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ORIGINAL RESEARCH ARTICLE

Cost Effectiveness of Dabrafenib as a First-Line Treatment in Patients with *BRAF* V600 Mutation-Positive Unresectable or Metastatic Melanoma in Canada

Thomas E. Delea · Jordan Amdahl · Alice Wang · Mayur M. Amonkar · Marroon Thabane

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Abstract

Objective To evaluate the cost effectiveness of dabrafenib versus dacarbazine and vemurafenib as first-line treatments in patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma from a Canadian healthcare system perspective.

Methods A partitioned-survival analysis model with three mutually exclusive health states (pre-progression, post-progression, and dead) was used. The proportion of patients in each state was calculated using survival distributions for progression-free and overall survival derived from pivotal trials of dabrafenib and vemurafenib. For each treatment, expected progression-free, post-progression, overall, and quality-adjusted life-years (QALYs), and costs were calculated. Costs were based on list prices, a clinician survey, and published sources. A 5-year time horizon was used in the base case. Costs (in 2012 Canadian dollars [CA$]) and QALYs were discounted at 5 % annually. Deterministic and probabilistic sensitivity analyses were conducted.

Results Dabrafenib was estimated to yield 0.2055 more QALYs at higher cost than dacarbazine. The incremental cost-effectiveness ratio was CA$363,136/QALY. In probabilistic sensitivity analyses, at a threshold of CA$200,000/QALY, there was an 8.2 % probability that dabrafenib is cost effective versus dacarbazine. In deterministic sensitivity analyses, cost effectiveness was sensitive to survival distributions, utilities, and time horizon, with the hazard ratio for overall survival for dabrafenib versus dacarbazine being the most sensitive parameter. Assuming a class effect for efficacy of *BRAF* inhibitors, dabrafenib was dominant versus vemurafenib (less costly, equally effective), reflecting its assumed lower daily cost. Assuming no class effect, dabrafenib yielded 0.0486 more QALYs than vemurafenib.

Conclusions At a threshold of CA$200,000/QALY, dabrafenib is unlikely to be cost effective compared with dacarbazine. It is not possible to make reliable conclusions regarding the relative cost effectiveness of dabrafenib versus vemurafenib based on available information.

Key Points for Decision Makers

From a Canadian public healthcare system perspective, dabrafenib was estimated to provide more quality-adjusted life-years (QALYs; discounted) at a higher cost than dacarbazine. At a threshold of CA$200,000/QALY, dabrafenib is not cost effective compared with dacarbazine.

Based on list prices, the expected lifetime cost of melanoma treatment with dabrafenib is likely to be less than that with vemurafenib. However, there is uncertainty regarding the actual costs of vemurafenib to Canadian provinces and the relative effectiveness of the two *BRAF* inhibitors. It is therefore not possible to make reliable conclusions regarding the relative cost effectiveness of dabrafenib versus vemurafenib based on available information.

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T. E. Delea (✉) · J. Amdahl · A. Wang
Policy Analysis Inc. (PAI), Four Davis Court,
Brookline, MA 02445, USA
e-mail: tdelea@pai2.com

M. M. Amonkar
GlaxoSmithKline, 1250 South Collegeville Road,
Collegeville, PA 19426, USA

M. Thabane
GlaxoSmithKline, 7333 Mississauga Rd N,
Mississauga, ON L5N 6L4, Canada

1 Introduction

Approximately 60 % of melanomas harbor *BRAF* substitution mutations of valine (V) for glutamate (E) at residue 600 (V600E) [1, 2]. Vemurafenib and dabrafenib are orally available, small-molecule inhibitors of mutant *BRAF* kinase that have antitumor effects against melanoma cell lines with *BRAF* V600 mutations [2].

BRAF Inhibitor in Melanoma (BRIM)-3 (ClinicalTrials.gov identifier: NCT01006980) was a phase III, randomized, open-label study comparing vemurafenib (960 mg orally twice daily) to dacarbazine (1,000 mg/m^2 intravenously every 3 weeks) in previously untreated patients with *BRAF* V600E mutation-positive metastatic melanoma [3]. In the interim analyses of overall survival (OS) and progression-free survival (PFS), vemurafenib improved OS (hazard ratio [HR], 0.37; 95 % confidence interval [CI], 0.26–0.55; $p < 0.001$) and PFS (HR, 0.26; 95 % CI, 0.20–0.33; $p < 0.001$; median PFS, 5.3 vs 1.6 months) [3]. The data and safety monitoring committee subsequently recommended that patients receiving dacarbazine be allowed to cross over to receive vemurafenib. Based on these results, vemurafenib was approved for treatment of *BRAF* V600 mutation-positive unresectable or metastatic melanoma by Health Canada and has since become the standard of care for these patients in many Canadian provinces [4]. PFS and OS were subsequently updated based on a February 2012 data cut. Based on the February 2012 data, the HR for PFS was 0.38 (95 % CI, 0.32–0.46; $p < 0.0001$) [5, 6]. The HR for OS was 0.76 (95 % CI, 0.63–0.93; $p < 0.01$) without adjustment for crossover and 0.64 (95 % CI, 0.53–0.78; $p < 0.0001$) adjusting for crossover using the rank-preserving structural failure time model (RPSFTM) approach [6].

BREAK-3 (ClinicalTrials.gov identifier: NCT01227889) was a phase III, randomized, open-label study comparing dabrafenib (150 mg orally twice daily) with dacarbazine (1,000 mg/m^2 intravenously every 3 weeks) in previously untreated patients with *BRAF* V600E mutation-positive metastatic melanoma [7]. At the December 2011 cut-off date, the estimated median PFS was 5.1 months for dabrafenib and 2.7 months for dacarbazine (HR, 0.30; 95 % CI, 0.18–0.51; $p < 0.0001$) [7]. Patients receiving dacarbazine were allowed to cross over to receive dabrafenib after progression. The HR for OS was 0.61 (95 % CI, 0.25–1.48), favoring dabrafenib [7]. At the June 2012 data cut, median PFS was 6.9 months for dabrafenib and 2.7 months for dacarbazine (HR, 0.37; 95 % CI, 0.23–0.57; $p < 0.0001$) [8]. OS was subsequently updated again at the December 2012 data cut without adjustment for crossover (HR, 0.76; 95 % CI, 0.48–1.21) [8] and with adjustment for crossover using the RPSFTM approach (HR, 0.55; 95 % CI, 0.21–1.43) (unpublished data: Latimer N et al. 2013).[1] Dabrafenib was approved by Health Canada for the treatment of *BRAF* mutation-positive unresectable or metastatic melanoma [9].

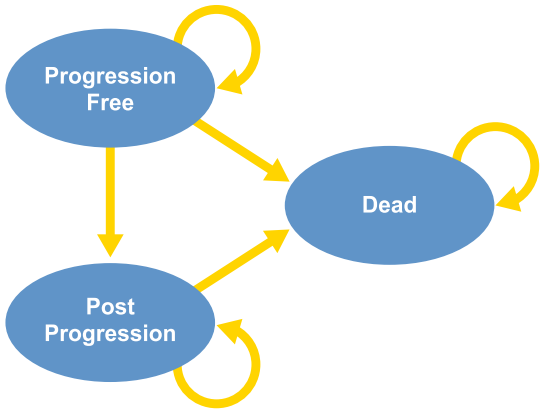

Fig. 1 Schematic of a partitioned-survival model

The objective of this analysis was to compare the cost effectiveness of dabrafenib with dacarbazine and vemurafenib as first-line treatments for patients with *BRAF* V600 mutation-positive metastatic/unresectable melanoma from a publically funded healthcare system perspective in Canada.

2 Methods

2.1 Overview

A partitioned-survival analysis model, similar to that used in prior economic assessments of treatments for advanced or metastatic cancers [10, 11], including the recent evaluation of the cost effectiveness of vemurafenib in *BRAF* mutation-positive metastatic melanoma included in Roche's submission to the National Institute for Health and Clinical Care Excellence (NICE) [12], was used (Fig. 1). The structure of the model used in the Roche submission to the pan-Canadian Oncology Drug Review (pCODR) was not reported, but was likely the same as that used in their submission to NICE. The population of interest was treatment-naïve patients with *BRAF* V600E mutation-positive metastatic melanoma eligible for treatment with a *BRAF* inhibitor. The comparators of interest were dabrafenib, dacarbazine, and vemurafenib. The time horizon was 260 weeks (5 years), beginning with the start of treatment,

[1] Latimer N, Abrams K. Adjusting for treatment crossover in the BREAK-3 clinical trial—stage 1 feasibility analysis results, February 2013 update. 2013.

which was selected to be consistent with that recommended by the Economic Guidance Panel (EGP) of pCODR in their assessment of the cost effectiveness of vemurafenib because of uncertainty of outcomes beyond this point [13]. A Canadian publicly funded healthcare system perspective was used, which considered direct healthcare costs related to treatment of metastatic melanoma. The primary measure of cost effectiveness was the incremental cost per quality-adjusted life-year (QALY) gained with dabrafenib versus dacarbazine and versus vemurafenib. Costs and QALYs were discounted using a 5 % annual rate [14]. The cost-effectiveness analysis presented here did not directly involve human or animal studies, and therefore was exempt from approval by an ethics committee.

2.2 Model Structure

With the partitioned-survival analysis modeling approach, patients are assumed to be in one of three mutually exclusive health states: alive with no progression (PFS), alive with progression (post-progression survival [PPS]), or dead. The proportion of patients in each health state over time (the model used a 1-week cycle duration) was calculated using empirical and/or parametric survival distributions for PFS and OS. Costs and health-related quality of life (HRQoL) were assumed to depend on treatment and expected time in each disease state. Expected PFS and OS were calculated as the area under the curve (AUC) for the PFS and OS distributions, respectively. Expected PPS was calculated as the area between the PFS and OS curves or the difference between expected PFS and expected OS. The model allowed for the consideration of 'one-off' costs and decrements in HRQoL associated with treatment initiation, adverse events (AEs), progression, and death.

The model was used to generate estimates of expected costs, progression-free life-years (PFLYs), post-progression life-years (PPLYs), overall life-years (LYs), lifetime costs, and QALYs for each comparator; the differences between dabrafenib and dacarbazine and dabrafenib and vemurafenib with regard to these outcomes; and the incremental cost-effectiveness ratios for dabrafenib versus dacarbazine and dabrafenib versus vemurafenib.

2.3 Model Estimation

Literature to inform the model inputs was identified from systematic reviews [15] supplemented by targeted (i.e., non-systematic) reviews to identify specific parameter estimates. Model inputs are summarized in Table 1 [16–20] and detailed below. Additional details regarding the parameter estimates used in the model are provided in the electronic supplementary material.

2.3.1 *Estimation of Progression-Free Survival and Overall Survival*

For estimation purposes, PFS and OS were divided into two main segments: the trial period and the projection period. PFS for dabrafenib and dacarbazine during the trial period were based on Kaplan–Meier investigator-assessed PFS from the June 2012 data cut-off date of BREAK-3 (Fig. 2) [8]. The trial periods for PFS were defined as 71.1 and 53.1 weeks for dabrafenib and dacarbazine, respectively, based on the maximum failure or censoring time for investigator-assessed PFS in BREAK-3 [7]. PFS for dabrafenib and dacarbazine during the projection period were estimated based on log-normal survival distributions fit to individual patient-level data (IPD) from BREAK-3 using accelerated failure time regression.

Parametric survival distributions were fit to IPD using accelerated failure-time regression (SAS PROC LIFEREG, SAS Institute Inc, Cary, NC, USA). When fitting parametric survival distributions to PFS, the exponential, Weibull, log-logistic, log-normal, and Gamma distributions were considered. The goodness-of-fit of the distributions was evaluated based on visual inspection, Akaike Information Criterion (AIC), and by comparing the restricted mean (i.e., AUC) for the fitted distributions with those for the empirical distributions. The AUC for PFS for dabrafenib and dacarbazine to end of follow-up was relatively insensitive to the choice of survival distribution. Not unexpectedly, the one parameter exponential model did not generally provide a good fit. Although the three-parameter Gamma distribution generally provided the best fit, it tended to generate long-tailed distributions that might bias the comparison in favor of active treatment. Amongst the remaining (two parameter) models, the curves and fit statistics were all very similar. However, the log-normal tended to provide the best fit (marginally) followed by the log-logistic. In light of these findings, the log-normal survival distribution was used for PFS for both dabrafenib and dacarbazine.

OS for dacarbazine during the trial period was based on the RPSFTM-adjusted OS for dacarbazine from the December 2012 data cut-off date of BREAK-3 (PFS data in BREAK-3 were not updated at the December 2012 data cut-off) [8, 21]. The RPSFTM approach calculates counterfactual failure times for each patient, reflecting survival had the patients not received treatment, under the assumption that patients who cross over achieve the same benefits as those initially randomized to the active treatment group [22]. The duration of the trial period for OS for dacarbazine was 37.6 weeks based on the maximum censoring or failure time for the RPSFTM Kaplan–Meier OS for dacarbazine. Because of the relatively small number of randomized patients, relatively short follow-up in BREAK-3,

Table 1 Model inputs

HRs for PFS and OS				Source/reference
PFS				See Table S1, ESM
$HR_{PFS\ dabrafenib\ vs\ dacarbazine}$ (95 % CI)			0.37 (0.24–0.58)	
$HR_{PFS\ vemurafenib\ vs\ dacarbazine}$ (95 % CI)			0.38 (0.32–0.46)	
$HR_{PFS\ vemurafenib\ vs\ dabrafenib}$ (95 % CI)			1.03 (0.64–1.65)	
OS				See Table S1, ESM
$HR_{OS\ dabrafenib\ vs\ dacarbazine}$ (95 % CI)			0.55 (0.21–1.43)	
$HR_{OS\ vemurafenib\ vs\ dacarbazine}$ (95 % CI)			0.64 (0.47–0.88)	
$HR_{OS\ vemurafenib\ vs\ dabrafenib}$ (95 % CI)			1.16 (0.43–3.14)	
Model parameter	**Dabrafenib**	**Dacarbazine**	**Vemurafenib**	**Source/reference**
Utility values, mean (SE)				
Progression-free versus perfect health	0.233 (0.024)	0.250 (0.046)	0.233 (0.024)	Estimated from BREAK-3 EQ-5D data (unpublished data)
Post-progression versus progression-free	0.090 (0.056)	0.073 (0.04)	0.090 (0.056)	Estimated from BREAK-3 EQ-5D data (unpublished data)
Estimated daily cost of drug, CA$	253.32[a,b]	15.92[c]	372.34[a,d]	IMS Brogan
Administration/dispensing cost per cycle of drug, CA$	8.40	215.01	8.40	Leighl et al. [16] Ontario Ministry of Health and Long-Term Care. Schedule of benefits for Physician Services under the Health Insurance Act, January 1, 2013 [20] Mittmann et al. [17] Ontario Drug Benefit Program: Dispensing Fees. Ontario Ministry of Health and Long-Term Care, 2012 [19]
Estimated monthly costs of other care associated with treatment, CA$				
Outpatient visits	74.51	97.53	74.51	Ontario Schedule of Benefits A443 [18]
Complete blood count	7.72	10.10	7.72	Ontario Schedule of Laboratory Fees L393 [18]
Complete metabolic panel	29.72	39.02	29.72	Ontario Schedule of Laboratory Fees L111, L045, L005, L208, L226, L204, L061, L053, L251, L067, L191, L223, L222, and L030 [18]
Lactate dehydrogenase	4.41	5.90	4.41	Ontario Schedule of Laboratory Fees L145 [18]
CT scan of abdomen and/or pelvis	43.64	44.97	43.64	Ontario Schedule of Laboratory Fees X126 and X233 [18]
CT scan of chest	31.80	31.48	31.80	Ontario Schedule of Laboratory Fees X125 [18]
CT scan of brain	5.42	5.42	5.42	Ontario Schedule of Benefits X188 [20]
PET-CT scan	2.83	2.83	2.83	Ontario Schedule of Benefits J707 [20]
Bone scintigraphy	8.75	8.75	8.75	Ontario Schedule of Benefits J850 [20]
ECHO	0.16	0	0.16	Ontario Schedule of Benefits G310-Technical Component [20]
Chest X-ray	6.53	7.18	6.53	Ontario Schedule of Benefits X092 [20]

Table 1 continued

Model parameter	Dabrafenib	Dacarbazine	Vemurafenib	Source/reference
Total	215.47	253.17	215.47	
PPS costs per month, CA$	93.96	93.96	93.96	Estimated from Ontario Schedule of Benefits [20], Ontario Schedule of Laboratory Fees [18], survey of Canadian physicians (unpublished)
Expected cost of PTACT per patient, CA$				See Tables S15–S18, ESM
Vemurafenib	0	13,226	0	
Ipilimumab	4,918	4,676	4,918	
Dacarbazine	289	153	289	
Temozolomide	142	0	142	
Paclitaxel	319	0	319	
Carboplatin	154	0	154	
Total	5,822	18,055	5,822	

CA Canadian, *CI* confidence interval, *CT* computed tomography, *ECHO* echocardiogram, *EQ-5D* EuroQol 5-Domain health questionnaire, *ESM* electronic supplementary material, *HR* hazard ratio, *OS* overall survival, *PET* positron-emission tomography, *PFS* progression-free survival, *PPS* post-progression survival, *PTACT* post-treatment anti-cancer therapy, *SE* standard error

[a] Patients receiving dabrafenib and vemurafenib were assumed to receive a 28-day supply of medicine with each prescription, with any unused medication discarded

[b] The unit cost of dabrafenib was estimated to be CA$63.33 per 75-mg tablet based on list prices in the IMS Brogan database (http://www.imshealth.com/portal/site/imshealth?CURRENT_LOCALE=en_ca). The average cost per 28-day course of dabrafenib is CA$7,092.96

[c] The average unit cost of dacarbazine was estimated to be CA$0.1736 per mg based on population-weighted averages of list prices across provinces from the IMS Brogan database. When multiple formulations of dacarbazine were available, the formulation with the lowest unit price was used. The average cost per 28-day course of vemurafenib is CA$445.82. No wastage of dacarbazine was assumed because it is available in multiple formulations as a powder for reconstitution

[d] The unit cost of vemurafenib was estimated to be CA$46.54 per 240-mg tablet based on list prices in the IMS Brogan database. The average cost per 28-day course of vemurafenib is CA$10,425.34

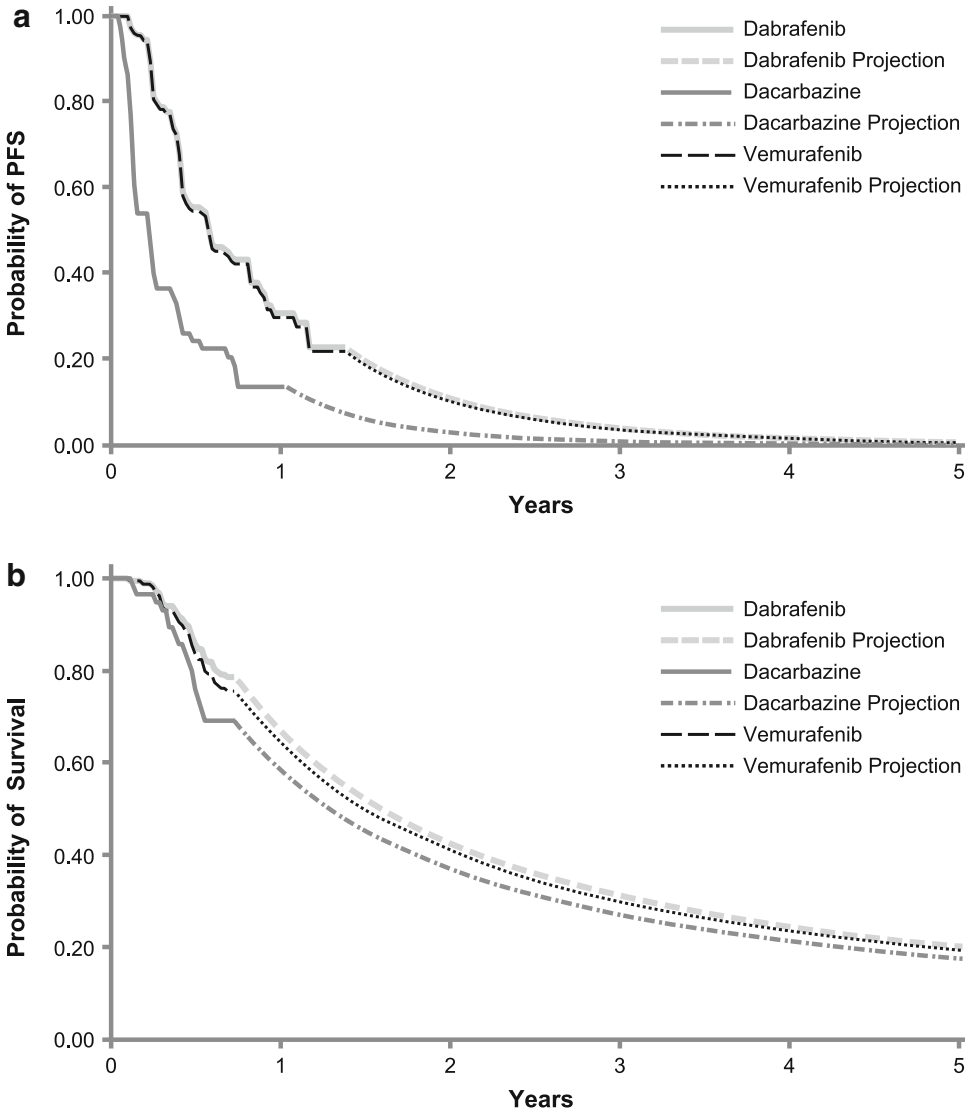

Fig. 2 Estimated **a** progression-free survival (PFS) based on the June 2012 cut-off date for BREAK-3 and **b** overall survival for dabrafenib, dacarbazine, and vemurafenib used in the no class effect/BRIM-3 based on the December 2012 data cut-off date for BREAK-3

and recensoring of observations required by the RPSFTM approach, data on RPSFTM-adjusted OS for dacarbazine were sparse [7]. Accordingly, projections of OS based on parametric curves fit to the RPSFTM-adjusted OS data for dacarbazine (as done for PFS) would be associated with substantial uncertainty. Therefore, OS for dacarbazine during the projection period was based on survival data for 7,635 patients with metastatic melanoma from the American Joint Committee on Cancer (AJCC) melanoma registry [23]. The published AJCC survival curves for patients with metastatic melanoma by site of metastases (skin, subcutaneous, or distant nodes; lung with or without skin/subcutaneous; and nonpulmonary visceral) were digitized and then combined by weighting the curves based on the relative proportions of patients in the corresponding stages in the BREAK-3 trial [7]. To facilitate analyses, the model used a parametric distribution fit to these data. In fitting the parametric distribution to the AJCC survival, both Weibull and log-logistic distributions were explored. The log-logistic curve provided an excellent fit based on visual inspection and AUC and was therefore used in the model (Fig. 3).

OS for dabrafenib during the trial period was based on the Kaplan–Meier OS for dabrafenib from the December 2012 data cut-off date of BREAK-3 [8]. Even though the observed OS data for dabrafenib at this cut-off date extended to 96 weeks, using OS data for dabrafenib beyond 37.6 weeks would represent an unadjusted indirect treatment comparison (ITC) of dabrafenib and dacarbazine over this period because OS for dacarbazine was based on AJCC data and would be subject to confounding. Therefore, the trial period for OS for dabrafenib was assumed to be equivalent to that for dacarbazine (37.6 weeks). For the projection period, OS for dabrafenib was calculated by

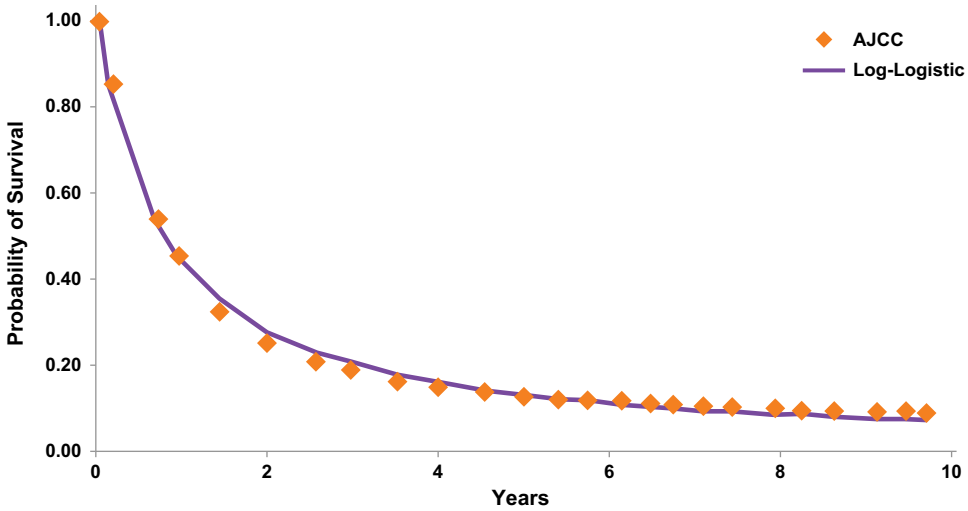

Fig. 3 Kaplan–Meier and log-logistic fitted BREAK-3 case-mix adjusted overall survival from AJCC melanoma registry. *AJCC* American Joint Committee on Cancer

applying an estimate of the HR for dabrafenib versus dacarbazine to the OS for dacarbazine. To inform estimation of the HR for dabrafenib versus dacarbazine during the projection period, the HRs observed in the BREAK-3 trial [7] were compared with those in BRIM-3 [3] to assess whether there were any similar patterns and whether the longer follow-up in BRIM-3 might provide some guidance on the durability of the treatment effect of *BRAF* inhibitors in general. Based on an analysis of kernel-smoothed HRs from the RPSFTM-adjusted analysis of OS in BRIM-3, the HR for OS for vemurafenib versus dacarbazine was determined to cross 1.0 at 43.5 weeks (inputs and distributions are shown in the electronic supplementary material, Table S1). The HR of dabrafenib versus dacarbazine was therefore assumed to increase linearly from 0.55 (HR for RPSFTM-adjusted OS for dabrafenib versus dacarbazine in BREAK-3) at 37.6 weeks (beginning of the projection period) to 1.00 by 43.5 weeks, then remain at 1.00 for the rest of the projection period [7].

PFS and OS for vemurafenib were estimated by applying estimates of the HRs for PFS and OS for vemurafenib versus dabrafenib to the estimated PFS and OS distributions for dabrafenib (as described above). The former were based on adjusted ITCs of the HRs for PFS and OS for dabrafenib versus dacarbazine from BREAK-3 [7] and for vemurafenib versus dacarbazine from BRIM-3 [3] through the common comparator of dacarbazine using the method of Bucher et al. (i.e., frequentist approach) [24]. The efficacy of dabrafenib and vemurafenib in the BREAK-3 and BRIM-3 trials, respectively, are similar, suggesting the possibility of a class effect [25]. Because there is no evidence to support that the effectiveness of dabrafenib and vemurafenib are different, cost effectiveness was also estimated assuming that PFS and OS with vemurafenib would be equivalent to that with dabrafenib (class effect).

2.3.2 *Utilities*

In BREAK-3, data from the EuroQol 5-Domain (EQ-5D) health questionnaire were collected at screening, weeks 6, 12, and 15, upon disease progression, and approximately 30 days post-progression [26]. In the model, the mean decrements in utility during PFS versus perfect health for dabrafenib and dacarbazine were based on the mean disutility values (versus perfect health [1.0]) from the June 2012 data cut-off date of BREAK-3 [21]. The mean disutility for post- versus pre-progression was based on the mean difference in utility post- versus pre-progression for patients receiving dabrafenib in BREAK-3. Since very few patients completed the 30-day post-progression EQ-5D assessment, these assessments may be biased because of informative censoring and were therefore not included in the estimation of post-progression utility values. Because 56 % of patients randomized to receive dacarbazine in BREAK-3 crossed over to dabrafenib as of the June 2012 data cut-off date (unpublished data), the post-progression utility values were potentially confounded; therefore, post-progression utility for patients initially receiving dacarbazine was assumed to be equal to that for patients initially receiving dabrafenib (accordingly, the decrement in utility for post- versus pre-progression for dacarbazine was calculated as the difference between the estimated post-progression utility for dabrafenib and the estimated pre-progression utility for dacarbazine) [21]. Because comparable EQ-5D data for vemurafenib were lacking, pre- and post-progression utility values for vemurafenib were assumed to be equal to those for dabrafenib [21].

2.3.3 *Medication and Administration Costs*

Dosages were assumed to be those employed in the BREAK-3 and BRIM-3 trials [3, 7]. Drug costs were based

on list prices from the IMS Brogan database (IMS Health, Danbury, CT, USA; http://www.imshealth.com). The cost of dispensing oral medications was from the Ontario Drug Benefit Program [19]. The cost of intravenous administration of dacarbazine was calculated as the sum of the costs of preparation, nursing and support, physician consultation, and chemotherapy chair time, which were estimated based on published sources [16, 17, 20]. The Bank of Canada Inflation Calculator was used to adjust all costs to 2012 prices. Additional information on dosages is available in the electronic supplementary material, Tables S2 and S3, while additional information on medication and administration costs is available in Tables S4–S6 of the electronic supplementary material.

2.3.4 *Costs of Treating Adverse Events*

The model includes the cost of treating treatment-related grade 3 or 4 AEs. Grade 1 or 2 AEs are generally self-limiting and therefore unlikely to be associated with substantial treatment costs and were not considered. AEs considered in the model (neutropenia, palmar-plantar erythrodysesthesia, photosensitivity, pyrexia, and squamous cell carcinoma) were those with an incidence of 5 % or greater for dabrafenib, dacarbazine, or vemurafenib in either the BREAK-3 or BRIM-3 trials, and/or those considered important from a clinical or economic perspective based on clinical expert opinion. Estimates of AE incidence for dabrafenib and dacarbazine were from BREAK-3, and those for vemurafenib were from BRIM-3. Costs of treating each AE, which were assumed to be independent of treatment strategy, were estimated by multiplying the incidence of the AE reported by 14 Canadian clinicians (12 oncologists and two dermatologists) by the Canadian-specific unit cost estimates for treating that AE. The 14 clinicians were part of a nationwide group of 59 Canadian physicians who participated in a cross-sectional online survey conducted between November 30, 2012 and January 10, 2013 to understand patterns of treatment and healthcare resource utilization among patients with metastatic melanoma in Canada and were chosen because they fully completed the survey. Additional information on the costs

Table 2 Base-case results

	Dabrafenib	Direct comparison		Indirect comparison			
				Class effect		No class effect	
		Dacarbazine	Difference	Vemurafenib	Difference	Vemurafenib	Difference
Effectiveness							
PFLYs	0.9448	0.4577	0.4872	0.9448	0.0000	0.9212	0.0236
PPLYs	1.3218	1.5612	–0.2394	1.3218	0.0000	1.2710	0.0508
LYs	2.2667	2.0189	0.2478	2.2667	0.0000	2.1922	0.0744
QALYs	1.6198	1.4008	0.2191	1.6198	0.0000	1.5673	0.0525
Effectiveness, discounted							
PFLYs	0.9230	0.4513	0.4718	0.9230	0.0000	0.9008	0.0222
PPLYs	1.2074	1.4492	–0.2418	1.2074	0.0000	1.1608	0.0467
LYs	2.1305	1.9005	0.2300	2.1305	0.0000	2.0616	0.0689
QALYs	1.5256	1.3201	0.2055	1.5256	0.0000	1.4770	0.0486
Costs, discounted, CA$							
Study medication	89,746	2,613	87,133	131,904	–42,158	128,842	–39,095
Administration	110	1,697	–1,587	110	0	107	3
Adverse events	23	103	–80	94	–72	95	–72
Diagnostic testing	1,086	0	1,086	1,086	0	1,086	0
Other costs, PFS	2,387	1,371	1,016	2,387	0	2,329	57
Other costs, PPS	17,847	30,791	–12,944	17,847	0	17,946	–99
Total	111,199	36,576	74,623	153,429	–42,230	150,405	–39,206
Cost effectiveness, CA$							
Cost per PFLY gained			158,175		Dominant		Dominant
Cost per LY gained			324,459		Dominant		Dominant
Cost per QALY gained			363,136		Dominant		Dominant

CA Canadian, *LY* life-year, *PFLY* progression-free life-year, *PFS* progression-free survival, *PPLY* post-progression life-year, *PPS* post-progression survival, *QALY* quality-adjusted life-year

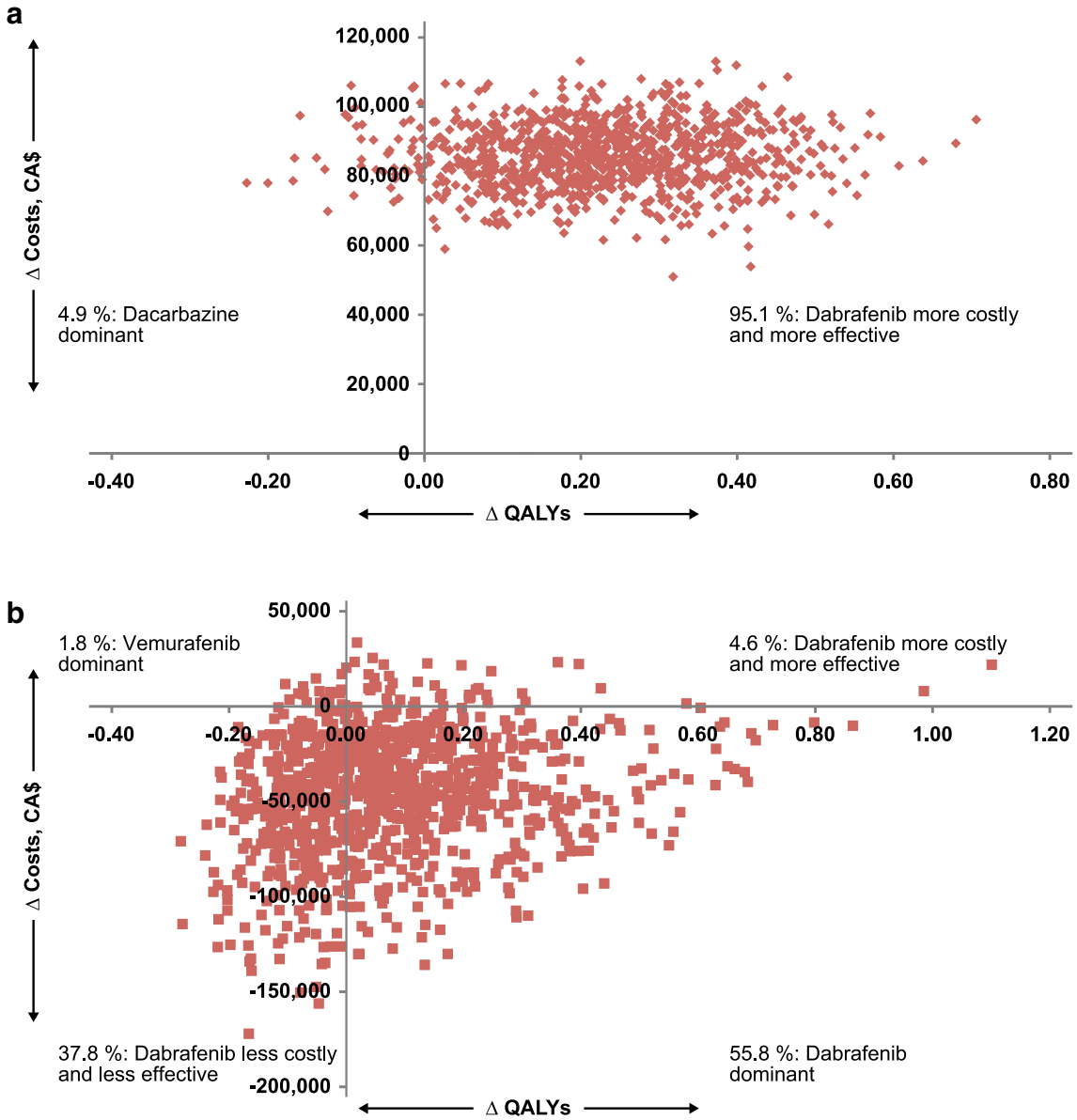

Fig. 4 Results of probabilistic sensitivity analyses for **a** dabrafenib versus dacarbazine and **b** dabrafenib versus vemurafenib (no class effect), based on data from the December 2012 data cut-off date for BREAK-3. *CA* Canadian, *QALYs* quality-adjusted life-years

of treating AEs is available in the electronic supplementary material, Tables S7–S12.

2.3.5 Other Costs

A *BRAF* mutation test was estimated to cost CA$500 per test, and 8.6 % of the tests were estimated to yield an invalid result and require retesting (unpublished report, 2012; bioMérieux, Saint-Laurent, Québec, Canada).[2] Given that at least 50 % of all patients tested for the *BRAF* V600 mutation are *BRAF* mutation positive [1, 2], the one-time cost of *BRAF* testing per patient treated with dabrafenib or vemurafenib was estimated to be CA$1,086.

The costs of post-treatment anti-cancer therapy (PTACT) for dabrafenib and dacarbazine were based on the utilization of PTACT in BREAK-3. Lacking data on PTACT utilization from BRIM-3, PTACT costs for vemurafenib were assumed to equal those for dabrafenib. 'Other' disease-related costs not considered above included costs of routine follow-up visits, laboratory tests, and scans (Table 1). For the model, these costs were assumed to be conditioned on treatment and progression and were based

[2] BioMérieux. THxID-BRAF preliminary performance for medico-economic modeling. May 25 2012.

on resource use estimates from the aforementioned survey of Canadian clinicians and published unit cost estimates. Additional information on other costs incurred during PFS and PPS is available in the electronic supplementary material, Tables S13–S18.

2.4 Model Validation

The Excel workbook used for this evaluation was validated by the investigators and independent expert analysts from the York Health Economics Consortium. The model was validated by taking model inputs and entering them into existing models for evaluating the cost effectiveness of advanced cancers and comparing the results. No material differences between the results generated by the model used in this evaluation and those generated by the validation models were identified.

2.5 Analyses

Pairwise comparisons of dabrafenib versus dacarbazine and dabrafenib versus vemurafenib were conducted. For the comparison with vemurafenib, results were generated alternatively based on results of the ITC of BREAK-3 and BRIM-3 ('no class-effect analyses') and based on the assumption of equal PFS and OS for dabrafenib and vemurafenib ('class-effect analyses'). For each analysis, base-case results were generated along with deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) [27]. Details regarding the input values used in the PSA are included in the electronic supplementary material, Table S19. Cost-effectiveness acceptability curves were generated based on the results of the PSA. The DSA were represented as tornado diagrams.

3 Results

3.1 Dabrafenib Versus Dacarbazine

Compared with dacarbazine, dabrafenib yields 0.4718 more PFLYs and 0.2418 fewer PPLYs (both discounted) (Table 2). Overall LYs are 0.2300 higher with dabrafenib compared with dacarbazine. Dabrafenib yields 0.2055 more discounted QALYs than dacarbazine. Medication costs are CA$87,133 higher with dabrafenib versus dacarbazine, although the administration/dispensing costs are CA$1,587 less for oral dabrafenib versus intravenous dacarbazine. Additionally, *BRAF* mutation testing costs for dabrafenib are CA$1,086. Other melanoma-related costs during PFS are CA$1,016 higher with dabrafenib, reflecting longer PFS. Other melanoma-related costs during PPS are CA$12,944 lower with dabrafenib because of lower use of PTACT with dabrafenib (10 % of dacarbazine patients received vemurafenib versus no dabrafenib patients) and lower terminal care costs, reflecting a higher projected probability of survival at the end of the 5-year time horizon. Total incremental costs are CA$74,623 higher with dabrafenib compared with dacarbazine. The estimated cost effectiveness of dabrafenib versus dacarbazine is CA$363,136 per QALY gained.

The PSA results are depicted in a cost-effectiveness plane (Fig. 4a). Dabrafenib yields more QALYs in 95.1 % of simulations. Figure 5a shows the cost-effectiveness acceptability curves for dabrafenib versus dacarbazine. The probability of the cost effectiveness of dabrafenib is approximately 8.2 % at a cost-effectiveness threshold of CA$200,000 per QALY gained.

In DSA, cost effectiveness is most sensitive to the HR for OS for dabrafenib versus dacarbazine, the disutility of PFS versus perfect health, the time horizon (1–10 years), and the HR for PFS for dabrafenib versus dacarbazine (Fig. 6).

3.2 Dabrafenib Versus Vemurafenib

The base-case results for comparison of dabrafenib and vemurafenib are shown in Table 2. Results are presented alternatively, assuming the same PFS and OS for vemurafenib as dabrafenib ('class effect') and assuming different PFS and OS for vemurafenib, with vemurafenib PFS and OS based on the ITC of BREAK-3 and BRIM-3 ('no class effect'). Because of the class-effect assumption for PFS and OS for *BRAF* inhibitors and the assumption that pre-progression utility values were the same for dabrafenib and vemurafenib, there is no variability in the QALYs gained for dabrafenib versus vemurafenib. Therefore, the comparison resolves to a cost analysis. Medication costs are CA$42,158 lower with dabrafenib versus vemurafenib. Thus, dabrafenib provides the same QALYs as vemurafenib, but costs less, and is therefore cost-saving.

Because medication costs represent the largest share of total costs, and the most important random component contributing to these costs is the duration of therapy, which is also assumed to be equal for dabrafenib versus vemurafenib (as a consequence of its linkage to PFS), there is—by assumption—relatively little variability in the incremental costs of dabrafenib versus vemurafenib. Therefore, the PSA for the comparisons of dabrafenib with vemurafenib for this analysis is not reported. In DSA, dabrafenib is dominant relative to vemurafenib in all scenarios examined, based on the estimated lower cost of dabrafenib.

In the analyses in which PFS and OS for vemurafenib were based on the ITC of BREAK-3 and BRIM-3 ('no class effect'), dabrafenib yields 0.0222 more PFLYs and 0.0467 more PPLYs (both discounted) than vemurafenib

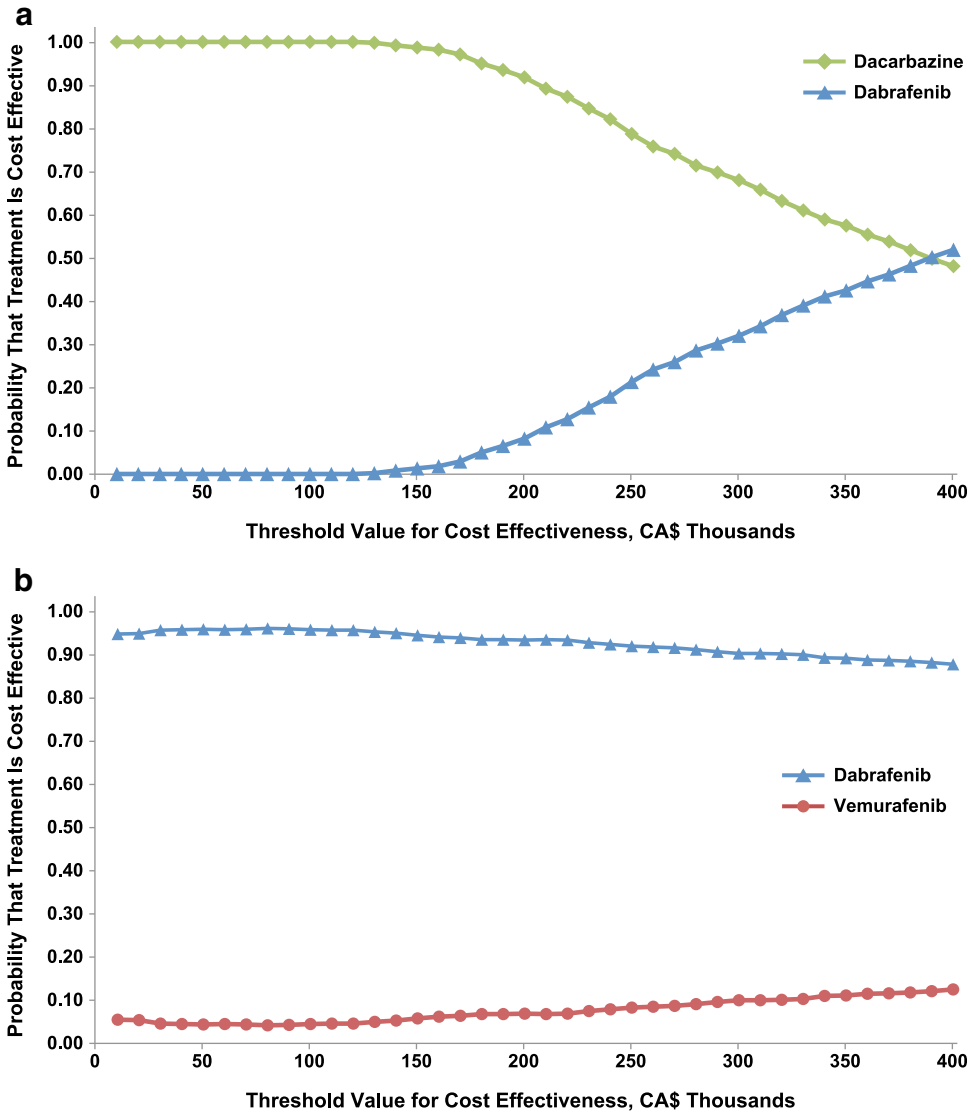

Fig. 5 Acceptability curves for **a** dabrafenib versus dacarbazine and **b** dabrafenib versus vemurafenib (no class effect), based on data from the December 2012 data cut-off date for BREAK-3. *CA* Canadian

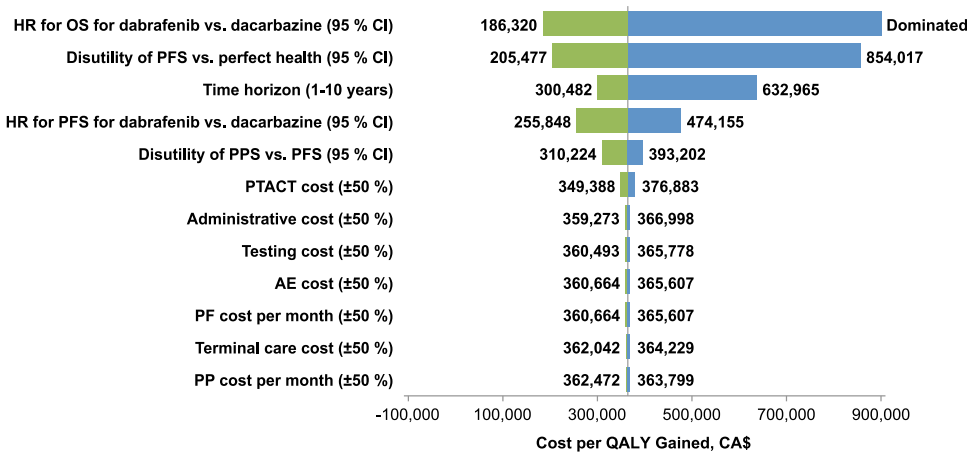

Fig. 6 Tornado diagram for the cost effectiveness of dabrafenib versus dacarbazine. *AE* Adverse event, *CA* Canadian, *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PF* progression-free, *PFS* progression-free survival, *PP* post-progression, *PPS* post-progression survival, *PTACT* post-treatment anti-cancer therapy, *QALY* quality-adjusted life-year

(Table 2). Overall LYs are 0.0689 higher with dabrafenib versus vemurafenib. Dabrafenib yields 0.0486 more discounted QALYs than vemurafenib. Medication costs are CA$39,095 less with dabrafenib versus vemurafenib as a consequence of its lower price. Incremental costs of AEs (CA$72 less with dabrafenib), other costs during PFS

(CA$57 more with dabrafenib), and other costs during PPS (CA$99 less with dabrafenib) are minimal. Expected total costs are CA$39,206 lower with dabrafenib versus vemurafenib. Because dabrafenib is estimated to provide slightly greater effectiveness at a lower cost than vemurafenib, it is dominant in the base case. In PSA, dabrafenib is dominant in 55.8 % of simulations and vemurafenib in 1.8 % of simulations (Fig. 4b). The acceptability curve is shown in Fig. 5b. In DSA, dabrafenib is dominant in all scenarios examined (not shown).

4 Discussion

This study evaluated the cost effectiveness of dabrafenib, an oral, small-molecule inhibitor of mutant *BRAF* V600E kinase, versus dacarbazine and vemurafenib as first-line treatment for patients with *BRAF* V600E mutation-positive unresectable/metastatic melanoma, from a Canadian healthcare system perspective, based on results of the BREAK-3 and BRIM-3 studies and other published sources. Dabrafenib was projected to yield 0.2055 more discounted QALYs than dacarbazine at an estimated incremental cost of CA$74,623. The cost effectiveness of dabrafenib versus dacarbazine was estimated to be CA$363,136 per QALY gained. In DSA, this finding was most sensitive to the assumed beneficial effects of dabrafenib on OS and to a lesser extent PFS, disutility associated with PFS versus perfect health, and the model time horizon (Fig. 5).

Based on similar overall response and median PFS, a 'class effect' with respect to the effectiveness of the selective *BRAF* inhibitors dabrafenib and vemurafenib may be reasonably assumed [25]. Assuming a class effect, dabrafenib is cost saving compared with vemurafenib, reflecting the lower assumed unit price for dabrafenib versus vemurafenib. In the analysis assuming no class effect for *BRAF* inhibitors, dabrafenib is dominant, yielding 0.0486 more QALYs than vemurafenib at an estimated savings of CA$39,206.

Economic evidence has been tentatively incorporated in reimbursement decision making in Canada with the inception of the pCODR, which was launched in 2010 to provide common recommendations for all provinces except Québec on the clinical effectiveness and cost effectiveness of new cancer drugs. In 2012, pCODR evaluated vemurafenib for use as first-line treatment of patients with *BRAF* mutation-positive metastatic melanoma. In the pCODR final recommendation for vemurafenib, the EGP's best estimate of the incremental cost-utility ratio in untreated patients was CA$221,668 to CA$275,707 per QALY, not including the costs of *BRAF* mutation testing [13]. The pCODR Expert Review Committee judged that vemurafenib was not cost effective within this range and that the price of vemurafenib of CA$372.32 per day would need to be substantially reduced for it to be considered cost effective. The pCODR also recently evaluated ipilimumab, a monoclonal antibody targeting CTLA-4 that was approved on February 1, 2012 for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease [28]. The EGP's best estimate of the incremental cost-utility ratio for ipilimumab in previously treated patients was approximately CA$269,299 per QALY when ipilimumab 3 mg/kg is compared with an undisclosed comparator, assuming a 5-year time horizon and incorporating drug wastage into the economic evaluation [29].

The pCODR published its recommendation for dabrafenib in metastatic melanoma in December of 2013. In their final recommendation for dabrafenib, the pCODR recommended dabrafenib for funding as a first-line treatment for patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma in Canada, conditional on improving cost effectiveness to an acceptable level [30]. The pCODR was satisfied that there is an overall net clinical benefit of dabrafenib compared with dacarbazine. However, the pCODR also concluded that, in the absence of a direct comparison of clinical effectiveness with vemurafenib, the uncertainty in the economic analyses was too great for the committee to determine the net clinical benefit or cost effectiveness of dabrafenib compared with vemurafenib. The model described in this paper was the basis of the economic evaluation that was included in the manufacturer's submission to pCODR. However, whereas the cost-effectiveness analysis submitted to pCODR used PFS and OS data from the June 2012 data cut-off date from BREAK-3, the analyses included in this report used data from the December 2012 data cut-off date. While the precise estimates of cost effectiveness differed, the results and conclusions were qualitatively similar.

4.1 Limitations

This study has several limitations. First, because of the incomplete follow-up at the time of the latest analysis of OS in BREAK-3 and the recensoring associated with the use of the RPSFTM required to adjust for the potentially confounding effects of crossover, data on long-term OS with dabrafenib and especially dacarbazine were limited. Therefore, OS for dacarbazine during the projection period was based on mortality data from the AJCC melanoma registry [23]. The benefits of dabrafenib on OS, expressed as the HR for dabrafenib versus dacarbazine, were assumed to extend only 43.5 weeks after treatment initiation. Based on these and other assumptions, the projected gain in

expected OS with dabrafenib in the base case is approximately one-half the projected gain in expected PFS; i.e., the model projects a decrement in expected PPS for dabrafenib versus dacarbazine equal to one-half the gain in PFS. As there is no reason to believe that, after controlling for crossover, initial treatment with dabrafenib rather than dacarbazine would have a detrimental effect on PPS, projections of the benefits of dabrafenib versus dacarbazine on OS from the model are likely conservative. This conservative bias was partly a consequence of the 5-year time horizon used in the base case. While this time horizon is consistent with the pCODR Evidence Review Group's recommendations in their evaluation of vemurafenib, OS at the end of the 5-year projection was estimated to be 20 % for dabrafenib and 16 % for vemurafenib. Our base-case results do not capture the potential gain in LYs and QALYs associated with that difference in survival.

There is additional uncertainty regarding the comparisons of dabrafenib versus vemurafenib because of the lack of controlled trials directly comparing these therapies and the need to employ an ITC. The ITC of OS for dabrafenib and vemurafenib is potentially confounded by differences between the BREAK-3 and BRIM-3 trials in patients and methods that may have modified the estimated treatment effects of dabrafenib versus dacarbazine and vemurafenib, as measured by the RPSFTM-adjusted HRs for OS in the BREAK-3 and BRIM-3 trials. Any such effect modification would violate the similarity assumption required for the ITC. In particular, the duration of follow-up for OS was different between the trials and if the HRs for OS are not constant (i.e., no proportional hazards), then the comparisons would be confounded. Because the completeness of follow-up for PFS was similar for the two trials, the ITC of PFS is less likely to be confounded than that for OS. The HRs for PFS for dabrafenib versus dacarbazine (HR, 0.37) in BREAK-3 [8] and for vemurafenib versus dacarbazine (HR, 0.38) in BRIM-3 [5] were virtually identical. These data support the analysis assuming class effects for dabrafenib and vemurafenib.

The cost of vemurafenib used in this analysis was based on its list price, consistent with the value used in the pCODR assessment of vemurafenib [13]. However, in Canada, drug prices may vary by province and dabrafenib may not be cost effective compared with vemurafenib in all Canadian provinces. Utility values in this study were based on EQ-5D data from BREAK-3. Because EQ-5D assessments were not routinely collected beyond progression in BREAK-3, post-progression utility values from BREAK-3 may not reflect HRQoL during the entire post-progression period.

A final potential limitation of this study pertains to the applicability of the findings to other settings. The analyses were based on Canadian cost estimates, which may not be representative of cost estimates in other settings. As a consequence, the findings of this study may not be readily applicable to other settings.

5 Conclusions

Dabrafenib may not be cost effective compared with dacarbazine, depending on the threshold used. Although clinical data support the assumption of a class effect for dabrafenib and vemurafenib, the relative effectiveness of the two drugs with respect to their effects on OS is highly uncertain. Additionally, the cost of the *BRAF* inhibitors may vary across Canadian provinces. Therefore, it is not possible to make reliable conclusions regarding the relative cost effectiveness of dabrafenib versus vemurafenib based on available information.

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Conflict of interest TED, JA, and AW are employees of Policy Analysis Inc. (PAI), which has received research funding and consulting fees from GlaxoSmithKline (GSK) for activities related to this study, and received support for travel to meetings to present the study results. PAI also received consulting fees and research funding from GSK for activities unrelated to this study. MMA and MT are employees of and hold stock in GSK. GSK authors were involved in the concept and design of the study, the analysis and interpretation of the data, and contributed to the writing and critical review and approval of the manuscript. All authors had access to and full control of the original data and agree to allow the journal to review this data if requested.

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