CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

Dabrafenib (Tafinlar) in combination with Trametinib (Mekinist)

(Novartis Pharmaceuticals Inc.)

Indication: Dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a BRAF V600 mutation

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
DAB+TRAM	dabrafenib in combination with trametinib
ICER	incremental cost-effectiveness ratio
ITC	indirect treatment comparison
LY	life-year
NSCLC	non-small cell lung cancer
OS	overall survival
pCODR	pan-Canadian Oncology Drug Review
PERC	pCODR Expert Review Committee
PDC	platinum-doublet chemotherapy
PEM+PDC	pembrolizumab plus platinum-doublet chemotherapy
PFS	progression-free survival
QALY	quality-adjusted life-year
RECIST	Response Evaluation Criteria in Solid Tumors

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	dabrafenib (Tafinlar, 50 mg and 75 mg, capsules) in combination with trametinib (Mekinist, 0.5 mg and 2.0 mg, tablets)
Submitted price	dabrafenib, 50 mg: $44.88 per capsule dabrafenib, 75 mg: $67.32 per capsule trametinib, 0.5 mg: $76.98 per tablet trametinib, 2.0 mg: $307.94 per tablet
Indication	Patients with metastatic non-small-cell lung cancer (NSCLC) with a BRAF V600 mutation.
Health Canada approval status	Approved
Health Canada review pathway	Priority review
NOC date	May 18, 2018
Reimbursement request	Patients with metastatic NSCLC with a BRAF V600 mutation and who have not received any prior anti-cancer therapy for metastatic disease.
Sponsor	Novartis Pharmaceuticals Canada Inc.
Submission history	Previously reviewed: Yes Indication: In combination for the treatment of patients with advanced NSCLC with a BRAF V600 mutation and who have been previously treated with chemotherapy Recommendation date: November 2, 2017 Recommendation: Do not reimburse Previously reviewed: Yes Indication: For the adjuvant treatment of patients with melanoma with a BRAF V600 mutation and involvement of lymph node(s), following complete resection Recommendation date: May 3, 2019 Recommendation: Conditional on cost-effectiveness being improved to an acceptable level. Previously reviewed: Yes Indication: In combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF 600 mutation Recommendation date: July 21, 2015 Recommendation: Conditional on cost-effectiveness being improved to an acceptable level.

NOC = Notice of Compliance; NSCLC = non-small cell lung cancer

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	• Patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600 mutation who have who have not received any prior anti-cancer therapy for metastatic disease – reimbursement request • Patients with metastatic non-small cell lung cancer (NSCLC) with a BRAF V600 mutation who have who have received prior anti-cancer therapy for metastatic disease
Treatment	Dabrafenib in combination with trametinib (DAB+TRAM)
Comparators	No prior anti-cancer therapy for metastatic disease: • Pembrolizumab in combination pemetrexed and platinum chemotherapy (PEM+PDC) • Platinum-doublet chemotherapy (PDC) Previously treated with anti-cancer therapy for metastatic disease: • Immuno-oncology agents (nivolumab; pembrolizumab) • Note: this population lies outside the reimbursement request and was not the focus of the pharmacoeconomic review
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (10 years for the analysis of untreated patients; 5 years for the analysis of treated patients)
Key data source	Cohort C of the study BRF113928, sponsor's indirect treatment comparison of the study BRF113928 and Flatiron database
Submitted results for base case	No prior anti-cancer therapy • Based on the sequential analysis, the ICER for DAB+TRAM versus PEM+PDC = $166,552 per QALY (incr. costs = $91,920; incr. QALYs = 0.51) Previously treated with anti-cancer therapy • ICER for DAB+TRAM versus immuno-oncology agents = $846,112 per QALY (incr. costs = $132,472; incr. QALYs = 0.16).
Key limitations	No prior anti-cancer therapy (reimbursement population) • The CADTH Clinical Review identified several limitations with the sponsor-submitted indirect-treatment comparison and concluded that the comparative efficacy for each treatment was unclear. Consequently, CADTH made no assumption about the relative efficacy of treatment. • The parametric function that the sponsor selected to extrapolate the OS curve for DAB+TRAM (i.e., generalized gamma function) overestimated expected survival at the end of the modeled time horizon, according to the clinical experts consulted by CADTH for this review. • Relevant comparators were excluded: pembrolizumab monotherapy or atezolizumab-based therapies.

CADTH reanalysis results	• CADTH reanalyses addressed the reimbursement population exclusively (no prior anti-cancer therapy) and included: the progression-free survival (PFS) and overall survival (OS) outcomes from the BRF113928 study to DAB+TRAM and all comparators (PEM+PDC, PDC); and a revised parametric function to characterize the OS extrapolation for DAB+TRAM.
	  ○ The adjustment to comparative efficacy resulted in equivalent incremental effectiveness for all treatments (DAB+TRAM, PEM+PDC, PDC).
	  ○ DAB+TRAM was dominated by PEM+PDC (i.e., was $21,506 more costly; equivalent QALYs) and was not among the optimal strategies (i.e., not on the efficiency frontier)

Component	Description
	○ At a WTP threshold of $50,000 per QALY, DAB+TRAM had a 28% chance of being cost-effective (i.e., less costly). DAB+TRAM would require a price reduction of at least 88% to be considered cost-effective compared with PDC. ○ DAB+TRAM was consistently more costly than the included comparators in scenario analyses, with equivalent QALYs. ○ Cost-effectiveness of DAB+TRAM compared to pembrolizumab monotherapy atezolizumab-based therapies is unknown.

ICER = incremental cost-effectiveness ratio; LY = life-year; NSCLC = non-small cell lung cancer; PSM = partitioned survival model; QALY= quality-adjusted life-year; incr. = incremental; ITC = indirect treatment comparison; DAB+TRAM = dabrafenib plus trametinib; PEM+PDC = pembrolizumab plus platinum-doublet chemotherapy; PDC = platinum-doublet chemotherapy

Conclusions

Based on the CADTH Clinical Review of the sponsor's ITC, the relative efficacy of dabrafenib in combination with trametinib (DAB+TRAM) versus PD(L)1 + chemotherapy (i.e., pembrolizumab plus platinum-doublet chemotherapy (PEM+PDC)) or the first line chemotherapy (i.e., platinum-based chemotherapy (PDC)) remains unclear. Given the limitations within the clinical evidence, the CADTH Pharmacoeconomic analysis was unable to incorporate the ITC estimates into the model, resulting in an assumption of equivalent efficacy between treatments.

CADTH undertook re-analyses to address limitations in the sponsor's economic submission for the reimbursement population exclusively (no prior anti-cancer therapy), including revising the progression-free survival and overall survival extrapolations for the comparators to align with what was modeled for DAB+TRAM; and aligning the parametric function used to extrapolate the overall survival curve for DAB+TRAM with clinical expert feedback. According to the sequential analysis of the CADTH base case, DAB+TRAM was dominated by PEM+PDC (i.e., was $21,506 more costly; generated equivalent QALYs). The probability that DAB+TRAM represented the most cost-effective strategy was 28% if the WTP threshold was $50,000 per QALY. A price reduction of at least 88% is needed for DAB+TRAM to be cost-effective compared to PDC.

The CADTH reanalysis is still subject to considerable uncertainty since the clinical effectiveness of DAB+TRAM relative to PEM+PDC and PDC remains uncertain, and unknown with respect to other currently available treatments for metastatic NSCLC with the BRAF V600 mutation. Incremental costs were consistently higher with DAB+TRAM in CADTH scenario analyses, with equivalent estimated effectiveness. The comparative effects of DAB+TRAM relative to pembrolizumab monotherapy and atezolizumab-based therapies are unknown

Based on the sponsor's submitted budget impact analysis, introducing DAB+TRAM was associated with an estimated budget-impact of [redacted] over the first three years. CADTH re-analyses estimated a budget impact of $34,357,089 ($7,485,460 in year 1, $11,243,324 in year 2, $15,628,304 in year 3).

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Submitted BIA and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

References

1. Dabrafenib (tafinlar) in combination with trametinib (mekinist): clinical review report. *(CADTH drug reimbursement review)*. Ottawa (ON): CADTH; 2021.
2. Pharmacoeconomic evaluation. In: pan-Canadian Oncology Drug Review sponsor submission: Tafinlar (dabrafenib) 50 mg and 75 mg capsules and Mekinist (trametinib) 0.5 mg and 2 mg tablets. Dorval (QC): Novartis; 2020 Oct 1.
3. Health Canada. Notice of compliance: Tafinlar (dabrafenib, supplied as dabrafenib mesylate). 2018.
4. Health Canada. Notice of compliance: Mekinist (trametinib). 2018.
5. PrMekinist® (trametinib): 0.5 mg and 2 mg tablets [product monograph]. Dorval (AC): Novartis Pharmaceuticals; 2020 Sep 8.
6. PrTafinlar® (dabrafenib mesylate): 50 mg and 75 mg capsules [product monograph]. Dorval (AC): Novartis Pharmaceuticals; 2020 Sep 10.
7. Clinical study report: CDRB436E2201. A Phase II study of the BRAF inhibitor dabrafenib as a single agent and in combination with the MEK inhibitor trametinib in subjects with BRAF V600E mutation positive metastatic (stage IV) non-small cell lung cancer [internal sponsor's report]. Dorval (QC): Novatris Pharmaceuticals Canada Inc.; 2020 Mar 20.
8. Comparison of clinical outcomes among patients treated with dabrafenib plus trametinib in the DRB436E2201 trial versus a real-world, retrospective cohort of patients treated with standard of care for BRAF-mutated advanced non-small cell lung cancer. In: pan-Canadian Oncology Drug Review sponsor submission: Tafinlar (dabrafenib) 50 mg and 75 mg capsules and Mekinist (trametinib) 0.5 mg and 2 mg tablets [internal sponsor's report]. Dorval (QC): Novatris Pharmaceuticals Canada Inc.; 2020 Oct 1.
9. pan-Canadian Oncology Drug Review final economic guidance report: Pembrolizumab (Keytruda) non-small cell lung cancer. Ottawa (ON): CADTH; 2016: https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_fn_egr.pdf. Accessed 2021 Feb 26.
10. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *The Lancet Oncology.* 2017;18(10):1307-1316.
11. Gadgeel S, Rodriguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer. *J Clin Oncol.* 2020;38(14):1505-1517.
12. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J Clin Oncol.* 2009;27(8):1227-1234.
13. Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. *Ann Oncol.* 2005;16(7):1069-1075.
14. Chouaid C, Agulnik J, Goker E, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. *J Thorac Oncol.* 2013;8(8):997-1003.
15. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes.* 2008;6:84.
16. Répertoire québécois et système de mesure des procédures de biologie médicale - Édition 2020-2021. Québec (QC): Ministère de la Santé et des Services sociaux; 2020: https://publications.msss.gouv.qc.ca/msss/document-002602/?&date=DESC. Accessed 2021 Mar 8.
17. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2017: https://data.ontario.ca/dataset/ontario-case-costing-initiative-occi. Accessed 2021 Feb 26.
18. Ontario Ministry of Health, Ontario Ministry of Long-Term Care. Ontario drug benefit formulary/comparative drug index. 2020; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2021 Mar 8.
19. Schedule of benefits for laboratory services: effective July 1, 2020. Toronto (ON): Ontario Ministry of Health; 2020: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn2020.pdf. Accessed 2021 Feb 26.
20. Walker H, Anderson M, Farahati F, et al. Resource use and costs of end-of-life/palliative care: Ontario adult cancer patients dying during 2002 and 2003. *J Palliat Care.* 2011;27(2):79-88.
21. Budget Impact Analysis: In: pan-Canadian Oncology Drug Review sponsor submission: Tafinlar (dabrafenib) 50 mg and 75 mg capsules and Mekinist (trametinib) 0.5 mg and 2 mg tablets. [internal sponsor's report]. Dorval (QC): Novatris; 2020 Oct 1.
22. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-2350.