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Systematic Review and Indirect Treatment Comparison of Dabrafenib and Trametinib versus Other Treatments Used in Previously Untreated Metastatic Melanoma Patients

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Abstract

Objectives: A systematic literature review was undertaken with quantitative analysis, including meta-analysis and Bucher-adjusted indirect treatment comparisons (ITCs), to evaluate efficacy, safety, and tolerability of dabrafenib and trametinib monotherapy versus other first-line metastatic melanoma (MM) treatments.

Methods: Embase®, MEDLINE®, CCTR, and key conferences were searched through October 2012 for relevant randomized controlled trials. Using a random-effects network meta-analysis, dabrafenib and trametinib were compared directly versus dacarbazine (DTIC) and indirectly versus ipilimumab plus DTIC, temozolomide, and vemurafenib. A Rank Preserving Structural Failure Time Method was used to adjust overall survival (OS) estimates in studies that allowed treatment crossover upon progression.

Results: Forty-eight studies (147 publications) met the inclusion criteria; five (2462 patients) contributed to the meta-analysis. Both dabrafenib and trametinib showed a significant reduction in risk of progression directly versus DTIC and indirectly versus ipilimumab plus DTIC and temozolomide; comparable progression-free survival (PFS) indirectly versus vemurafenib; and lower risk of death directly versus DTIC and indirectly versus ipilimumab plus DTIC and vemurafenib (not significant). Dabrafenib demonstrated a significantly reduced risk of treatment discontinuations (due to any cause and to adverse events [AEs]), significantly fewer grade 3/4 AEs versus ipilimumab plus DTIC, and a significantly lower risk of grade 3/4 hematologic AEs (leukopenia, neutropenia, and thrombocytopenia) versus temozolomide. Dabrafenib showed significantly fewer dose interruptions/modifications (risk ratio [RR]=0.18; 95% CI=0.12–0.28; $p<0.001$) and a significantly lower incidence of photosensitivity (RR=0.05; 95% CI=0.01–0.19; $p<0.001$) versus vemurafenib.

Conclusions: ITCs of dabrafenib or trametinib in treatment-naïve MM patients showed significantly better PFS directly versus DTIC and indirectly versus ipilimumab plus DTIC and temozolomide, with efficacy comparable with that of vemurafenib. Dabrafenib showed important differences in tolerability and safety versus vemurafenib. Results require cautious interpretation given methodological assumptions and immature OS data for dabrafenib and trametinib. Head-to-head studies remain the gold standard for comparing treatments.

Keywords: Systematic review; Dabrafenib; Trametinib; First-line treatment; Metastatic melanoma; Indirect treatment comparisons; Dacarbazine

Introduction

Although melanoma represents less than 3% to 5% of all skin cancers, the global incidence is increasing faster than any other cancer in the world [1]. Approximately 200,000 new cases and approximately 46,000 deaths from melanoma were estimated globally in 2008 [2]. Activating mutations in *BRAF*, a constituent of the MAP kinase signal-transduction pathway, are found in approximately 50% of patients with advanced melanoma [3,4]. The two most common *BRAF* mutations, V600E and V600K, account for 95% of all *BRAF* mutations in melanoma. BRAF activates MEK1 and MEK2—which in turn activate downstream MAP kinases—and regulates tumor-cell proliferation and survival in many cancers, including melanoma [5].

Current treatment options for patients with advanced or metastatic melanoma include chemotherapy, immunotherapy, targeted therapy, surgery, and radiation. Until 2011, dacarbazine (DTIC) was the only single-agent chemotherapy approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of metastatic melanoma. Therefore, DTIC has typically been used as the reference drug for the evaluation of the safety and efficacy of new treatment options in clinical trials [6]. Temozolomide is a derivative of DTIC and is approved only in Australia for the treatment of patients with metastatic melanoma [7] but it is widely used as a first-line treatment option for these patients in the United States (US) and Europe. Ipilimumab, a monoclonal antibody targeting cytotoxic

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T-lymphocyte-associated antigen 4, and vemurafenib, a selective BRAF inhibitor, were approved in the US and Europe in 2011/2012. Dabrafenib, another selective BRAF inhibitor, and trametinib, a highly selective allosteric inhibitor of MEK1 and MEK2, were both approved in the US and Canada in 2013 for unresectable or metastatic melanoma with a *BRAF* V600 mutation. Dabrafenib monotherapy was also recently approved in Europe and Australia for patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation. Subsequent to the conduct of this study, newer treatments have become available for the treatment of MM and include the combination of dabrafenib and trametinib and two human programmed death receptor-1 (PD-1) blocking antibodies, nivolumab and pembrolizumab. Additional novel antibodies targeting programmed death-ligand 1 (e.g., MEDI4736) are also currently in development for the treatment of MM.

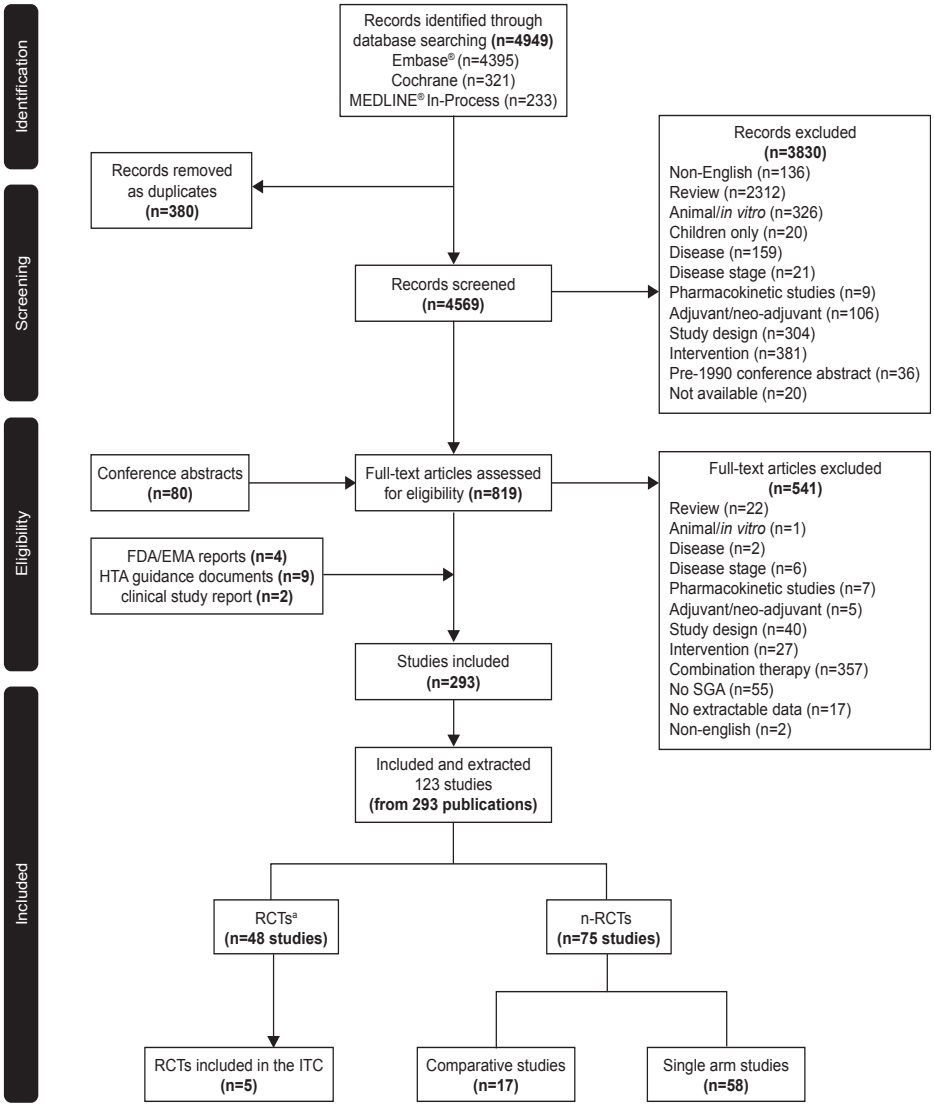
Most treatments approved for the treatment of MM have been evaluated against DTIC. In the absence of head-to-head trials of these treatments, comparative evidence from indirect treatment comparisons (ITCs) can be useful to guide the judicious selection of the most appropriate treatments. There are several statistical approaches to ITCs, both Bayesian and frequentist. One commonly used approach—the Bucher-adjusted ITC—makes use of the relative effects of two treatments to approximate their comparative efficacy via a common comparator arm [8].

The objective of this study was to systematically review the clinical literature and undertake a quantitative analysis, including meta-analysis and Bucher-adjusted ITCs, to evaluate the efficacy and safety of two recently approved treatments (dabrafenib and trametinib monotherapies) compared with other first-line treatments for patients with metastatic melanoma.

Methods

Literature searches and inclusion criteria

A protocol was prepared prior to conducting the systematic review. A comprehensive search strategy was designed to retrieve relevant clinical data from the published literature (Figure 1). Key biomedical



[a]One publication (Hill 1979) reported separate data for two trials (COG 7131 trial and COG 7131A trial), each was extracted as a separate study; EMA: European Medicines Agency; FDA: Food and Drug Administration; ITC: Indirect Treatment Comparison; nRCT: Non-Randomized Controlled Trial; RCT: Randomized Controlled Trial

Figure 1: Study identification, screening, and eligibility.

literature databases (MEDLINE® [US National Library of Medicine, Bethesda, MD, United States], Embase® [Elsevier, Philadelphia, PA, United States], and The Cochrane Library [The Cochrane Collaboration, Oxford, UK]) were searched from inception to October 22, 2012. MEDLINE® In-Process was also searched to ensure that non-indexed citations were retrieved. Additionally, proceedings from three conferences (American Society of Clinical Oncology, International Melanoma Congress presented by the Society for Melanoma Research, and European Society for Medical Oncology/European Cancer Organisation) from 2010 to 2012 were searched for abstracts to retrieve the latest studies, which had not yet been published in journals as full-text articles or to supplement results of previously published studies. Data reported in public assessment reports were searched from the EMA and FDA websites. Furthermore, Health Technology Assessment (HTA) guidance documents published in English were searched from the National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), Pan-Canadian Oncology Drug Review (PCODR), Pharmaceutical Benefits Advisory Committee (PBAC), Institute for Quality and Efficiency in Health Care (IQWiG), as well as the Agency for Healthcare Research and Quality (AHRQ). Clinicaltrials.gov and the Australian Clinical Trials Registry (www.actr.org.au) were also searched to identify trials in progress that were investigating the interventions of interest.

Search strategies (keywords) were developed specifically for each database and are provided in the S3 File. Randomized controlled trials (RCTs), non-randomized controlled trials, single-arm studies, and observational studies assessing the efficacy and safety of any first-line treatment for unresectable advanced or metastatic malignant melanoma (stage III or IV) were included in the review. Studies that enrolled a mixed population of stage I, II, III, and IV melanoma were included only if there was a subgroup analysis on the stage III or IV patient population. Included studies were classified according to line of therapy when the full publication was being screened. Studies that assessed patients receiving third-line therapies or above were excluded. Interventions included in the review were dabrafenib, trametinib, DTIC, ipilimumab, vemurafenib, fotemustine, and temozolomide. Key outcome measures included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), complete response (CR), and adverse events (AEs). Additional searches for relevant studies included references cited within the retrieved articles and systematic reviews, Google, and the websites of licensing agencies and HTA agencies.

Trial selection, quality assessment, and data extraction

Trials had to meet predefined eligibility criteria to be included in the review. Retrieved citations were initially screened for inclusion based on their title and abstract. Full-text copies were obtained for those that met the inclusion criteria and for studies in which it was unclear, on the basis of the abstract alone, whether the inclusion criteria were met or not. Screening was conducted by two independent reviewers, and any discrepancies between reviewers were reconciled by a third independent reviewer. Studies that met the eligibility criteria at the second screening stage were extracted in parallel by two independent reviewers, and any discrepancies were reconciled by a third reviewer. When more than one publication was identified describing a single trial, the data were compiled into a single entry in the data extraction table. The data extracted from the included RCTs were quantitatively analyzed (direct and network meta-analysis), whereas evidence from non-randomized controlled trials was qualitatively discussed. A critical appraisal of all included studies was conducted using comprehensive assessment criteria based on the recommendations in the NICE Single Technology Appraisal guidelines [9] and is presented in the S4 File. The quality of the included RCTs was assessed by means of a Jadad score [10]. This article is limited to the evidence obtained from RCTs.

Statistical analyses

Direct comparisons and meta-analysis: A meta-analysis was conducted of studies that compared the same treatment groups for common outcomes (e.g., same treatments compared in multiple studies or with different dosages). Only licensed doses of the interventions from the EMA, PBAC, or FDA were included in the analyses. All doses within the licensed range for a particular intervention were pooled as one treatment group for that intervention. The meta-analyses were conducted using Stata statistical software (METAN command; StatCorp, College Station, TX, United States). The reported outputs included both fixed- and random-effects model results, risk ratios (RRs) for dichotomous outcomes and their 95% CIs, hazard ratios (HRs) for continuous outcomes and their 95% CIs, and I^2—an indicator of observed heterogeneity. The fixed-effects model used the Mantel–Haenszel method [11], whereas the random-effects model used the DerSimonian and Laird approach [12]. The key assumption of a fixed-effects model is that one true effect size underlies all studies in the analysis. The key assumption of a random-effects model is that the effect sizes measurable in each pooled study are different but exchangeable.

Indirect treatment comparisons: The network diagram of first-line metastatic melanoma treatments, identified by the systematic review (Figure 2), highlights that several ITCs are possible with DTIC as a comparator, because it was common to each trial. Adjusted ITCs were performed according to the method of Bucher et al [13]. This method relies on the fact that the log of the effect size measure for drug A versus drug B is equal to the difference between the log effect size measures for drug A versus drug C and drug B versus drug C. This holds true for both dichotomous outcomes, for which RRs can be used as the effect size measure, and for time to event outcomes, for which HRs can be used as the effect size measure. The inputs in indirect analyses are the results from direct meta-analyses using the

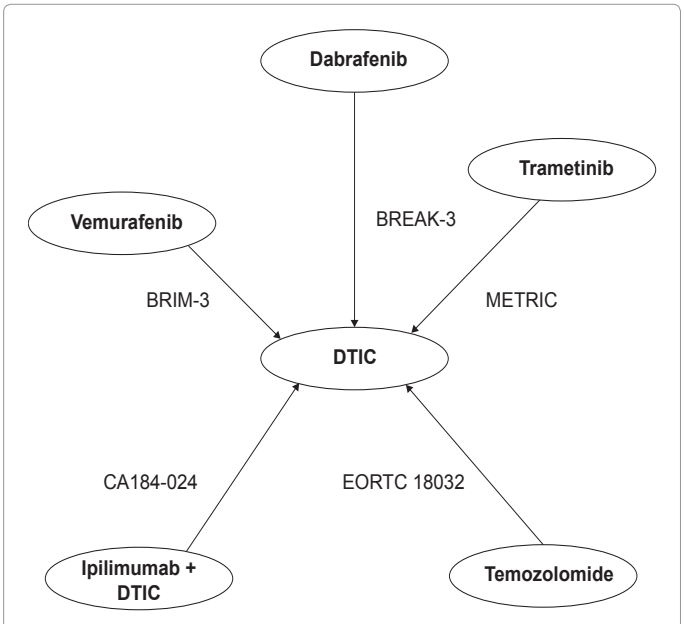


Figure 2: Network of available comparisons.

random-effects model. When a comparison between two drugs is made indirectly, this is judged to add an additional element of heterogeneity to the analysis. For this reason, inputs from the random-effects model are considered to be more suitable for use in indirect analyses. For safety and tolerability outcomes, the indirect comparisons were performed using two approaches: one based on the intention-to-treat population and the other based on the safety population.

Results

Study identification, screening, and eligibility

Figure 1 illustrates the inclusion and exclusion criteria of studies for the full review. The literature search yielded 4949 references—4569 after duplicates were removed. The abstracts of the studies were screened according to the criteria shown in Table 1. Of the 819 full-text reports of relevant citations (including 80 identified from the conference searches), 541 citations were excluded, which left a total of 293 studies that met the review's first-pass inclusion criteria (including nine studies identified in an HTA guidance document search, four from a public assessment reports search, and two clinical study reports provided by GlaxoSmithKline (GSK) [BREAK-3 and METRIC studies]). There were multiple publications per trial (one publication [14] reported two separate studies), and data from 123 studies (reported in 293 publications) were eventually extracted. Of these, 48 studies were RCTs (reported in 147 publications).

Treatment strategies and responses to treatment varied depending on the prior treatments received by the patients; therefore, all included RCTs were divided into four categories: treatment-naive (24 studies) [15-38], pre-treated (two studies) [39,40], mixed-therapy line (nine studies) [41-49], and therapy line unclear (11 studies) [14,50-58]. An additional two studies reported subgroup data for both the treatment-naive and the pre-treated groups, and data for both categories were extracted separately [59,60]. Because dabrafenib was assessed in treatment-naive patents and trametinib in treatment-naive and pre-treated patients, only studies with these two categories were included in the larger ITC.

The first part of this review presents the random-effects network meta-analysis, which directly compares efficacy outcomes of dabrafenib and trametinib monotherapy versus DTIC as well as of ipilimumab plus DTIC, temozolomide, and vemurafenib versus DTIC. The remainder of this article reports the ITC results using RCTs in the treatment-naive metastatic melanoma patient population for the newer melanoma treatments (dabrafenib, trametinib, vemurafenib, and ipilimumab plus

Criteria	Parameters	Rationale
Inclusion criteria	**Population** • Age: adults (≥ 18 years or ≥ 16 years if defined by author) • Sex: any • Race: any • Disease: advanced or metastatic malignant melanoma	• Mean age of diagnosis is 50 years. Approximately 20% of melanoma cases occur in young adults aged 15 to 39 years • Melanoma can occur in both men and women, although men are at a higher risk • Clinical trials and other studies usually enroll participants of all races to have a sample population representative of the larger population and to reduce bias. Patients with other types of skin cancers (non-melanoma skin cancers), such as basal cell and squamous-cell cancers, Kaposi sarcoma, and lymphoma of the skin, were not included
	Intervention • Dabrafenib (GSK2118436) • Trametinib (GSK1120212) • Ipilimumab • Vemurafenib • Dacarbazine or DTIC • Fotemustine	• The interventions listed were included as both monotherapy and combination therapy • These interventions were identified from clinical practices or ongoing clinical trials for the treatment of metastatic malignant melanoma
	Comparator • Any treatment from the above mentioned included list of interventions • Placebo or best supportive care • Any other chemotherapy • Any immunotherapy	• These comparators were selected to potentially enable both direct and indirect treatment comparisons between the interventions of interest
	Study design • RCTs with any blinding status • nRCTs • Observational studies • Single-arm studies	• RCTs are the gold standard of clinical evidence, minimizing the risk of confounding and allowing the comparison of the relative efficacy of interventions. To enhance the level of evidence, studies with double-blind, single-blind, and open-label designs were included • Apart from providing long-term benefit data, nRCTs will supplement evidence provided by RCTs. Observational studies include wider patient populations and present real-life effectiveness data
	Language restrictions • English only	• The restriction does not limit results substantially due to data availability provided in English
	Publication time frame • 1960 to October 22, 2012 for literature searches • 2010 to 2012 for conference searching	• Studies presented at conferences are usually published in journals within three years
Exclusion criteria	• No subgroup analysis for the disease or intervention of interest • Conference abstracts published before 1990	• Studies with no subgroup data for the disease were not included, because these studies could introduce heterogeneity into the review. Studies that enrolled a mixed population of stage I, II, III, and IV melanoma will be included only if there is a subgroup analysis of the stage III or IV patient population • Studies presented in very old conferences would have been published in journals as full-text articles and would have been retrieved from our searches
nRCT: non-Randomized Controlled Trial; RCT: Randomized Controlled Trial		

Table 1: Inclusion and exclusion criteria for systematic review.

DTIC), the previously approved single-agent chemotherapy (DTIC), and the derivative of DTIC (temozolomide). This included five studies that assessed treatment-naive patients with metastatic melanoma [22-25,60], which could be indirectly compared via DTIC as the common comparator (Figure 2).

Main characteristics and outcomes of included studies

Table 2 presents the main characteristics and outcomes of the five studies (totaling 2462 patients) included in the ITC. All studies compared against the 1000 mg/m^2 every three weeks (q3w) dose for DTIC except for the CA184-024 study, which used the 850 mg/m^2 q3w dose for both the ipilimumab plus DTIC and the DTIC arm. The METRIC study included paclitaxel as a comparator; however, the majority (86%) of patients in the treatment-naive subgroup, the focus of this ITC, received DTIC. In addition, demographic data for this trial were reported for the overall patient population and not for the subgroup population (treatment-naive or pre-treated).

	BREAK-3 [22,64]	**METRIC [60]**	**BRIM-3 [23,63]**	**CA184-024 [24]**	**EORTC 18032 [25]**
Comparison	Dabrafenib 150 mg bid vs DTIC 1000 mg/m^2 q3w	Trametinib 2 mg qd vs chemotherapy (DTIC 1000 mg/m^2 q3w or paclitaxel)	Vemurafenib 960 mg bid vs DTIC 1000 mg/m^2 q3w	DTIC 850 mg/m^2 q3w+ipilimumab 10 mg/kg q3w for 4 cycles vs DTIC 850 mg/m^2 q3w	Temozolomide 150 mg/m^2 od on days 1 to 7 q2w vs DTIC 1000 mg/m^2 q3w
Design	Multinational, multicenter, open-label, phase III RCT	Multinational, multicenter, open-label, phase III RCT	Multinational, multicenter, open-label, phase III RCT	Multinational, multicenter, double-blind, phase III RCT	Multinational, multicenter, open-label, phase III RCT
Number of patients	250 (dabrafenib: 187; DTIC: 63)	322 (trametinib: 214; chemotherapy: 108)	675 (vemurafenib: 337; DTIC: 338)	502 (ipilimumab+DTIC: 250; DTIC: 252)	859 (temozolomide: 429; DTIC: 430)
Inclusion criteria	• Patients aged ≥ 18 years, histologically confirmed advanced (unresectable stage III) or metastatic (stage IV) measurable disease according to RECIST Version 1.1 • *BRAF* V600E mutation–positive melanoma • ECOG PS 0-1	• Patients with histologically confirmed cutaneous advanced or metastatic melanoma (stage IIIC or stage IV) • *BRAF* V600E/K mutation–positive tumor • Subjects may have received no prior treatment or up to one prior regimen of chemotherapy for advanced or metastatic melanoma with measurable disease according to RECIST Version 1.1 • ECOG PS 0-1	• Patients aged ≥ 18 years, with unresectable, stage IIIC or stage IV melanoma • Positive for the *BRAF* V600E mutation on real-time polymerase chain reaction assay • ECOG PS 0-1 • Life expectancy of ≥ 3 months • Adequate hematologic, hepatic, and renal function	• Patients aged ≥ 18 years with previously untreated stage III (unresectable) or stage IV melanoma with measurable lesions • ECOG PS 0-1 • Life expectancy ≥ 16 weeks • Baseline serum lactate dehydrogenase level did not affect eligibility	• Patients aged ≥ 18 years with histologically confirmed, surgically incurable, or unresectable AJCC stage IV melanoma • WHO or ECOG status 0–1 • Adequate hematologic, renal, and hepatic function • Previous adjuvant cytokine or vaccine therapy for resected stage I to III disease, palliative surgery for distant metastatic disease, previous vaccine therapy (other than cytokine) for stage IV disease, and prior cytokine or chemotherapy for local–regional disease by isolated limb perfusion therapy • Recovered from any effects of major surgery or previous adjuvant treatment • Patients with cutaneous and mucosal melanoma allowed
Data cuts available/used	December 2011 (primary analysis) June 2012 (updated analyses) December 2012 (updated analyses for OS and AEs only)	October 2011 (primary analysis)	December 2010 (primary analysis) February 2012 (updated analyses for PFS and OS)	Unknown	Unknown
Primary study outcome(s)	PFS	PFS	PFS and OS	OS	OS
Median age, years (range)	Dabrafenib 53.0 (22–93); DTIC 50.0 (21–82)	Trametinib 54.5 (23–85); Chemotherapy 54.0 (21–77)	Vemurafenib 56.0 (21–86); DTIC 52.0 (17–86)	Ipilimumab+DTIC 57.5[a]; DTIC 56.4[a]	-
Males, %	59.6	53.7	56.4	60.0	58.6
ECOG, %					
0	67.2	63.7	68.0	70.9	69.4
1	31.2	36.3	32.0	29.1	30.6
Unknown	1.6				
***BRAF* V600E mutation, %**	100	87.3	88.6	Unknown	Unknown
Crossover allowed	Yes	Yes	Yes	No	No
Outcome assessor	Investigator and IRC	Investigator and IRC	Investigator and IRC	IRC[b]	Unknown

Frequency of response assessment	Weeks 6 and 12 and then every 9 weeks	Weeks 6, 12, 21, and 30 and then every 12 weeks	Weeks 6 and 12 and then every 9 weeks	Week 12; in patients with no disease progression, then at weeks 16, 20, and 24 and every 6 weeks through week 48 and then every 12 weeks	Every 9 weeks
PFS, median and HR (95% CI)	• 5.1 vs 2.7 months; 0.30 (0.18–0.51) (December 2011 data) • 6.9 vs 2.7 months; 0.37 (0.24–0.58) (June 2012 data)	• 4.8 vs 1.5 months; 0.45 (0.33–0.63) (ITT) • 4.8 vs 1.4 months; 0.44 (0.31–0.64)[c] • 4.8 vs 1.4 months; 0.44 (0.28–0.69)[d]	• 5.3 vs 1.6 months; 0.26 (0.20–0.33) (December 2010 data) • 6.9 vs 1.6 months; 0.38 (0.32–0.46)	• 0.76 (0.63–0.93)	• 2.3 vs 2.2 months; 0.92 (0.80–1.06)
OS,[e] HR (95% CI), % crossover	• 0.61 (0.25–1.48) (Dec. 2011 data) (44%) • 0.75 (0.44–1.29) (June 2012 data) (56%) • 0.76 (0.48–1.21 (Dec. 2012 data) (57%)	• 0.54 (0.32–0.92) (ITT) (47%) • 0.53 (0.30–0.94) (50%)[c] • 0.55 (0.26–1.13) (53%)[d]	• 0.37 (0.26–0.55) (Dec. 2010 data) (0%) • 0.76 (0.63–0.93) (Feb. 2012 data) (34%)	• 0.72 (0.59–0.87)	• 1.00 (0.86–1.17)
Key AEs, %	Dabrafenib vs DTIC: grade 2 or higher (hyperkeratosis 1% vs 0%, palmar-plantar erythrodysesthesia 8% vs 0%, SCC/ keratoacanthomas 6% vs 0%, neutropenia <1% vs 15%, nausea 1% vs 14%, pyrexia 11% vs 0%, arthralgia 6% vs 0%, fatigue 6% vs 5%)	Trametinib vs chemotherapy: grade 2 or higher (rash 27% vs 3%, fatigue 9% vs 10%, diarrhea 6% vs 5%, dermatitis 10% vs 0%, nausea 3% vs 11%, hypertension 15% vs 6%, peripheral edema 5% vs 0%, alopecia 2% vs 8%, constipation 1% vs 6%)	Vemurafenib vs DTIC: grade 2 or higher (arthralgia 21% vs 1%, rash 18% vs 0%, fatigue 13% vs 13%, cutaneous SCC 12% vs < 1%, keratoacanthomas 8% vs 0%, nausea 8% vs 13%, alopecia 8% vs 0%; pruritus 7% vs 0%, hyperkeratosis 6% vs 0%)	Ipilimumab+DTIC vs DTIC: all grades (elevation of alanine aminotransferase levels 33.2% vs 5.6%, elevation of aspartate aminotransferase levels 29.1% vs 5.6%, diarrhea 36.4% vs 24.7%, pruritus 29.6% vs 8.8%, rash 24.7% vs 6.8%)	Temozolomide vs DTIC: grade 3/4 (lymphopenia 45% vs 9%, thrombocytopenia 11% vs 6%, neutropenia 10% vs 16%, leukopenia 9% vs 8%, fatigue 6% vs 5%)

AE: Adverse Event; AJCC : American Joint Committee on Cancer; bid: twice per day; DTIC : Dacarbazine; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: Hazard Ratio; IRC: Independent Review Committee; ITT: Intention-to-treat; OS: Overall Survival; PFS: Progression-Free Survival; q3w: every three weeks; qd: every day; RCT: Randomized Controlled Trial; RECIST : Response Evaluation Criteria in Solid Tumors; SCC: Squamous Cell Carcinoma; WHO: World Health Organization

[a]Mean; [b]For all efficacy outcomes except survival; [c]Primary efficacy population (overall); [d]Primary efficacy population (first-line subgroup); [e]Reported HRs for OS not adjusted for crossover.

Table 2: Main characteristics and outcomes of included trials.

The studies varied widely in terms of the number of patients included, ranging from 250 [22] to 859 [25] (Table 2). The median or mean age reported in the studies ranged from 53.0 to 57.5 years, and the proportion of males with metastatic malignant melanoma among the included RCTs ranged from 53.7% [60,61] to 60.0% [24]. The Eastern Cooperative Oncology Group (ECOG) performance status in all studies was 0 or 1 at baseline (the BREAK-3 study also included 1.6% patients with an unknown ECOG status), which implied that the majority of patients in the included studies were completely ambulatory. Three of the five studies (BREAK-3, METRIC, and BRIM-3) included *BRAF* mutation–positive patients; in all studies, >80% of the patients had a V600E *BRAF* mutation [22,23,60] (Table 2).

BREAK-3, METRIC, and BRIM-3 also allowed for treatment crossover upon progression [22,23,60]. To adjust for confounding effects of treatment crossover on OS, the GSK trials (BREAK-3 [22] and METRIC [60]) used a randomization-based crossover method—the Rank Preserving Structural Failure Time Model (RPSFTM). Furthermore, considering different assumptions regarding the durability of treatment effect, results based on the 'on-treatment observed analysis' approach is presented here. This analysis estimated the treatment effect of the observed experimental group treatment compared with no treatment under the assumption that the treatment effect disappears upon treatment discontinuation [6,62]. In the BRIM-3 study [23], crossover from DTIC to vemurafenib was recommended after review of the interim analysis by an independent data and safety monitoring board. The RPSFTM method was also used to adjust for crossover in the BRIM study [63]. The most recent data for the PFS and OS endpoints were used for all studies (Table 2). The ITC used OS data that had been adjusted for crossover for all three studies (N. Latimer, personal communications; [63]). The most current/updated data were also evaluated for safety and tolerability outcomes (Table 2).

Direct comparisons

The direct comparisons versus DTIC for the efficacy outcomes for each of the five studies are presented in Table 3. The direct comparisons for the safety and tolerability outcomes are not presented because they have been described in detail within each publication [16-22].

Both dabrafenib and trametinib were associated with a significantly lower risk of progression compared with DTIC ($p<0.0001$). Other interventions, such as vemurafenib and DTIC plus ipilimumab, also showed a significant reduction in tumor progression over DTIC. Temozolomide showed a reduced risk of progression compared with DTIC, although the difference was not significant.

Progression-free survival						
Intervention	**Comparator**	**HR**	**95% CI**	**ln(HR)**	**SE**	***p* value**
Dabrafenib	DTIC	0.37[b]	0.24–0.58	–0.99	0.23	<0.0001
Trametinib		0.44[b]	0.28–0.69	–0.82	0.23	<0.0001
Vemurafenib		0.38[b]	0.32–0.46	–0.97	0.09	<0.001
Ipilimumab+DTIC[a,c]		0.76[b]	0.63–0.93	–0.27	0.10	0.01
Temozolomide[c]		0.92[b]	0.80–1.06	–0.08	0.07	0.27
Overall survival						
Intervention	**Comparison**	**HR**	**95% CI**	**ln(HR)**	**SE**	***p* value**
Dabrafenib[d]	DTIC	0.55[e]	0.21–1.43	–0.60	0.49	-
Trametinib[d]		0.56[e]	0.30–1.05	–0.58	0.32	-
Vemurafenib[f]		0.64[e]	0.53–0.78	–0.45	0.10	<0.0001
Ipilimumab+DTIC[g]		0.72[e]	0.59–0.87	–0.33	0.10	<0.001
Temozolomide[h]		1.00[e]	0.86–1.17	0.00	0.08	0.99
Overall response rate						
Intervention	**Comparison**	**RR**	**95% CI low**	**ln(RR)**	**SE**	***p* value**
Dabrafenib	DTIC	2.47	1.56–3.91	0.90	0.23	< 0.001
Trametinib		2.10	0.97–4.54	0.74	0.39	0.06
Vemurafenib		6.64	4.63–9.52	1.89	0.18	<0.001
Ipilimumab+DTIC		1.47	0.92–2.35	0.39	0.24	0.10
Temozolomide		1.53	1.04–2.25	0.43	0.20	0.03
Complete response						
Intervention	**Comparison**	**RR**	**95% CI low**	**ln(RR)**	**SE**	***p* value**
Dabrafenib	DTIC	1.43	0.50–4.10	0.36	0.54	0.50
Trametinib		3.84	0.20–73.06	1.34	1.50	0.37
Vemurafenib		4.76	1.64–13.86	1.56	0.54	0.004
Ipilimumab+DTIC		2.02	0.37–10.91	0.70	0.86	0.42
Temozolomide		2.01	0.61–6.61	0.70	0.61	0.25

DTIC: Dacarbazine; HR: Hazard Ratio; RPSFTM: Rank Preserving Structural Failure Time Model; RR: Risk Ratio; SE: Standard Error.
[a]PFS assessed by an Independent Review Committee; [b]Hazard ratios are used as reported in the study publications; [c]Adjusted HR reported in the study; [d]RPSFTM "on-treatment observed" analysis, adjusted for crossover; [e]Adjusted HR; [f]RPSFT analysis, adjusted for crossover; [g]HR adjusted for metastasis stage and performance status; [h]HR stratified for the initial performance status. HR confidence intervals estimated using log-rank test.

Table 3: Direct comparisons of efficacy outcomes[a].

Dabrafenib was associated with a lower hazard of death compared with DTIC; however, the differences were not statistically significant ($p>0.05$). Although trametinib showed a significantly lower hazard of death compared with DTIC for the overall study population, there was a lower but non-significant hazard of death for the population of interest in this article (i.e., treatment-naive subgroup). Of the other interventions assessed, vemurafenib and DTIC plus ipilimumab were associated with a significantly reduced risk of death in comparison with DTIC. Comparable efficacy of temozolomide was demonstrated relative to DTIC for OS.

Dabrafenib demonstrated a significantly higher ORR compared with DTIC ($p<0.001$). A higher response rate was also observed for trametinib when compared with DTIC, but the treatment difference was not statistically significant ($p=0.06$). Of the other interventions assessed, vemurafenib and temozolomide also showed a significantly higher ORR compared with DTIC. DTIC plus ipilimumab showed a higher ORR compared with DTIC ($p=0.10$), although the difference was not significant. Both dabrafenib and trametinib demonstrated a numerically higher CR compared with DTIC, but the treatment differences were not statistically significant ($p=0.50$ and $p=0.37$, respectively). Of the other interventions assessed, vemurafenib, temozolomide, and DTIC plus ipilimumab also showed a higher CR compared with DTIC; however, the difference approached statistical significance only with vemurafenib ($p=0.004$).

Indirect comparisons for efficacy outcomes

The ITCs of dabrafenib and trametinib versus other interventions via the common DTIC comparator are presented in Table 4. Monotherapy with trametinib or dabrafenib was associated with a significantly lower risk of progression when indirectly compared with DTIC plus ipilimumab and with temozolomide ($p \leq 0.05$). Dabrafenib also showed a comparable but numerically lower risk of progression indirectly versus vemurafenib, although the difference was not statistically significant. In contrast, trametinib showed a higher but statistically non-significant risk of progression indirectly versus dabrafenib and vemurafenib.

Both dabrafenib and trametinib were associated with a reduced risk of death compared with vemurafenib, DTIC plus ipilimumab, and temozolomide; however, treatment differences were not statistically significant. Trametinib was associated with an increased but statistically non-significant risk of death when indirectly compared with dabrafenib.

In addition, monotherapy with dabrafenib or trametinib showed improved ORRs over DTIC plus ipilimumab and temozolomide, although the differences were not statistically significant. Vemurafenib showed statistically significantly greater ORRs than did either dabrafenib or trametinib monotherapy, whereas trametinib monotherapy showed a lower but statistically non-significant ORR versus dabrafenib. Dabrafenib exhibited a lower CR rate compared with vemurafenib, DTIC plus ipilimumab, and temozolomide, although

	Comparison	HR	95% CI low	ln(HR)	SE	*p* value
Outcome	**Dabrafenib vs**					
PFS	Vemurafenib	0.97	0.60–1.57	−0.03	0.24	0.91
	Ipilimumab+DTIC	**0.49**	**0.30–0.79**	**−0.71**	**0.25**	**0.003**
	Temozolomide	**0.40**	**0.25–0.64**	**−0.92**	**0.24**	**0.0001**
OS	Vemurafenib	0.86	0.32–2.29	−0.15	0.50	0.76
	Ipilimumab+DTIC	0.76	0.29–2.03	−0.27	0.50	0.59
	Temozolomide	0.55	0.21–1.45	−0.60	0.49	0.23
	Trametinib vs					
PFS	Vemurafenib	1.16	0.71–1.88	0.15	0.25	0.55
	Ipilimumab+DTIC	**0.58**	**0.35–0.95**	**−0.54**	**0.25**	**0.03**
	Temozolomide	**0.48**	**0.30–0.77**	**−0.74**	**0.24**	**0.00**
	Dabrafenib	1.19	0.63–2.23	0.17	0.32	0.59
OS	Vemurafenib	0.88	0.45–1.69	−0.13	0.33	0.69
	Ipilimumab+DTIC	0.78	0.40–1.50	−0.25	0.33	0.45
	Temozolomide	0.56	0.29–1.07	−0.58	0.33	0.08
	Dabrafenib	1.02	0.32–3.20	0.02	0.58	0.98
	Comparison	**RR**	**95% CI low**	**ln(RR)**	**SE**	***p* value**
	Dabrafenib vs					
ORR	Vemurafenib	**0.37**	**0.21–0.67**	**−0.99**	**0.30**	**0.001**
	Ipilimumab+DTIC	1.68	0.87–3.23	0.52	0.34	0.12
	Temozolomide	1.62	0.89–2.94	0.48	0.30	0.12
CR	Vemurafenib	0.30	0.07–1.35	−1.20	0.75	0.12
	Ipilimumab+DTIC	0.71	0.10–5.19	−0.34	1.01	0.74
	Temozolomide	0.71	0.15–3.50	−0.34	0.81	0.68
	Trametinib vs					
ORR	Vemurafenib	**0.32**	**0.13–0.74**	**−1.15**	**0.43**	**0.01**
	Ipilimumab+DTIC	1.42	0.58–3.51	0.35	0.46	0.44
	Temozolomide	1.37	0.58–3.25	0.31	0.44	0.47
	Dabrafenib	0.85	0.35–2.08	−0.16	0.46	0.72
CR	Vemurafenib	0.80	0.04–18.51	−0.22	1.60	0.89
	Ipilimumab+DTIC	1.90	0.06–57.02	0.64	1.75	0.71
	Temozolomide	1.91	0.08–46.00	0.65	1.62	0.69
	Dabrafenib	2.68	0.12–61.25	0.99	1.60	0.54

DTIC: Dacarbazine; HR: Hazard Ratio; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; RR: Risk Ratio; SE: Standard Error
[a]For PFS, June 2012 data for BREAK-3, October 2011 data for METRIC, and February 2012 data for BRIM-3 were used; for OS, December 2012 data for BREAK-3, October 2011 data for METRIC, and February 2012 data for BRIM-3, all adjusted for crossover were used. HRs and RRs <1 indicate a lower risk/incidence in favor of dabrafenib or trametinib versus the comparator.

Table 4: Indirect treatment comparisons for efficacy outcomes via common comparator (DTIC)[a].

the differences were not statistically significant. Trametinib was associated with a numerically higher CR rate compared with DTIC plus ipilimumab, temozolomide, and dabrafenib; however, the differences were not statistically significant. In comparison with vemurafenib, trametinib showed a lower CR rate; however, this difference was also not statistically significant.

Indirect comparisons for tolerability and safety outcomes

The METRIC (trametinib) study included a mixed patient population (both treatment-naive and pre-treated populations); however, unlike efficacy outcomes, AE data were not reported separately for treatment-naive patients. Direct comparison with DTIC and indirect comparisons with other comparators are therefore not possible in this subgroup. Hence, only indirect comparisons for dabrafenib versus the other interventions based on the safety population are presented in Table 5.

The ITC of dabrafenib with other interventions, via the common DTIC comparator, demonstrated a significantly reduced risk of treatment discontinuations due to any cause with dabrafenib than with DTIC plus ipilimumab and temozolomide ($p<0.05$) and a significantly reduced risk of treatment discontinuations due to AEs with dabrafenib than with DTIC plus ipilimumab ($p<0.05$). When compared with vemurafenib, dabrafenib had a lower risk of treatment discontinuations due to AEs but a higher risk of treatment discontinuations due to any cause, although neither of these results was statistically significant.

There were significantly fewer dose interruptions/modifications (RR=0.18; 95% CI=0.12–0.28; $p<0.001$) for dabrafenib when indirectly compared with vemurafenib. Additionally, dabrafenib had significantly fewer grade 3/4 AEs when indirectly compared with DTIC plus ipilimumab (RR=0.49; 95% CI=0.32–0.73; $p=0.0006$).

For those specific AEs that could be compared indirectly, dabrafenib had a statistically non-significant increased risk of any-grade arthralgia, constipation, headache, neutropenia, pyrexia, and vomiting versus vemurafenib. Dabrafenib was associated with a statistically significantly lower incidence of photosensitivity (RR=0.05; 95% CI=0.01–0.19; $p<0.001$) versus vemurafenib. Compared with vemurafenib, dabrafenib also had a statistically non-significant ($p>0.05$) reduced risk of all-grade anemia, cutaneous squamous-cell carcinoma (SCC), appetite

	Comparison	RR	95% CI low	ln(RR)	SE	*p* value
Tolerability outcomes						
Treatment discontinuations due to any cause	Vemurafenib	1.15	0.88–1.51	0.14	0.14	0.33
	Ipilimumab+DTIC	**0.56**	**0.45–0.70**	**–0.58**	**0.11**	**<0.0001**
	Temozolomide	**0.54**	**0.44–0.68**	**–0.61**	**0.11**	**<0.0001**
Treatment discontinuations due to adverse events	Vemurafenib	0.75	0.12–4.57	–0.29	0.92	0.76
	Ipilimumab+DTIC	**0.16**	**0.03–0.87**	**–1.81**	**0.85**	**0.03**
	Temozolomide	**0.13**	**0.02–0.77**	**–2.01**	**0.89**	**0.02**
Safety outcomes						
General						
Any adverse events	Vemurafenib	0.98	0.90–1.07	–0.02	0.04	0.65
	Ipilimumab+DTIC	1.01	0.93–1.09	0.01	0.04	0.80
Any serious adverse events	Vemurafenib	0.60	0.33–1.09	–0.51	0.30	0.10
Any treatment-related adverse events	Vemurafenib	0.88	0.73–1.05	–0.13	0.09	0.16
Any treatment-related serious adverse events	Vemurafenib	0.90	0.20–4.03	–0.11	0.77	0.89
Any grade 3/4 adverse events	Ipilimumab+DTIC	**0.49**	**0.32–0.73**	**–0.72**	**0.21**	**0.0006**
	Temozolomide	0.83	0.56–1.23	–0.19	0.20	0.35
Adverse events leading to death	Vemurafenib	2.65	0.11–61.66	0.97	1.60	0.54
	Temozolomide	2.60	0.11–60.15	0.96	1.60	0.55
Any dose interruptions/modifications	Vemurafenib	**0.18**	**0.12–0.28**	**–1.71**	**0.22**	**<0.001**
All grades						
Anemia	Vemurafenib	0.41	0.13–1.26	–0.89	0.57	0.12
Arthralgia/joint pain	Vemurafenib	1.33	0.17–10.44	0.29	1.05	0.79
Constipation	Vemurafenib	2.22	1.00–4.95	0.80	0.41	0.05
	Ipilimumab+DTIC	0.90	0.42–1.91	–0.11	0.38	0.78
Cutaneous squamous cell carcinoma	Vemurafenib	0.26	0.01–7.97	–1.35	1.75	0.44
Decreased appetite	Vemurafenib	0.52	0.19–1.40	–0.65	0.50	0.20
	Ipilimumab+DTIC	0.99	0.39–2.49	–0.01	0.47	0.98
Diarrhea	Vemurafenib	0.59	0.25–1.39	–0.53	0.44	0.23
	Ipilimumab+DTIC	0.82	0.36–1.88	–0.19	0.42	0.65
Fatigue	Vemurafenib	0.90	0.50–1.60	–0.11	0.29	0.72
	Ipilimumab+DTIC	0.91	0.51–1.60	–0.10	0.29	0.74
Headache	Vemurafenib	1.79	0.69–4.67	0.58	0.49	0.23
	Ipilimumab+DTIC	**3.38**	**1.29–8.83**	**1.22**	**0.49**	**0.01**
Hyperproliferative skin lesions/hyperkeratosis	Vemurafenib	0.20	0.01–6.06	–1.61	1.73	0.36
Nausea	Vemurafenib	0.73	0.49–1.08	–0.31	0.20	0.12
	Ipilimumab+DTIC	**0.54**	**0.37–0.79**	**–0.62**	**0.19**	**0.0014**
Neutropenia	Vemurafenib	3.20	0.51–20.12	1.16	0.94	0.22
Palmar-plantar erythrodysesthesia syndrome	Vemurafenib	0.65	0.04–10.71	–0.43	1.43	0.76
Photosensitivity/phototoxicity	Vemurafenib	**0.05**	**0.01–0.19**	**–3.00**	**0.73**	**<0.001**
Pyrexia/fever	Vemurafenib	1.18	0.52–2.64	0.17	0.41	0.69
	Ipilimumab+DTIC	0.58	0.26–1.29	–0.55	0.41	0.18
Rash	Vemurafenib	0.67	0.03–13.44	–0.40	1.53	0.79
	Ipilimumab+DTIC	6.21	0.37–104.49	1.83	1.44	0.20
Thrombocytopenia	Vemurafenib	0.50	0.09–2.81	–0.69	0.88	0.43
Vomiting	Vemurafenib	1.13	0.62–2.06	0.12	0.31	0.70
	Ipilimumab+DTIC	0.63	0.35–1.12	–0.47	0.30	0.11
Grades 3 and 4						
Anemia	Temozolomide	0.10	0.01–1.23	–2.33	1.29	0.07
Arthralgia/joint pain	Vemurafenib	0.48	0.02–13.05	–0.73	1.68	0.67
Cutaneous squamous cell carcinoma	Vemurafenib	0.26	0.01–7.97	–1.35	1.75	0.44
Decreased appetite	Ipilimumab+DTIC	0.08	0.00–2.43	–2.48	1.72	0.15
Diarrhea	Vemurafenib	0.57	0.01–30.83	–0.56	2.03	0.78
	Ipilimumab+DTIC	0.04	0.00–3.19	–3.10	2.18	0.15
Fatigue	Vemurafenib	1.58	0.06–40.06	0.46	1.65	0.78
	Ipilimumab+DTIC	0.70	0.03–15.38	–0.36	1.58	0.82
	Temozolomide	1.34	0.06–29.08	0.30	1.57	0.85
Hyperproliferative skin lesions/hyperkeratosis	Vemurafenib	0.29	0.01–18.49	–1.24	2.11	0.56
Leukopenia	Temozolomide	**0.04**	**0.00–0.78**	**–3.23**	**1.52**	**0.03**

Nausea	Vemurafenib	1.43	0.05–44.73	0.36	1.76	0.84
	Ipilimumab+DTIC	0.71	0.02–23.80	–0.35	1.79	0.85
	Temozolomide	0.96	0.04–25.40	–0.04	1.67	0.98
Neutropenia	Vemurafenib	1.00	0.07–13.90	0.00	1.34	1.00
	Temozolomide	**0.06**	**0.01–0.51**	**−2.76**	**1.07**	**0.01**
Thrombocytopenia	Temozolomide	**0.06**	**0.01–0.58**	**−2.86**	**1.17**	**0.01**
Vomiting	Vemurafenib	1.43	0.05–41.06	0.36	1.71	0.84
	Ipilimumab+DTIC	0.79	0.03–20.19	–0.24	1.66	0.88
	Temozolomide	0.75	0.03–17.29	–0.28	1.60	0.86

DTIC: Dacarbazine; SE: Standard Error; RR: Risk Ratio.
[a]Safety outcomes for all grades and grades 3/4 for dabrafenib vs other interventions, were compared indirectly using a common comparator (DTIC) and based on the safety population. For outcomes in this table: December 2012 data for BREAK-3, October 2011 data for METRIC, and December 2010 data for BRIM-3 were used; text in bold specifies statistically favorable results in favor of dabrafenib; RRs <1 indicate a lower risk/incidence in favor of dabrafenib versus the comparator.

Table 5: Indirect treatment comparisons for tolerability and safety outcomes for dabrafenib versus other interventions[a].

loss, diarrhea, fatigue, hyperproliferative skin lesions, nausea, palmar-plantar erythrodysesthesia syndrome, rash, and thrombocytopenia. Dabrafenib had a statistically non-significant (p>0.05), numerically decreased risk of grade 3/4 arthralgia, cutaneous SCC, diarrhea, and hyperproliferative skin lesions and an increased risk of fatigue, nausea, and vomiting versus vemurafenib. There was an equal risk (RR=1.0) of grade 3/4 neutropenia when dabrafenib was indirectly compared with vemurafenib.

When indirectly compared against DTIC plus ipilimumab, dabrafenib showed a significantly increased risk of any-grade headache (RR=3.38; 95% CI=1.29–8.83; p=0.01) and a significantly decreased risk of any-grade nausea (RR=0.54; 95% CI=0.37–0.79; p=0.0014). It also showed a statistically non-significant reduction (p>0.05) in the risk of any-grade constipation, appetite loss, diarrhea, fatigue, pyrexia, and vomiting and a statistically non-significant (p>0.05) increased risk of rash versus DTIC plus ipilimumab. For grade 3/4 appetite loss, diarrhea, fatigue, nausea, and vomiting, dabrafenib showed a statistically non-significant reduction in risk versus DTIC plus ipilimumab.

Dabrafenib showed a significantly lower risk of grade 3/4 leukopenia (RR=0.04; 95% CI=0.00–0.78; p=0.03), neutropenia (RR=0.06; 95% CI=0.01–0.51; p=0.01), and thrombocytopenia (RR=0.06; 95% CI=0.01–0.58; p=0.01) when compared against temozolomide. Dabrafenib also showed a statistically non-significant reduction in risk of grade 3/4 anemia, nausea, and vomiting and a statistically non-significant increased risk of grade 3/4 fatigue.

Discussion

This systematic review of the clinical literature, and quantitative analysis, was the first to compare the recently approved dabrafenib or trametinib monotherapy versus other commonly prescribed treatment options for the treatment of patients with metastatic melanoma. Given the absence of head-to-head trials, comparative evidence from ITCs can be useful to guide the judicious selection of the most appropriate treatments.

When compared with chemotherapy and immunotherapy, first-line treatment with dabrafenib monotherapy or trametinib monotherapy demonstrated a significantly better PFS when directly compared with DTIC and when indirectly compared with ipilimumab plus DTIC or temozolomide. Furthermore, patients who received either dabrafenib or trametinib monotherapy showed a statistically significant reduced risk of progression, a statistically non-significant reduced hazard of death, and improved ORRs. In terms of tolerability and safety, a more favorable profile for dabrafenib was also observed. Patients who received dabrafenib demonstrated a significantly reduced risk of treatment discontinuations due to any cause versus ipilimumab plus DTIC and versus temozolomide and a significantly reduced risk of treatment discontinuations due to AEs versus ipilimumab plus DTIC. In terms of safety, patients who received dabrafenib demonstrated significantly fewer grade 3/4 AEs when indirectly compared with DTIC plus ipilimumab. For the nine specific any-grade AEs that could be compared, dabrafenib was associated with a significantly lower risk of nausea and a significantly higher risk of headache than ipilimumab plus DTIC. Dabrafenib also showed, compared with DTIC plus ipilimumab, a lower risk of developing (i) six of the remaining seven any-grade AEs and (ii) all of the five grade 3 or 4 AEs that could be indirectly compared (both not significant). For the ITC versus temozolomide, dabrafenib showed a significantly lower risk of the three grade 3/4 AEs and a statistically non-significant lower risk of three of the remaining four any-grade AEs.

Given the absence of head-to-head studies that evaluated vemurafenib versus dabrafenib or trametinib, it was difficult to compare the relative clinical efficacy of these treatments for patients with *BRAF* V600 metastatic melanoma. In this article, vemurafenib was indirectly compared with dabrafenib and trametinib. A numerically lower risk of progression was observed for dabrafenib versus vemurafenib, although the difference was not statistically significant. In contrast, trametinib showed a higher (also statistically non-significant) risk of progression versus dabrafenib and vemurafenib when compared indirectly. Both dabrafenib and trametinib were associated with a reduced risk of death versus vemurafenib; however, treatment differences were not statistically significant. Vemurafenib showed statistically significantly greater ORRs and non-significantly greater CRs than either dabrafenib or trametinib monotherapy. Trametinib was associated with an increased but statistically non-significant risk of death when indirectly compared with dabrafenib.

Given the side-by-side comparison (Table 2) of OS for the phase 3 trials for dabrafenib (BREAK-3) and vemurafenib (BRIM-3) at various data cut-offs, a few observations need to be noted. The smaller size of the BREAK-3 trial and the fact that, as per study design, DTIC patients could crossover to the active dabrafenib arm upon progression, were the likely reasons for the lack of statistically significant OS results from the study. Patients in the BRIM-3 study were also permitted to crossover to active vemurafenib treatment but only after a protocol amendment following the interim data analysis in December 2010. Consequently a smaller proportion had done so by the end of follow-up and the BRIM-3 ITT dataset was arguably less confounded. It is likely that this crossover had an effect on the HR over time. As the BRIM-3 data matured, the HR appeared similar (HR=0.76) to that observed in BREAK-3 despite a smaller proportion of patients having crossed over

to the active vemurafenib arm. The estimated median OS in BREAK-3 at the most recent data cut (December 2012) was 18.6 months (95% CI=16.6–NR) for dabrafenib versus 15.6 months (95% CI=12.7–NR) for DTIC (HR=0.76; 95% CI=0.48–1.21) although the actual medians had not yet been reached (42% deaths across both arms). Similar PFS (6.9 months) and ORR (59% versus 57%) rates were also reported for dabrafenib (BREAK-3) and vemurafenib (BRIM-3), respectively [63,64]. Together, these results suggest that the efficacy of dabrafenib is similar to that of vemurafenib.

Concerning tolerability outcomes, compared with vemurafenib, dabrafenib had a lower risk of treatment discontinuations due to AEs but a higher risk of treatment discontinuations due to any cause, although neither of these results were statistically significant. Notably, dabrafenib was significantly better than vemurafenib when assessed for dose interruptions/modifications ($p<0.05$)—an important measure when treating a life-threatening disease because any dose reductions or interruptions could prevent patients from achieving the maximum clinical benefit from their treatment. In terms of safety outcomes, dabrafenib could be indirectly compared with vemurafenib for 17 any-grade AEs and eight grade 3/4 AEs. Of these, dabrafenib was associated with a significantly lower risk ($p<0.05$) of any-grade photosensitivity, a numerically lower risk ($p>0.05$) of 10 of the other any-grade AEs, and a numerically higher risk ($p<0.05$) of the remaining six compared with vemurafenib. There were no significant differences for grade 3/4 AEs, although dabrafenib showed a statistically non-significant lower risk of developing four AEs and higher risk of developing three AEs versus vemurafenib. Therefore, some important differences exist between the tolerability and safety profiles of vemurafenib and dabrafenib.

The strengths of this review and of the network meta-analysis included the comprehensive searches for all relevant literature that were conducted from the inception of the clinical databases to October 2012. Furthermore, data reported in public assessment reports from EMA and the FDA were searched to fill data gaps, if any. Additionally, HTA guidance documents published in English were searched from NICE, SMC, PCODR, PBAC, IQWiG, and AHRQ to retrieve any relevant information not available in the published data. Finally, all the ITCs were feasible via a single common comparator.

Although this review sought, wherever possible, to reduce the risk of bias during the review processes and analyses, the findings may still be subject to certain limitations. The evidence base contributing to the quantitative analysis was too sparse to draw definitive conclusions regarding efficacy, safety, and tolerability. Additionally, the OS data for dabrafenib and trametinib are still immature. Due to the lack of head-to-head randomized comparisons between all interventions of interest, adjusted indirect comparisons were performed. These results should be interpreted with caution because of the underlying assumptions of this method which relate to homogeneity and the similarity of trials. Finally, it is important to note that the ITCs for tolerability and safety outcomes could only be performed where similar outcomes were reported across the trials of interest. In several instances, low AE incidence rates resulted in RRs with large CIs. Hence, such results need to be interpreted with caution and by taking into account the clinical relevance of the safety outcome.

Two phase 3 clinical trials evaluating the recently-approved combination of dabrafenib and trametinib, versus a BRAF inhibitor alone (dabrafenib in COMBI-d and vemurafenib in COMBI-v) and another phase 3 clinical trial evaluating the combination of vemurafenib and cobimetinib versus vemurafenib, have shown that dual inhibition of MEK and mutant BRAF kinases in MM shows greater initial tumour response, improves progression free and/or overall survival, prevents or delays MAP kinase-driven acquired resistance, and decreases the frequency and severity of some of the AEs that occur owing to paradoxical MAP kinase pathway activation from BRAF-inhibitor monotherapy [65-67]. Hence, it would be useful to include combination regimens, as well as the recently-approved anti-PD-1 treatments nivolumab and pembrolizumab, in a future systematic review and indirect treatment comparison.

Conclusion

Monotherapy with dabrafenib or trametinib significantly improved PFS versus DTIC in head-to-head trials and versus ipilimumab plus DTIC and temozolomide through ITCs. Dabrafenib and trametinib both demonstrated comparable PFS and OS, although different tolerability and safety profiles, when indirectly compared with vemurafenib. These data may provide guidance in the selection of the most appropriate treatment for patients with metastatic melanoma. However, the results must be interpreted cautiously given the methodological assumptions and immature OS data for monotherapy with dabrafenib or trametinib. Head-to-head studies remain the gold standard for comparing treatments.

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Conflicts of Interest Disclosure

Mayur M. Amonkar, Ceilidh Stapelkamp and Michelle Casey were employees of GlaxoSmithKline at the time of the study and hold stock in GlaxoSmithKline. Suzanne Swann is an employee of GlaxoSmithKline and holds stock in GlaxoSmithKline. All other authors have nothing to disclose.

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