all trials, with males comprising the majority of patients. Most patients had metastatic disease. Few patients demonstrated evidence of brain metastasis, which was often an exclusion criterion for enrolment among included trials. In the majority of trials, patient populations

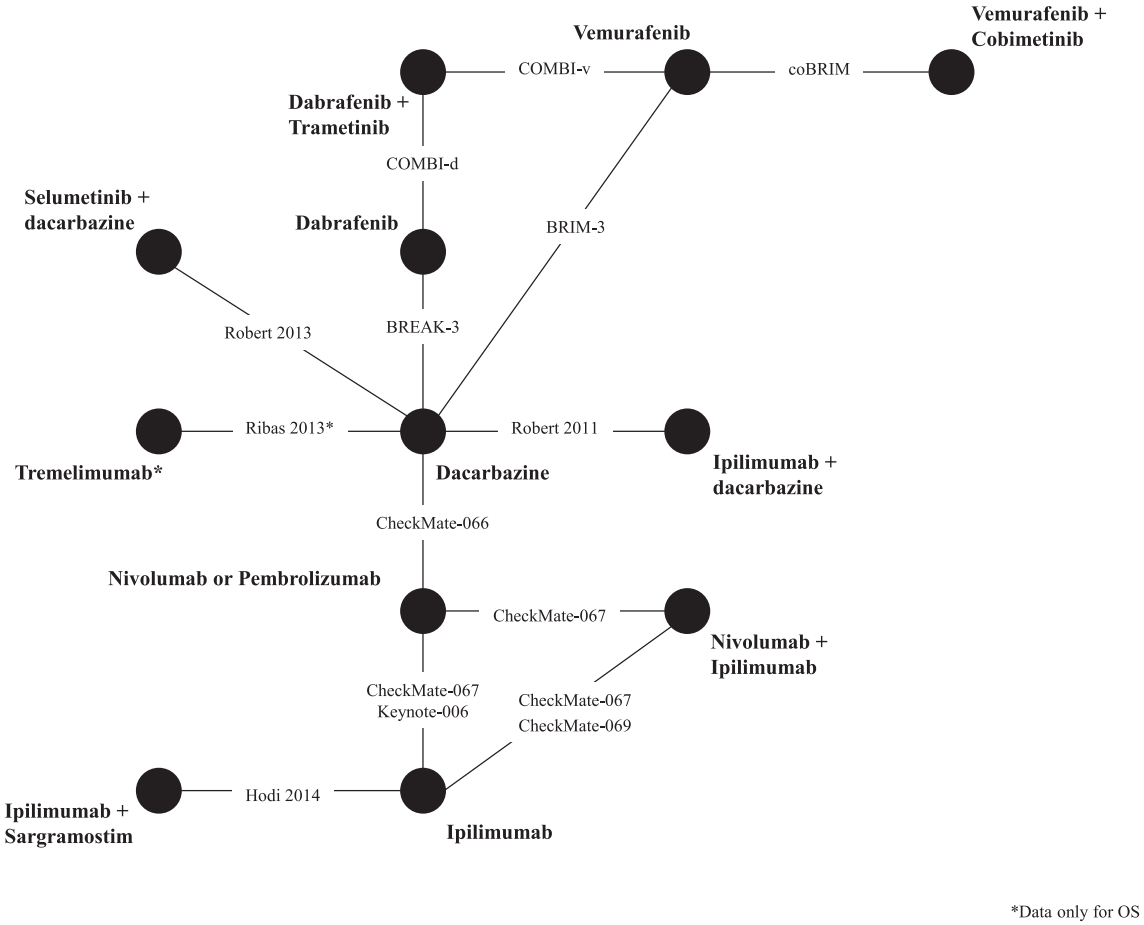

Fig. 1. Network of evidence for overall survival and progression-free survival outcomes.

were either all BRAF-mutated or a mixture of BRAF-mutated and wild-type. Mutation status was not reported in two trials [36,37]. The reported PFS and OS outcomes from each trial are presented in Table A.2.

Individual treatment-level outcomes

The network diagram for the treatment-level analyses is presented in Fig. 1. Nearly all comparisons were informed by a single trial. Outcomes for tremelimumab were only available for OS [36]. Relative treatment effects for both PFS and OS are presented in Table 1.

Progression-free survival

As most comparisons were informed by a single trial, and the DICs for the fixed (21.15) and random (22.83) models were similar, the fixed effects model was selected as the appropriate fit. Relative treatment effects with respect to PFS are presented below the diagonal in Table 1.

Differences between treatments within the same treatment class (dabrafenib vs. vemurafenib; combination dabrafenib with trametinib vs. combination vemurafenib with cobimetinib) were not statistically important. Combination dabrafenib with trametinib was more efficacious than most treatments in the network, though the relative effects compared to combination vemurafenib with cobimetinib (HR 0.98, CrI 0.73, 1.31) and to combination nivolumab with ipilimumab (HR 0.83, CrI 0.58, 1.18) were not statistically important. All treatments, with the exception of ipilimumab with sargramostim (HR 0.66, CrI 0.40, 1.07), were statistically superior to dacarbazine. These findings are reflected in the SUCRA results (Table A.4), which suggest that dabrafenib with trametinib (SUCRA 94.1) and combination vemurafenib with cobimetinib (SUCRA 92.1) are likely to rank as the preferred treatments in the network.

The results of the edge-splitting exercise revealed evidence of inconsistency in the network (Table A.5). Specifically, comparisons between combination dabrafenib with trametinib and dabrafenib, combination dabrafenib with trametinib and vemurafenib, and between nivolumab or pembrolizumab and combination nivolumab with ipilimumab were statistically important based only on direct evidence, but not based on indirect evidence. Although point estimates demonstrated consistent direction of effect, the CrIs for indirect evidence were wider and caused some discrepancies in the statistical importance of findings.

Overall survival

The relative treatment effects for OS (Table 1) were also estimated through a fixed effects NMA, as most contrasts were informed by a single trial and the DICs for the fixed (25.99) and random (27.19) effects models were similar.

Treatment with combination nivolumab with ipilimumab was statistically superior compared to all other treatments with the exception of combination ipilimumab with sargramostim (HR 0.66, CrI 0.28, 1.57). Consistent with this, treatment with combination nivolumab with ipilimumab was likely to rank as the preferred treatment option (SUCRA 98.1) and dacarbazine was likely to be the least favorable treatment option (SUCRA 5.5). Differences in OS between treatments within the same treatment class were not statistically important. Complete SUCRA results are presented in Table A.4.

Inconsistency comparisons between direct and indirect evidence for OS (Table A.5) revealed that combination dabrafenib with trametinib

Table 1
Results of NMA, treatment-level network.

	Overall survival										
Dabrafenib BRAF	0.94 (0.66, 1.34)	**1.39 (1.07, 1.83)**	1.34 (0.87, 2.06)	**1.64 (1.04, 2.58)**	**2.26 (1.36, 3.77)**	1.10 (0.68, 1.80)	0.86 (0.57, 1.31)	1.50 (0.58, 3.91)	1.09 (0.71, 1.68)	0.81 (0.43, 1.52)	0.75 (0.51, 1.11)
1.26 (0.97, 1.64)	**Vemurafenib BRAF**	**1.48 (1.15, 1.91)**	**1.42 (1.11, 1.82)**	**1.74 (1.28, 2.37)**	**2.41 (1.64, 3.53)**	1.17 (0.82, 1.68)	0.91 (0.71, 1.18)	1.60 (0.66, 3.90)	1.16 (0.89, 1.52)	0.87 (0.51, 1.47)	**0.80 (0.67, 0.97)**
0.71 (0.58, 0.87)	**0.56 (0.46, 0.68)**	**Dabrafenib + trametinib BRAF + MEK**	0.96 (0.67, 1.36)	1.17 (0.79, 1.74)	**1.62 (1.03, 2.55)**	0.79 (0.51, 1.22)	**0.62 (0.44, 0.87)**	1.08 (0.43, 2.72)	0.78 (0.55, 1.12)	0.58 (0.33, 1.04)	**0.54 (0.40, 0.73)**
0.72 (0.51, 1.02)	**0.58 (0.46, 0.72)**	1.02 (0.76, 1.37)	**Vemurafenib + cobimetinib BRAF + MEK**	1.22 (0.82, 1.82)	**1.69 (1.07, 2.67)**	0.83 (0.53, 1.28)	**0.64 (0.45, 0.92)**	1.12 (0.45, 2.84)	0.82 (0.57, 1.17)	0.61 (0.34, 1.09)	**0.56 (0.41, 0.77)**
1.37 (0.94, 2.00)	1.09 (0.81, 1.46)	**1.94 (1.38, 2.73)**	**1.90 (1.31, 2.74)**	**Nivolumab or pembrolizumab PD-1**	**1.38 (1.10, 1.74)**	**0.67 (0.56, 0.81)**	**0.53 (0.39, 0.71)**	0.92 (0.40, 2.12)	**0.67 (0.49, 0.91)**	**0.50 (0.29, 0.87)**	**0.46 (0.36, 0.59)**
0.86 (0.58, 1.26)	**0.68 (0.50, 0.93)**	1.21 (0.85, 1.73)	1.18 (0.81, 1.73)	**0.62 (0.57, 0.69)**	**Nivolumab + ipilimumab PD-1 + CTLA-4**	**0.49 (0.38, 0.63)**	**0.38 (0.26, 0.55)**	0.66 (0.28, 1.57)	**0.48 (0.33, 0.71)**	**0.36 (0.20, 0.66)**	**0.33 (0.24, 0.47)**
2.09 (1.40, 3.13)	**1.66 (1.19, 2.31)**	**2.95 (2.03, 4.28)**	**2.88 (1.94, 4.30)**	**1.52 (1.31, 1.77)**	**2.44 (2.04, 2.92)**	**Ipilimumab CTLA-4**	0.78 (0.55, 1.11)	1.36 (0.60, 3.08)	0.99 (0.69, 1.42)	0.74 (0.41, 1.32)	**0.68 (0.50, 0.93)**
--	--	--	--	--	--	--	**Tremelimumab CTLA-4**	1.75 (0.72, 4.26)	1.27 (0.98, 1.64)	0.95 (0.56, 1.60)	0.88 (0.74, 1.04)
2.16 (1.22, 3.82)	**1.72 (1.02, 2.89)**	**3.05 (1.76, 5.28)**	**2.99 (1.69, 5.25)**	**1.57 (1.02, 2.42)**	**2.52 (1.62, 3.91)**	1.03 (0.69, 1.55)	--	**Ipilimumab + sargramostim CTLA-4 + Cytokine**	0.73 (0.30, 1.77)	0.54 (0.20, 1.48)	0.50 (0.21, 1.20)
2.51 (1.77, 3.57)	**2.00 (1.54, 2.59)**	**3.55 (2.59, 4.85)**	**3.47 (2.46, 4.89)**	**1.83 (1.35, 2.49)**	**2.93 (2.13, 4.05)**	1.2 (0.85, 1.69)	--	1.16 (0.69, 1.97)	**Ipilimumab + dacarbazine CTLA-4 + Chemo**	0.75 (0.44, 1.27)	**0.69 (0.57, 0.84)**
2.07 (1.21, 3.51)	**1.64 (1.02, 2.64)**	**2.91 (1.75, 4.84)**	**2.85 (1.68, 4.82)**	1.50 (0.91, 2.49)	**2.41 (1.44, 4.03)**	0.99 (0.58, 1.67)	--	0.95 (0.49, 1.85)	0.82 (0.50, 1.33)	**Selumetinib + dacarbazine MEK + Chemo**	0.93 (0.56, 1.52)
3.29 (2.46, 4.39)	**2.61 (2.19, 3.10)**	**4.63 (3.62, 5.92)**	**4.53 (3.42, 6.02)**	**2.39 (1.89, 3.03)**	**3.83 (2.96, 4.95)**	**1.57 (1.19, 2.08)**	--	1.52 (0.93, 2.49)	**1.31 (1.08, 1.59)**	**1.59 (1.02, 2.48)**	**Dacarbazine Chemo**
Progression-free survival											

Relative treatment effects for overall survival (above the diagonal) and progression-free survival (below the diagonal) are presented as hazard ratios with corresponding 95% credible intervals.
An OR $<$ 1 is indicative of a more favorable outcome.
All comparisons are read as row versus column.
Statistically important differences are bolded.

and dabrafenib, combination dabrafenib with trametinib and vemurafenib, combination nivolumab with ipilimumab and nivolumab or pembrolizumab, and dacarbazine and vemurafenib were statistically important based on only direct evidence. With the exception of combination nivolumab with ipilimumab compared to nivolumab or pembrolizumab, the direction and magnitude of estimated effects remained consistent.

Updated treatment class-level analyses

The updated fixed effects class-level NMAs (Table A.3) generally upheld the conclusions of the previously published treatment class-level analyses on PFS and OS. However, the incorporation of recently published OS data for combination nivolumab with ipilimumab (PD-1 + CTLA-4) suggested that this treatment class is statistically superior to every treatment class with respect to OS, with the exception of combination CTLA-4 with cytokine (HR 0.63, CrI 0.27, 1.49). Thus, combination PD-1 with CTLA-4 inhibitors was predicted to be the most preferred treatment class with respect to OS (SUCRA 98.1). With respect to PFS, combination BRAF with MEK inhibitors remained the most preferable treatment class in the network (SUCRA 97.6).

Discussion

Recent developments in targeted therapies and immune checkpoint inhibitors have led to a range of improved treatment options for patients with advanced melanoma. Consistent with our previous review and NMA, this analysis, based on individual treatments rather than on treatment class, supported the use of combination dabrafenib and trametinib (BRAF with MEK inhibitors) and combination nivolumab with ipilimumab (PD-1 with CTLA-4 inhibitors). Specifically, combination treatment with dabrafenib and trametinib was the preferred treatment for PFS while combination nivolumab with ipilimumab was the preferred option for OS. The efficacy profiles of the two combination BRAF with MEK inhibitor treatments were similar, both with respect to each other and with respect to other treatments. Across both PFS and OS, dacarbazine (chemotherapy) was likely to rank as the least preferred treatment option.

At the time of our original treatment class-based review and NMA, OS data for combination PD-1 with CTLA-4 inhibitors was unavailable. However, the updated review identified recently published OS data from the CheckMate-066 [26,33], CheckMate-067 [23,28,38], CheckMate-069 [12,21], and COMBI-d [27,29] trials. After incorporating these results in our NMA, we found that combination PD-1 with CTLA-4 inhibitors was statistically superior to every other treatment class, with the exception of combination CTLA-4 inhibitors with cytokine, with respect to OS.

Our analyses and conclusions are based on evidence retrieved through an extensive search of the literature, including a recent update (November 2018). The included trials are of high quality and are considered to carry a low risk of bias, as reported previously [16]. Similar inclusion criteria across the trials also added confidence in our ability to estimate comparisons across the network of evidence. However, few trials were identified in the evidence base, leading to a sparse network, with most treatment contrasts informed by a single trial. Additionally, the inclusion of some mixed-population trials, where results were not reported separately for BRAF-mutated and BRAF wild-type patients, may have introduced heterogeneity into the evidence base. The decision to include these trials was made in order to facilitate the development of a connected network that linked targeted therapies and immunotherapies and was supported by evidence suggesting that immunotherapies tend to demonstrate efficacy irrespective of BRAF mutation status [12,49,50]. The chance of heterogeneity from inclusion of mixed BRAF populations is reflected in subgroup analysis of the combination immune checkpoint inhibitor study CheckMate-067 [23,38], which raises the possibility of preferential benefit in the experimental arm for BRAF-mutated versus wild-type tumors. Yet, use of targeted therapies as front-line treatment of BRAF-mutated melanoma may be preferred for highly symptomatic patients with bulky metastasis [51]. Previously untreated patients included in the trials of immune checkpoint inhibitors may have been selected for more indolent disease, thus limiting the generalizability of our results in the BRAF-mutated population. Comparisons between the treatment class-level and individual treatment-level analyses may be inadvertently biased, as not all treatments could be included in both network scopes. However, the treatment class-level analysis was purposefully conducted based on all

available evidence to comprehensively reflect the evidence landscape. Future analyses may incorporate disconnected trials or observational evidence in the NMA [52,53]. Finally, the current analysis was based on relative treatment effects estimated on the constant, rather than time-varying, hazard ratio [17]. The limitations of this approach should be considered, such as the need to assume proportional hazards, and future investigations may examine the relative treatment effects of these interventions based on the shape and scale of their survival curves [54,55].

The evidence in favor of targeted therapies and immune checkpoint inhibitors to date is promising. For example, a pooled analysis of OS data from 10 prospective and two retrospective studies of ipilimumab found three-year survival rates of approximately 22% [56]. Similarly, in a phase I and II trial, BRAF inhibitor-naïve patients treated with dabrafenib 150 mg twice daily with trametinib 2 mg daily were found to have PFS rates over 20% after 3 years, with a median OS of more than 2 years [57]. The rapid response of targeted therapy is also attractive, particularly in the case of the patient with extensive tumor growth and a high symptom burden. However, the availability of these new treatment options necessitates clinicians and decision makers to gain a thorough understanding of the comparative clinical profiles. Thus, the intent of this treatment-level analysis was to further explore and describe the relative treatment effects of targeted therapies and immunotherapies. Based on our treatment-level analysis, combination BRAF with MEK inhibitor therapy (combination dabrafenib with trametinib; combination vemurafenib with cobimetinib) and combination PD-1 with CTLA-4 inhibitor therapy (combination nivolumab with ipilimumab) were associated with the most favorable outcomes with respect to PFS and OS, respectively. However, clinical decisions should also weight the toxicity profiles of available treatment options. While our understanding of the treatment landscape has evolved, the findings of our analysis are based on relatively few trials in a sparse network of evidence and thus should be interpreted with caution. Further research in the field of advanced melanoma, specifically in the context of emerging immunotherapies, is needed to reinforce these findings.

Funding

No funding was received for the purpose of this study.

Disclosure

The authors have declared no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2019.02.001.

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