CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Dabrafenib and Trametinib (Tafinlar and Mekinist) for Melanoma Adjuvant Therapy

May 3, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

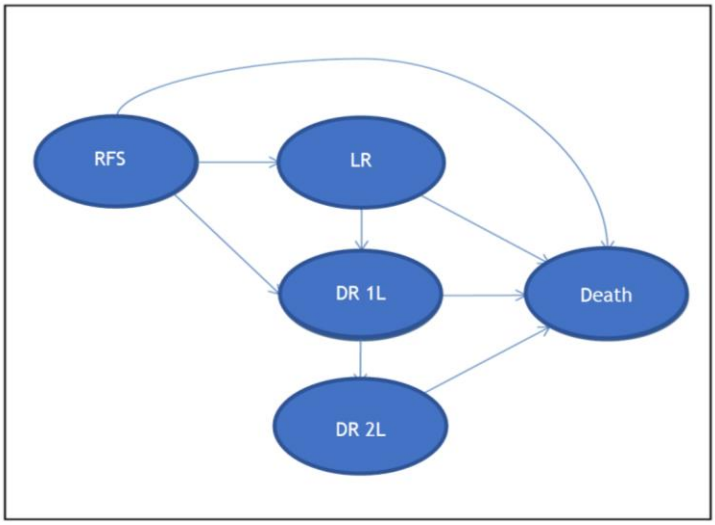
1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Novartis Pharmaceuticals Canada Inc. compared the combination of dabrafenib and trametinib (D+T) to watchful observation (i.e., placebo) for high-risk BRAF V600 mutation-positive melanoma patients after surgical resection (Table 1). The modelled population was identical to that of the COMBI-AD phase III randomized controlled trial;[1] patients with completely resected cutaneous melanoma (stages IIIA, IIIB, IIIC, per American Joint Committee on Cancer [AJCC] 7th edition) with BRAF V600E and V600K mutations, which is consistent with the patient population who would be considered eligible for D+T in Canada.

In a secondary scenario analysis, the cost-effectiveness of the D+T combination was compared to high-dose interferon (HDI), the only regimen that is currently funded as an adjuvant therapy for high-risk melanoma patients in Canada.

Table 1: Submitted Economic Model.

Funding Request/Patient Population Modelled	Patients with completely resected cutaneous melanoma (stages IIIA, IIIB, IIIC per AJCC 7th edition) with BRAF V600E and V600K mutations (modeled patient population aligns with the submitted funding request).
Type of Analysis	Cost-effectiveness and Cost-utility Analyses
Type of Model	A non-homogenous, semi-Markov model
Comparator	1. Watchful observation (base case) 2. High-dose interferon (scenario analysis)
Year of costs	2017
Time Horizon	35 years
Perspective	Canadian public payer
Cost of Dabrafenib Cost of Trametinib	• $66.34 per 75 mg capsule • $265 per day (daily dose is 300mg) • $6,671 per 30-day treatment cycle adjusted for relative dose intensity of 84% • The maximum number of treatment cycles is 12 • $304.17 per 2 mg tablet • $304.17 per day (daily dose is 2 mg) • $8,258 per 30-day treatment cycle adjusted for relative dose intensity of 90.5% • The maximum number of treatment cycles is 12
Base-case analysis Cost of Placebo Scenario analysis Cost of HDI (induction)	• $0 • $125.82 per 10 IU vial • $488.18 per day (daily dose is 20 IU per m^2) • $9763.6 per 28-day cycle (days of use = 20 days)

Cost of HDI (maintenance)	• $8909.31 per 28-day cycle adjusted for relative dose intensity of 91% • $ 2,061 admin fees per cycle • $10,970.25 total cost per cycle • The maximum number of treatment cycles is 1 • $125.82 per 10 IU vial • $244.09 per day (daily dose is 10 IU per m^2) • $2929.08 per 28-day cycle (days of use = 12 days) • $2387.21 per 28-day cycle adjusted for relative dose intensity of 81.5% • $1,237 admin fees per cycle • $3,623.77 total cost per cycle • The maximum number of treatment cycles is 11
Model Structure	A semi-Markov model was used with five health states: i) relapse-free state, ii) loco-regional recurrence (LR), iii) distant recurrence first-line (DR 1L), iv) distant recurrence second-line (DR 2L), and v) death. All patients started from the initial RFS state and moved either to the LR or DR 1L or death states. Patients from the LR state could move to DR 1L or death states; patients from DR 1L state could move to DR 2L or death states, and from DR 2L state to death (absorbing) state. The model was divided into two periods: the first 50 months, corresponding to the maximum follow-up in the COMBI-AD trial, and the extrapolated period beyond 50 months to the end of the time horizon (35 years).  **Figure A: Model Framework.**
Key Data Sources	COMBI-AD trial data; Canadian Physician Survey; literature data
Note: *Drug costs for all comparators in this table are based on DeltaPA. Quintile IMS DeltaPA- accessed on August 15, 2017. All calculations are based on body surface area (BSA) = 1.94 m^2.*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of D+T combination with watchful observation is appropriate. The Submitter also provided an indirect treatment comparison to HDI. The CGP noted that HDI is rarely used in Canadian clinical practice due to high toxicity. Based on this input from the CGP, the EGP has only presented the reanalysis for the comparison to watchful observation.

The CGP considered that the combination of D+T in the adjuvant setting for patients with completely resected melanoma offers a clinically meaningful benefit in RFS and a potential OS benefit.
The CGP noted that combination D+T is a safer and better tolerated treatment option than HDI. They agreed that the adoption of D+T as adjuvant treatment following surgery likely represents an improvement over current available strategies. The CGP noted that the most prevalent toxicities observed with D+T were those associated with pyrexic syndrome, which include fever, chills, headache, fatigue and nausea. All these items were considered in the economic analysis.

A few issues were identified with respect to the generalizability of the COMBI-AD trial results:

- It was unclear if patients initially treated with prior adjuvant systemic therapies (e.g., HDI) could be eligible for combination D+T and whether they would benefit. This issue was not addressed in the economic model since it was based on the COMBI-AD trial, which excluded these patients.
- It was unclear how initial adjuvant therapy might impact the choice of subsequent metastatic treatments (if disease progresses), since there are no data to guide this treatment decision. In the economic model the choice of therapy was based on the COMBI-AD trial; however, these therapies may not accurately reflect the treatment options offered in Canada.
- The comparative efficacy and safety of other systemic treatments offered in the adjuvant setting is unclear. Patients with BRAF-mutated melanoma may benefit from non-BRAF-directed therapies such as immune checkpoint inhibitor therapy. The model compared D+T with watchful observation and HDI only and did not consider other comparators.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered D+T in combination provides a meaningful clinical benefit in the adjuvant setting for stage III melanoma patients. They stated that the only currently funded therapy for these patients is HDI, which has significant toxicity, poor tolerability and minimal clinical benefit in terms of metastatic relapse. The model considered a comparison of D+T with HDI in a scenario analysis. The use of D+T combination therapy may require more BRAF testing, as testing would be required for all high-risk patients and not just for metastatic patients. The economic model incorporated the costs of BRAF testing in the economic analysis but not in the budget impact analysis (BIA) since it was conducted from the perspective of the Canadian provincial public drug plans (PDP).

Registered clinicians concluded that D+T will replace HDI or observation alone, though it is unclear how it may impact the choice of further metastatic treatments. Potential treatment choices for V600 mutation-positive patients included oral targeted therapies, pembrolizumab, or combination immunotherapy with ipilimumab and nivolumab. The choice of metastatic treatment in the economic model was based on the subsequent treatments patients received in the COMBI-AD trial.

Clinicians indicated that the risk of metastatic relapse for stage IIC patients is actually higher than that of stage IIIA patients. Clinicians suggested considering treatment with D+T combination for stage IIC patients, and that indication drift to include stage IIC patients could be expected. The economic model was based on the COMBI-AD trial that excluded stage IIC patients.

Summary of patient input relevant to the economic analysis
Two patient advocacy groups provided input. Patients with melanoma indicated longer survivorship, cure, slowing/halting of disease progression, quality of life and manageable side effects as important factors in their illness and for new therapy. For stage III patients who were receiving D+T as adjuvant treatment, few had been on interferon before. They all indicated that side effects of interferon were worse than that of the combination therapy. Patients indicated fever, joint pain, fatigue and rash as side effects of D+T but noted that the large majority of these were manageable. Patients emphasized that there is no current available treatment for stage III melanoma, and both patients and caregivers would like to receive access to therapy that would prevent recurrences. All indicated factors were adequately considered in the economic analysis.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG identified the following factors to consider while implementing a funding recommendation for combination D+T:

Currently funded treatment: PAG is seeking information on D+T in comparison with HDI. The submitter evaluated the cost-effectiveness of combination D+T in comparison to HDI as a secondary scenario analysis.

Eligible population: PAG is seeking guidance for the use of D+T for patients who are currently being treated with HDI, and the appropriate treatment duration for these patients. The model was based on the COMBI-AD trial that excluded patients who had received prior systemic therapy, and hence did not address this issue.

Implementation factors: PAG noted that additional resources to administer, monitor and treat adverse events (AEs) might be required. The economic model incorporated the frequencies and management of AEs of grade 3 and higher. The resource utilization such as frequency of clinic visits and diagnostic tests were estimated based on a Canadian Physician Survey and were addressed in the model.

Sequencing with current therapies: The choice and initiation of subsequent metastatic treatments in the economic model was based on the COMBI-AD trial data. PAG noted that adjuvant nivolumab may become available and were seeking guidance on the best-recommended treatment for BRAF mutation positive patients in the adjuvant setting. The submitted model did not address the comparison of D+T combination with nivolumab.

1.3 Submitted and EGP Reanalysis Estimates

In the submitted cost-effectiveness analysis, the D+T treatment group had higher life expectancy than placebo by 3.1 years with an increased cost of $84,278 and an ICER of $27,183/LY. In the cost-utility analysis, the difference in QALYs was 2.6 favouring D+T and resulting in an ICUR of $32,399/QALY (Table 2).

Using trial data only, D+T versus placebo resulted in 0.37 life years gained, contributing to 14% of life years gained. The 86% life year gain comes from the extrapolated data up to 35 years of time horizon.

The main cost drivers of the submitted model were relative dose intensity (RDI) and medication costs. RDIs were based on the average daily dose reported in the COMBI-AD trial and were tested in sensitivity analyses (including the value of RDI = 100%).

The main drivers of clinical outcome (LYs, QALYs) were the choice of curves used for modelling RFS, hazard ratios (HRs) applied to RFS and time-to-second-line treatment or death (TT2L) curves (time to DR 2L state) and the time horizon of the model.

The major identified limitation was the uncertainty related to the OS benefit that was estimated indirectly through projections of RFS. The Submitter fitted different distributions to model RFS and selected the log-logistic unrestricted cure model based on visual and statistical fit, and clinical plausibility.

Table 2: Submitted and EGP Estimates – Deterministic Analysis – D+T versus Placebo.

Estimates (range/point)	Submitted	EGP Reanalysis (lower bound)	EGP Reanalysis (upper bound)
ΔE (LY)	3.10	2.51	1.44
Progression-free	3.96	3.33	2.0
Post-progression	-0.86	-0.82	-0.56
ΔE (QALY)	2.6	2.17	1.24
Progression-free	3.21	2.75	1.65
Post-progression	-0.61	-0.58	-0.41
ΔC ($)	$ 84,278	$85,327	$104,621
ICUR estimate ($/QALY)	**$32,399**	$39,339	$84,271

Note: Deterministic results have been provided since the probabilistic results by health state were not available in the submitted model. Probabilistic results can be found in Table 3.

In the scenario analysis (deterministic analysis) comparing D+T with HDI, the D+T group had higher life expectancy than the HDI group by 0.74 years with an increased cost of $79,146, and an ICER of $106,414/LY. In the cost-utility analysis, the difference in QALYs was 0.64 favouring D+T and resulting in an ICUR of $124,240/QALY.

The main assumptions and limitations of the submitted economic evaluation were:
Most of the key model variables were based on the COMBI-AD trial data and the assumptions were reasonable and appropriate. However, a few concerns were identified, which are listed below in order of importance.

Overall survival: The main limitation was that direct evidence was not used to estimate OS because the trial's survival data are immature; therefore, OS was not modeled directly. Rather, it was estimated indirectly from parametrized RFS curves assuming if a patient develops an event in the RFS state, then that particular "relapse" event was either LR, or DR 1L or death with a specified probability that varies depending on treatment strategy and time since treatment initiation. The distribution of event type was based on the COMBI-AD trial data.

Though the survival gain (area in-between the two survival curves) with D+T was only slightly higher (by ~0.07 year) for the modeled versus COMBI-AD trial data for the four-year time horizon, the actual survival curves were converging at the end of 48 months (based on a limited number of patients at risk), while the modeled curves were diverging. This makes the estimation of OS data highly uncertain and may overestimate the benefits of the D+T combination.

None of the distributions applied to the RFS curves (that could be tested in the model) provided a better fit for OS. Therefore, the EGP varied the HR applied to the RFS curve (log-logistic unrestricted cure model) for the D+T strategy by +25% (making the HR=1.25) in order to model a more conservative estimate of the survival difference between the treatment strategies and determine the resultant impact on the ICUR.

Time horizon: The Submitter extrapolated survival curves out to 35 years based on four-years of clinical data. The CGP considered this to be overly optimistic. Based on the CGP's recommendation, as well as

considering uncertainties related to the available OS data, the EGP reduced the time horizon from 35 years to 25 years, to represent a more clinically realistic scenario.

The EGP also explored the impact of a 10-year time horizon in a reanalysis, since it was used as the base case for the pCODR review on adjuvant nivolumab for stage III melanoma. Both regimens (nivolumab and D+T) were administered as an adjuvant treatment for high-risk BRAF mutated melanoma patients after surgical resection. However, there were some differences in patient populations and follow-up duration between pivotal trials CheckMate 238 and COMBI-AD. The CheckMate 238 trial evaluated nivolumab in resected stage III and resected stage IV patients, the latter stage being associated with worse prognosis. Furthermore, patient follow- up in the CheckMate 238 trial was limited to two years while the follow-up in COMBI-AD was approximately double at four years; hence, extrapolation of patient outcomes and costs beyond 10 years is less uncertain with the COMBI-AD trial data. As per the AJCC 8th edition, 10-year survival estimates for stages IIIA-IIIC vary between 60% and 88%, and are 24% for stage IIID. Considering these differences in patient population, follow-up time, and survival rates the EGP felt that using a 10-year time horizon may underestimate survival benefits, and therefore elected to use a 25-year time horizon for the base-case scenario. For the worst-case scenario the EGP conducted a reanalysis using a 10-year time horizon.

Subsequent metastatic therapies: The choice of subsequent therapies was based on the COMBI-AD trial data. Specifically, everyone receiving D+T would have the same metastatic treatment as those patients in the D+T group of the COMBI-AD trial, and everyone receiving placebo would have the same metastatic treatment as those patients in the watchful observation group of the COMBI-AD trial. The CGP considered this distribution may not be representative of the Canadian health system and proposed distributions with greater weights for the single agents pembrolizumab and nivolumab, and for combination ipilimumab-nivolumab as first-line metastatic treatment. The economic model did not allow for accurately evaluating the impact of proposed treatment distributions on the ICUR. However, rough estimation showed that the ICUR would shift toward lower values.

Progression following LR: The Submitter used RFS curves to estimate the probabilities of DR and death after LR, assuming that progression from LR to subsequent states would increase proportionately among patients in the LR state versus the RFS state. The assumed HRs were estimated to be 4.47 over 1-12 months, and 1.69 over 13-58 months based on the study by Salama et al.[2] The Salama et al study included patients with melanoma of all stages with and without BRAF mutation from a single institution (Duke University Medical Center database). Hence, it is unclear if this study reflected the progression-free survival for the current patient population. The EGP tested this assumption in sensitivity analyses by varying the HR estimates (both 4.47 and 1.68) by ±25% around its base value.

Costs and resource use: The Submitter considered the following costs: BRAF mutation testing, medication (adjuvant setting and metastatic therapies), drug administration (for i.v. drugs), monitoring and follow-up in adjuvant and metastatic settings, treating recurrence, adverse events-related costs, and end-of life care. Costs were based on Ontario-Case costing.[3] In the reanalysis, the cost of dispensing for oral drugs ($8.83, Ontario dispensing fees) was added.

The remaining assumptions in the model had limited impact on the ICUR in sensitivity analyses.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model (Table 3):

- HR=1.25 was applied to the D+T RFS curves in the RFS state
- The time horizon was limited to 25 years
- Assuming ±25% of HR applied to RFS curves in the LR state
- Dispensing fees ($8.83 per cycle) for oral drugs

Table 3: Detailed Description of EGP Reanalysis for D+T versus Placebo.

One-way and multi-way sensitivity analyses - Deterministic Analysis					
Description of Reanalysis	**ΔC**	**ΔE QALYs**	**ΔE LYs**	**ICUR (QALY)**	**Δ from baseline submitted ICER**
1. HR=1.25 applied to RFS D+T curve at RFS state (log-logistic unrestricted model)	$102,865	1.52	1.8	$67,809	$35,410
2. Assuming 25-year time horizon	$85,586	2.15	2.49	$39,769	$7,370
3. Assuming 10-year time horizon	$93,513	0.98	1.05	$95,191	$62,792
4. HR applied to RFS curve at LR state +25%	$83.951	2.62	3.12	$32,033	$ -366
5. HR applied to RFS curve at LR state -25%	$85,212	2.55	3.04	$33,411	$1,012
6. Oral drug dispensing fees	$84,305	2.60	3.10	$32,425	$26
EGP's Reanalysis for the Best Case Estimate - Deterministic and Probabilistic Analyses					
Description of Reanalysis	**ΔC**	**ΔE QALYs**	**ΔE LYs**	**ICUR**	**Δ from baseline submitted ICER**
Baseline (Submitter's best case - deterministic analysis)	**$84,278**	**2.60**	**3.10**	**$32,399**	--
Baseline (Submitter's probabilistic analysis)	$85,632	2.59	3.09	$33,068	--
[LOWER BOUND]					
Assuming 2, 4 and 6 together (deterministic)	$85,327	2.17	2.51	$39,339	-$6,940
Assuming 2, 4 and 6 together (probabilistic)	$86,669	2.16	2.50	$40,167	-$7,768
Worst-case scenario: Assuming 3, 4 and 6 together (deterministic)	$93,287	0.99	1.06	$94,018	-$61,617
Worst-case scenario: Assuming 3, 4 and 6 together (probabilistic)	$94,227	0.99	1.06	$95,303	-$62,904
[UPPER BOUND]					
Assuming 1, 2, 5, and 6 together (deterministic)	$104,621	1.24	1.44	$84,271	-$51,872
Assuming 1, 2, 5, and 6 together (probabilistic)	$105,737	1.23	1.42	$85,850	-$53,451
Worst-case scenario: Assuming 1, 3, 5, and 6 together (deterministic)	$109,992	0.63	0.67	$175,557	-$143,158
Worst-case scenario: Assuming 1, 3, 5, and 6 together (probabilistic)	$110,821	0.62	0.67	$177,525	-$145,126

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that influenced the BIA results the most were percentage of the eligible population, treatment duration, and RDI. Increases in the values of these factors increased the budget impact.

The key limitation was that the BIA considered only the cost of treatments. Other costs associated with the management of melanoma (e.g., administration costs, BRAF testing) were not included in the analysis. The inclusion of BRAF testing on the BIA was explored by the EGP. After accounting for BRAF testing fees, the three-year cumulative incremental cost of the D+T combination compared to standard of care increased by 1.9%.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for the D+T combination when compared to watchful observation is:

- Between $40,167/QALY and $85,850/QALY.
- Within this range, the best estimate would likely be: $85,850/QALY with a conservative RFS/OS benefit for D+T versus watchful observation. If the Submitter's assumption holds regarding modeled RFS curves then the ICUR will be $40,167/QALY.
- The extra cost of the D+T combination is between $86,669 and $105,737. The main factors that influence the ΔC are the drug costs and RDI.
- The extra clinical effect of the D+T combination is between 1.23 and 2.16. The main factors that influenced the ΔE were choice of HRs applied to RFS and TT2L curves (time to DR 2L state) and the time horizon of the model.
- The deterministic results were similar to the probabilistic sensitivity results.

Overall conclusions of the submitted model:

- The model structure was appropriate and uncertainty was addressed in a number of scenario analyses, one-way sensitivity and probabilistic analyses.
- Comparing D+T combination to watchful observation yields to an ICUR between $40,167/QALY to $85,850/QALY.
- The major identified limitation was the high uncertainty related to OS benefit given divergences in the modeled OS curves compared to observed COMBI-AD trial data.
- Based on the submitted economic model, the ICUR for D+T versus HDI is $124,240/QALY.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Melanoma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of dabrafenib and trametinib in combination for the adjuvant treatment of BRAF-mutated melanoma. A full assessment of the clinical evidence of dabrafenib and trametinib adjuvant treatment for BRAF-mutated melanoma is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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