pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Dabrafenib (Tafinlar) and Trametinib (Mekinist)

Submitted Reimbursement Request:
In combination for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a *v-Raf murine sarcoma viral oncogene homolog B* (*BRAF*) V600 mutation and who have not received any prior anticancer therapy for metastatic disease.

Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: March 18, 2018	**Submission Date:** October 1, 2020
Initial Recommendation: April 1, 2021	**Final Recommendation:** May 28, 2021

Approximate per patient drug costs, per month (28 Days)	• Dabrafenib costs $44.88 per 50 mg capsule and $67.32 per 75 mg capsule • Trametinib costs $76.98 per 0.5 mg tablet and $307.94 per 2.0 mg tablet • At the recommended dose of 150 mg twice daily (300 mg) of dabrafenib and 2 mg once daily of trametinib, the combination regimen costs $16,162 per 28-day course.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of dabrafenib in combination with trametinib as treatment for patients with metastatic non-small cell lung cancer (NSCLC) with a *v-Raf murine sarcoma viral oncogene homolog B* (*BRAF*) V600 mutation who have not received any prior anticancer therapy for metastatic disease, if the following conditions are met:

- cost-effectiveness is improved to an acceptable level
- feasibility of adoption (budget impact) is addressed.

Eligible patients include those with good performance status. Treatment should continue until disease progression or unacceptable toxicity.

pERC made this recommendation because it considered there may be a net clinical benefit of dabrafenib plus trametinib based on the clinically meaningful overall response rate (ORR), the durability of response, and the manageable toxicity profile observed in patient cohort C from Study BRF113928. pERC also considered the need for a targeted treatment option in these patients who have an identified driver mutation. However, pERC acknowledged that because of the non-comparative design of the available evidence, there was considerable uncertainty about the magnitude of clinical benefit of dabrafenib plus trametinib compared to currently available treatment options (immunotherapy and/or platinum-

	based chemotherapy) with respect to outcomes important to decision-making, including overall survival (OS), progression-free survival (PFS), and quality of life (QoL). Further, there was also a lack of mature OS data from Study BRF113928 to validate the observed clinical benefit of response outcomes. pERC agreed that dabrafenib plus trametinib aligns with the following patient values: offers convenient oral administration that reduces caregiver burden, provides symptom control, has a manageable toxicity profile, and fulfills a need for a targeted treatment option. pERC concluded that, at the submitted price, dabrafenib plus trametinib were more costly than pembrolizumab plus platinum-doublet chemotherapy (PDC) and PDC alone but that incremental effectiveness was uncertain. This uncertainty was due to a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation. The sponsor's pharmacoeconomic submission did not include relevant treatment comparators (pembrolizumab monotherapy; atezolizumab-based therapies), and so the cost-effectiveness of dabrafenib plus trametinib in comparison to these therapies is unknown. The sponsor's estimate of the 3-year budget impact was underestimated and was most sensitive to assumptions about market share of dabrafenib plus trametinib and the proportion of NSCLC patients with a *BRAF* V600 mutation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing arrangements to improve cost-effectiveness and budget impact** Given that pERC considered there may be a net clinical benefit of dabrafenib plus trametinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of the combination. pERC concluded that a reduction in drug price would be required to improve the cost-effectiveness of dabrafenib plus trametinib to an acceptable level and to improve the budget impact. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on 4 main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Lung cancer is the leading cause of cancer death in Canada, with an estimated 20,800 deaths in 2020. NSCLC accounts for about 88% of all lung cancer cases, with most patients presenting with non-curable disease; approximately 50% and 30% of patients are diagnosed with stage IV and locally advanced stage III disease, respectively. Given the high proportion of patients presenting with advanced stages, as well as the high proportion of early-stage patients who recur despite surgery or high-dose radiotherapy, the expected relative 5-year survival is 18%. *BRAF* mutations, which occur in non-squamous NSCLC, account for approximately 2% of lung adenocarcinomas. Therefore, it is estimated that approximately 373 patients had *BRAF* V600E–mutated NSCLC in 2020. Treatment decisions for advanced or metastatic NSCLC in the first-line setting are typically dependent on the driver mutation status (i.e., presence or absence) of patients. Targeted therapies are currently available for *epidermal growth factor receptor* (*EGFR*) and *anaplastic lymphoma kinase* (*ALK*) mutation–positive disease, as well as for *c-ros oncogene 1* (*ROS1*) translocations. However, there remains a need for effective therapeutic targets to advance treatment options in NSCLC patients who are *BRAF* V600 mutation–positive; these patients are currently treated with non-targeted standard-of-care regimens for advanced or metastatic non-squamous NSCLC that includes immunotherapy with or without PDC.

pERC deliberated the results from a small (n = 36) single arm (cohort C) of a non-comparative, open-label, phase II trial, Study BRF113928, that evaluated the combination of dabrafenib plus trametinib in previously untreated adult patients with *BRAF* V600E–mutant stage IV NSCLC. pERC noted that in Cohort C of Study BRF113928, a large proportion of patients experienced a response as assessed by investigator. The ORR by investigator assessment, which was the primary end point of the trial, met the pre-specified threshold for clinically meaningful treatment effect because the lower 95% confidence limit exceeded the null hypothesis ORR of 30%, which was based on the response rates observed with platinum-based chemotherapy. pERC noted that the ORR was driven by partial responses but that the data on median duration of response (DOR) indicated that responses were durable, and similar results for ORR were obtained by independent review committee assessment. pERC concluded that the ORR and DOR observed in the trial were clinically meaningful, but there was a lack of mature survival data from the trial to validate the observed clinical benefit on response outcomes.

pERC discussed the limitations of relying on non-comparative evidence and concluded that there is considerable uncertainty surrounding the magnitude of clinical benefit of dabrafenib plus trametinib compared to currently available treatment options (i.e., immunotherapy and/or platinum-based chemotherapy) with respect to outcomes important to decision-making, including OS, PFS, and QoL. pERC discussed that while the incidence of *BRAF* V600 mutation–positive NSCLC is low, the incidence and prevalence of lung cancer is high, and conducting a randomized controlled trial with appropriate comparators would be feasible. However, pERC acknowledged that it is unlikely that a randomized controlled trial will be forthcoming considering the combination is now considered standard of care in other countries including the US.

pERC discussed the indirect treatment comparison (ITC) that was submitted by the sponsor that compared outcomes of patients with advanced or metastatic *BRAF*-mutated V600 NSCLC who were treated with dabrafenib plus trametinib (using data from cohort C) to historical control patients who had been treated in the first-line setting with pembrolizumab plus PDC or PDC alone (using data from a real-world evidence [RWE] data base). pERC noted that pembrolizumab monotherapy was not included as a comparator in the analysis. The results of the ITC suggested that, in terms of OS, dabrafenib plus trametinib was similar in efficacy when compared to pembrolizumab plus PDC and was superior in efficacy when compared to PDC alone. Based on these results, some pERC members questioned whether there was a need for reimbursement of the combination since it did not demonstrate superiority over pembrolizumab plus PDC. However, given the small sample sizes of the patient cohorts and the limitations of the ITC identified by

the CADTH Methods Team, pERC agreed there was uncertainty with respect to the comparative efficacy estimates obtained from the analysis for dabrafenib plus trametinib versus both comparators.

pERC deliberated the safety of dabrafenib plus trametinib and noted that all patients in Cohort C of Study BRF113928 experienced at least 1 adverse event (AE). The AEs that occurred most frequently among treated patients included pyrexia, nausea, diarrhea, fatigue, peripheral edema, decreased appetite, dry skin, and vomiting. pERC noted that most patients experienced grade 3 or 4 AEs, of which the majority were pyrexia, elevation in alanine aminotransferase, and hypertension. pERC discussed that while AEs requiring dose interruption or delay or dose reduction were high, the rate of treatment discontinuation as a consequence of AEs was much lower. Overall, pERC agreed with the Clinical Guidance Panel (CGP), as well as the registered clinicians and patient advocacy group providing input and concluded that the toxicity profile of the combination of dabrafenib plus trametinib was manageable through the use of dose adjustment and supportive medications. However, pERC was unable to deliberate on the impact of dabrafenib plus trametinib on patient QoL because data on this outcome were not collected in the trial.

pERC also considered the need for a targeted treatment option in these patients who have an identified driver mutation. pERC discussed that the CGP, and the registered clinicians and patient advocacy group providing input for this submission, all emphasized the preference for patients with an identified driver mutation to be treated with targeted therapy upfront as first-line therapy opposed to non-targeted treatments based on the available evidence and the knowledge that the specificity of targeted therapy has led to superior outcomes in patients with other driver mutations in NSCLC (i.e., *EGFR*, *ALK*, and *ROS1*). pERC also noted the patient advocacy groups' concerns that patients with BRAF-mutated NSCLC do not have equitable access to effective target therapies compared to Canadian NSCLC patients with other mutations or to *BRAF*-mutated patients in other countries where dabrafenib plus trametinib is the accepted standard of care.

In summary, pERC concluded that there may be a net clinical benefit of dabrafenib plus trametinib based on the clinically meaningful ORR, the durability of response, and the manageable toxicity profile observed in patient cohort C from Study BRF113928. pERC also considered the need for a targeted treatment option in these patients who have an identified driver mutation. However, pERC acknowledged that because of the non-comparative design of the available evidence, there was considerable uncertainty about the magnitude of clinical benefit of dabrafenib plus trametinib compared to currently available treatment options (immunotherapy and/or platinum-based chemotherapy) with respect to outcomes important to decision-making, including OS, PFS, and QoL. Further, there was also a lack of mature OS data from Study BRF113928 to validate the observed clinical benefit on response outcomes.

pERC discussed the patient advocacy input that was received supporting this submission and noted that patients value treatments that are effective in terms of delaying progression and improving survival, offer better symptom control, have manageable side effects, improve QoL, and reduce the burden placed on caregivers. While pERC reiterated that the evidence from Cohort C of Study BRF113928 cannot address whether dabrafenib plus trametinib delays progression, prolongs survival, and improves QoL compared to currently available treatments, pERC agreed with the CGP that tumour regression does improve cancer symptoms. pERC also agreed that compared to current treatments, the oral administration of dabrafenib plus trametinib permits patients to better manage their own care and, in turn, reduces the burden on caregivers. However, pERC noted that patients expressed concern about the high cost of this treatment which might render it inaccessible for some patients; and further acknowledged that there is unequal access to paid oral treatment options in Canada. Therefore, pERC concluded that dabrafenib plus trametinib aligns with the patient values of offering a convenient oral administration that reduces caregiver burden, provides symptom control, having a manageable toxicity profile, and fulfilling a need for a targeted treatment option.

pERC reviewed the cost-effectiveness evidence of dabrafenib plus trametinib compared to pembrolizumab plus PDC and PDC alone. pERC noted that the limitations within the sponsor's ITC contributed meaningful uncertainty to estimates of incremental effectiveness. Therefore, the economic evidence provided by the Economic Guidance Panel made no assumption about relative efficacy of these treatments and considered them equally effective within the base case reanalysis. pERC discussed this approach and suggested that there was nevertheless good reason to conclude that dabrafenib plus trametinib is more efficacious than PDC; the relative effectiveness of dabrafenib plus trametinib versus pembrolizumab plus PDC was still uncertain. In the absence of reliable cost-effectiveness evidence, pERC suggested that a price reduction was warranted such that dabrafenib plus trametinib should be priced similarly to pembrolizumab plus PDC

as it was not possible to estimate a price reduction that would result in dabrafenib plus trametinib being cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY). pERC also noted that the sponsor had not included comparative evidence for pembrolizumab monotherapy and atezolizumab-based therapies, and that the cost-effectiveness of dabrafenib plus trametinib compared to these regimes was unknown.

pERC also discussed the budget impact analysis. pERC noted that the dabrafenib plus trametinib market share and the percentage of patients progressing from stage III disease to metastatic disease were likely underestimated in the sponsor's base case, leading to a considerable increase in the estimated budget impact over 3 years. The budget impact was also sensitive to the percentage of NSCLC with a *BRAF* V600 mutation.

Upon reconsideration of the Initial Recommendation, pERC reviewed the feedback received from all stakeholder groups and focused its deliberation on the feedback received from the PAG, which was the only stakeholder group that disagreed with the Initial Recommendation and did not support early conversion to a Final Recommendation. The PAG requested clarity on a number of issues that included the following: issuing a recommendation based on a small cohort of patients, the unmet need for treatment options considering currently available therapies, appropriateness of accepting ORR as an outcome important to decision-making considering previous submissions in NSCLC which did not receive a positive recommendation based on ORR as the primary clinical outcome, and whether additional data on dabrafenib plus trametinib are forthcoming. pERC agreed with the CGP that it is unlikely that higher quality evidence (i.e., RCT comparing dabrafenib plus trametinib to currently available treatments) on the combination therapy will be forthcoming, considering it is now considered standard of care in countries outside of Canada. pERC discussed the consistency of the evidence from Study BRF113928 and the submitted RWE evidence for all efficacy outcomes and agreed with the CGP that despite the lack of comparative evidence to current available therapies, there is an unmet need for additional treatment options since metastatic NSCLC is incurable and most patients die from their disease. pERC also considered that all stakeholders (patient advocacy and registered clinician groups) emphasized the preference for patients with an identified driver mutation to be treated with targeted therapy upfront as first-line therapy as opposed to non-targeted treatments. In light of these considerations, pERC concluded that the Initial Recommendation should be upheld.

As part of the reconsideration pERC also discussed the feedback received from 1 registered clinician group on the appropriateness of a time-limited switch in therapy to dabrafenib plus trametinib for patients currently on other first-line treatments for NSCLC in the absence of disease progression. A summary of pERC's deliberations related to this issue is provided in the summary table in Appendix 1.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the sponsor's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from 1 patient advocacy group: Lung Cancer Canada (LCC)
- input from 2 registered clinician groups: 3 clinicians on behalf of the Ontario Health Cancer Care Ontario Lung Cancer Advisory Committee (CCO) and 15 clinicians on behalf of LCC
- input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, LCC
- Two clinician groups, CCO and LCC
- The PAG
- The sponsor, Novartis Pharmaceuticals Canada Inc.

The pERC Initial Recommendation was to recommend reimbursement of dabrafenib plus trametinib as treatment for patients with metastatic NSCLC with a *BRAF* V600 mutation who have not received any prior anticancer therapy for metastatic disease, conditional upon cost-effectiveness being improved to an acceptable level and feasibility of adoption (budget impact) being addressed.

Feedback on the pERC Initial Recommendation indicated that the sponsor, patient advocacy group, and both registered clinician groups agreed or agreed in part with the Initial Recommendation and supported early conversion to a Final Recommendation; while PAG disagreed with the Initial Recommendation and did not support early conversion. The PAG cited concerns and requested clarity related to the quality of the submitted evidence (i.e., small cohort of patients), the unmet need considering currently funded therapies, and the appropriateness of accepting ORR as an outcome important to decision-making.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the efficacy and safety of dabrafenib and trametinib in combination for the treatment of adult patients with metastatic NSCLC with *BRAF* V600 mutation who have not received any prior anticancer therapy for metastatic disease.

Studies included: One small, single-arm, non-comparative, open-label, phase II trial

One trial met the inclusion criteria of the systematic review; patient cohort C of Study BRF113928 is an ongoing, phase II, open-label, single-arm, multi-centre trial conducted in 19 centres in 8 countries (North America, Europe, and Asia) that is evaluating the combination of dabrafenib plus trametinib in previously untreated adult patients with *BRAF* V600E-mutant stage IV NSCLC. Eligible patients are treated with oral dabrafenib (150 mg twice per day) plus oral trametinib (2 mg once per day) until disease progression, unacceptable toxicity, consent withdrawal, or death.

Patients enrolled in cohort C of the trial met the following key eligibility criteria:

- aged 18 years or older
- histologically or cytologically confirmed stage IV *BRAF* V600E-mutant NSCLC
- measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) less than or equal to 2
- estimated life expectancy of greater than or equal to 3 months
- no previous *BRAF* gene or Mekinist inhibitor therapy
- no brain metastases unless asymptomatic, untreated, and measuring less than 1 cm (or, if treated, were clinically or radiographically stable 3 weeks after local therapy).

Patient population: Small patient population with stage IV, non-squamous *BRAF* V600E-mutated NSCLC, median age of 67; most patients former smokers with ECOG PS of 1

A total of 36 patients were enrolled in Cohort C of Study BRF113928. The median age of patients was 67 years (interquartile range [IQR], 62 to 74), and most patients were female (61%; n = 22) and White (83%; n = 30). Most patients were former smokers (58%; n = 21); for these patients, the median time smoked was 30 (IQR, 10 to 40) years and the median pack-years smoked was 18 (IQR, 5 to 34). The median time from diagnosis was 2.05 months. All but 1 patient (who was enrolled due to a protocol deviation and had stage III cancer) had stage IV cancer at screening. Histology at initial diagnosis was determined as non-squamous adenocarcinoma in the majority of patients (89%; n = 32), and histological grade could not be assessed for half (50%; n = 18) of the trial population. At baseline, most patients had an ECOG PS of 1 (61%; n = 22). Tumour samples were available for 92% of patients (n = 33), of which 78% (n = 28) met the specifications for the Oncomine assay. Of these, 82% of patients (n = 23) were confirmed to have a *BRAF* V600E mutation. Two patients had brain metastases at baseline that were non-target lesions. A total of 34 (94%) patients received prior anticancer therapy, including surgery and other adjuvant treatments. Overall, 33 (92%) patients received surgery for lung cancer and 10 (28%) patients received prior radiotherapy. The most commonly reported anticancer agents in the adjuvant setting were cisplatin (14%) and carboplatin (8%), pemetrexed disodium (6%), vinorelbine (6%), and vinorelbine detartrate (6%).

Key efficacy results: Clinically meaningful response outcomes; short-term data on PFS and OS

The primary outcome was investigator-assessed ORR, defined as the proportion of patients with a confirmed complete response or partial response according to RECIST 1.1. Secondary outcomes assessed in the trial were ORR independent review committee assessment, PFS, DOR, OS, and safety. Health-related QoL was not evaluated in the trial. The analyses of time-to-event outcomes (i.e., DOR, PFS, and OS) were considered descriptive since no formal hypotheses or statistical testing was performed.

The data cut-off date for the primary efficacy analysis was April 28, 2017; an updated analysis was performed with a data cut-off date of June 22, 2019 (785 days from the first efficacy analyses). The median duration of follow-up was 15.9 months at the time of the primary efficacy analysis and 16.3 months at the time of the updated efficacy analysis.

At the primary analysis, the investigator-assessed ORR was 63.9% based on 23 patients who had a confirmed response, which included 2 patients (6%) who achieved a complete response and 21 patients (58%) who achieved a partial response. There were 27 patients (75.0%) who achieved disease control (23 with a confirmed response and 4 considered to have stable disease). At the time of the updated efficacy analysis, the ORR was maintained (63.9%; 95% confidence interval [CI], 46.2% to 79.2%). The median DOR by investigator assessment was 10.4 (95% CI, 8.3 to 17.9) months at the primary analysis and 10.2 (95% CI, 8.3 to 15.2) months at the updated analysis.

At the primary analysis, the median investigator-assessed PFS was 10.9 (95% CI, 7.0 to 16.6) months and PFS at 6 months was 72% (95% CI, 53% to 84%). At this analysis, 19 patients (53%) were alive and 17 (47%) patients had died; the median OS was 24.6 (95% CI, 12.3 to not estimable) months and 2-year OS was 51% (95% CI, 33% to 67%). At the updated analysis, median PFS was 10.8 (95% CI, 7.0 to 14.5) months and the median OS was 17.3 (95% CI, 12.3 to 40.2) months. OS at 12 months, 24 months, and 36 months was 74% (95% CI, 55% to 85%), 49% (95% CI, 32% to 65%), and 40% (95% CI, 24% to 56%), respectively.

Limitations: No comparison to current standard-of-care treatments

The most significant limitation of Study BRF113928 is that it is a single-arm trial with no placebo or control group(s). The lack of a comparator, the small sample size, and short duration of follow-up limit the conclusions that can be drawn regarding the efficacy and safety of dabrafenib plus trametinib compared to currently available treatments for previously untreated patients with *BRAF* V600E–mutant stage IV NSCLC. In addition, ORR was the primary end point, and it is unknown whether a clinically meaningful ORR translates into clinical benefits in terms of PFS and OS. Although the CGP noted that in clinical practice response rate is often related to survival, there is currently no strong empirical evidence to support ORR as a surrogate for OS in *BRAF* V600E–mutant stage IV NSCLC. In cohort C, ORR was largely driven by partial responses with only 2 of 36 patients achieving complete response. Moreover, the descriptive analyses of secondary time-to-event outcomes (i.e., DOR, PFS, and OS) in a trial with a small sample size further limit interpretation of the efficacy results. Another important limitation is the lack of health-related QoL measures, which are important for capturing the benefits of novel therapies from a

patient's perspective to confirm whether improvements in survival outcomes are accompanied by improved QoL for patients.

Safety: Manageable toxicity profile

All patients had at least 1 AE of any grade. At the time of the primary analysis, this was most commonly (> 30% of patients) reported to be pyrexia (64%, n = 23), nausea (56%, n = 20), diarrhea (36%, n = 13), fatigue (36%, n = 13), peripheral edema (36%, n = 13), decreased appetite (33%, n = 12), dry skin (33%, n = 12), and vomiting (33%, n = 12). Grade 3 and grade 4 AEs were reported in 69% (n = 25) of patients; the most common (> 2 patients) grade 3 and grade 4 events were pyrexia (11%, n = 4), alanine aminotransferase increase (11%, n = 4), hypertension (11%, n = 4), and vomiting (8%, n = 3). Serious AEs (SAEs) occurring in more than 2 patients included alanine aminotransferase increase (14%, n = 5), pyrexia (11%, n = 4), aspartate aminotransferase increase (8%, n = 3), and ejection fraction decrease (8%, n = 3). SAEs occurred in the majority of patients, of which alanine aminotransferase increase (14%; n = 5) and pyrexia (11%; n = 4) were the most common. One patient died from an SAE (cardiorespiratory arrest), which was considered unrelated to the study treatment. AEs led to permanent treatment discontinuation in 22% (n = 8) of patients, dose interruption or delay in 75% (n = 27) of patients, and dose reduction in 39% (n = 14) of patients.

Comparator information: ITC of dabrafenib plus trametinib compared to pembrolizumab plus PDC or PDC alone

Due to a lack of direct evidence comparing dabrafenib plus trametinib combination therapy to other existing first-line treatments for patients with previously untreated *BRAF* V600–mutated advanced NSCLC, the sponsor conducted an ITC to estimate the comparative efficacy of dabrafenib plus trametinib to relevant comparators. A propensity score weighted analysis (PSWA) was conducted that used data from Cohort C of Study BRF113928 (index trial) of first-line dabrafenib plus trametinib and RWE obtained from the Flatiron Enhanced Data Mart (EDM) database. Two RWE cohorts were derived from the Flatiron EDM database: RWE cohort 1 included patients treated with first-line PD1 plus chemotherapy regimens (i.e., pembrolizumab plus PDC) and RWE cohort 2 included patients treated with first-line chemotherapy regimens (i.e., platinum-based chemotherapy).

After adjusting for differences in baseline characteristics between Cohort C from Study BRF113928 and the RWE cohorts, the PSWA results showed that the hazard ratio (HR) for OS favoured dabrafenib plus trametinib over first-line platinum-based chemotherapy (HR = 0.51; 95% CI, 0.29 to 0.92; P = 0.03); for the comparison of dabrafenib plus trametinib versus first-line pembrolizumab plus PDC, the HR for OS was not statistically significant (HR = 0.57; 95% CI, 0.28 to 1.17; P = 0.13).

For PFS, the PSWA results showed that PFS favoured dabrafenib plus trametinib over first-line platinum-based chemotherapy (HR = 0.58; 95% CI, 0.35 to 0.97; P = 0.04); for the comparison of dabrafenib plus trametinib versus first-line pembrolizumab plus PDC, the HR for PFS was not statistically significant (HR = 0.96; 95% CI, 0.51 to 1.81; P = 0.90). However, crossover was observed based on visual inspection of the PFS Kaplan-Meier curves suggesting a violation of the proportional hazards assumption. Therefore, the PFS results should be interpreted with caution.

The CADTH Methods Team identified a number of methodological limitations of the PSWA that included the potential for residual confounding due to differences in baseline characteristics and missing data across the cohorts, discrepancies in the definitions of PFS and the manner in which PFS data were obtained between the index trial and the RWE cohorts, as well as small sample size and violation of the proportional hazards assumption for some analyses. Considering these limitations, the findings reported by the PSWA should be interpreted with caution. Given the uncertainty in the treatment effect estimates, the comparative efficacy of dabrafenib plus trametinib versus first-line pembrolizumab plus PDC and first-line platinum-based chemotherapy remains unclear based on the PSWA.

Need and burden of illness: Need for targeted treatments

Lung cancer is the second most common cancer in women and the third most common cancer in men in Canada. In the overall population (men and women combined), it is the most common cancer, with approximately 29,800 new cases in Canada in 2020. With approximately 21,200 lung cancer deaths in Canada, it is the most common cause of cancer death, accounting for approximately 25% of all Canadian cancer deaths. NSCLC accounts for about 88% of all lung cancer cases. Approximately 50% and 30% of patients are diagnosed with stage IV and locally advanced stage III NSCLC, respectively. The incidence of

NSCLC rises with age, and the median age at diagnosis is 70 years. Given the high proportion of patients presenting with advanced stages at diagnosis, the expected relative 5-year survival is only 18%.

Data from multiple studies have emerged demonstrating the importance of molecular profiling of lung adenocarcinomas. Therapeutic options for oncogenic driver mutations have demonstrated superior efficacy to standard chemotherapies and have dramatically changed the treatment paradigms for advanced NSCLC. Oral targeted therapies directed at the tyrosine kinase domain of the *EGFR*, *ALK*, and *ROS1* genes have all shown high objective response rates and improved PFS and have been incorporated into treatment algorithms. *BRAF* V600E mutations occur in approximately 2% of NSCLC adenocarcinomas and are considered oncogenic drivers that generally occur independently of other common oncogenic drivers, including *EGFR* mutations and *ALK* translocations. Currently, there are no funded targeted therapies for patients with a *BRAF* V600 driver mutation. Thus, there remains a need for therapies that will advance treatment options in these patients who have an identified driver mutation.

Registered clinician input: Well-tolerated, convenient oral option that fulfills an unmet need for a targeted treatment option

A total of 2 registered clinician inputs were provided for the review of combination dabrafenib and trametinib for the treatment of patients with metastatic NSCLC with a *BRAF* V600 mutation who have not received any prior anticancer therapy for metastatic disease: 1 joint input submission on behalf of 3 clinicians from CCO and 1 joint input submission on behalf of 15 clinicians from LCC. Overall, both groups of clinicians were supportive of the use of dabrafenib plus trametinib for metastatic NSCLC patients with the *BRAF* V600 mutation. The clinicians from CCO noted that this combination is a great option for elderly and comorbid patients as it is well tolerated. The clinicians were pleased with the oral nature of the drug combination, especially during the current COVID-19 pandemic, as it eliminates the need for patients to travel to the cancer centre or infusion site. Clinicians from CCO recommended the use of dabrafenib plus trametinib in the second-line setting for patients after first-line treatment with immunotherapy or the combination of chemotherapy and immunotherapy. In contrast, the clinicians from LCC recommended the use of the combination in the first-line setting. The clinicians from LCC explained that the use of first-line immunotherapy has not been well documented in patients with driver mutations, and the use of targeted inhibitors upfront provides a greater chance for long-term survival and an improved QoL. The clinicians from LCC stated that immunotherapy with platinum doublets is a good option in the second-line setting and docetaxel is an option in the third-line setting. Overall, both groups of clinicians emphasized that dabrafenib plus trametinib would address a high unmet need for NSCLC patients with the *BRAF* V600 mutation as it is a rare mutation for which there are currently no available targeted therapies.

PATIENT-BASED VALUES

Values of patients with *BRAF* V600-mutated NSCLC: Disease has significant physical and emotional impacts, and financial burden on patients and caregivers; unmet need for a targeted treatment option

One patient group input was provided by LCC for the review of dabrafenib in combination with trametinib for the treatment of patients with metastatic NSCLC with a *BRAF* V600 mutation. LCC gathered patient and caregiver input through surveys, patient and caregiver interviews, an Environmental Scan of social media and information from previous LCC submissions to pERC. A total of 4 patients and 2 caregivers provided input about treatment with dabrafenib plus trametinib. Symptoms of advanced NSCLC that most affected patients' QoL were cough, shortness of breath, and fatigue. The disease can cause a significant physical, emotional, and financial burden on patients and their caregivers. LCC identified a high unmet need for Canadian patients with advanced NSCLC with *BRAF* mutations, as currently there are no targeted therapies available for this small group of patients. Current treatments include chemotherapy, immunotherapy, and a combination of both immunotherapy and chemotherapy. Patients noted that chemotherapy was associated with side effects such as nausea, vomiting, and fatigue, and many patients eventually progress on the treatment. Patients reported a much more positive experiences with immunotherapy and the combination of chemotherapy and immunotherapy; however, LCC noted that, in the long-term, immunotherapy has been documented to have poor efficacy for patients with targeted mutations. Additionally, immunotherapy can be burdensome for patients as it can require multiple hospital visits, thus necessitating the need for an oral option such as dabrafenib in combination with trametinib.

Patient values on treatment: Delayed progression, longer survival, better symptom management, and manageable side effects

LCC reported on the experience with dabrafenib plus trametinib of 4 patients and 2 caregivers, all of whom reported an overall favourable experience with the drug combination. Patients reported that the drug combination helped reduce the size of the tumour and control their symptoms. Most patients reported very minimal side effects that were manageable. Patients noted that the drug had allowed them to return to their normal activities and regain their independence. Further, the oral combination reduced the burden on patients and caregivers compared to current IV modality treatments, which comparatively are associated with more side effects and hospital visits. However, a concern reported by 1 patient was the high cost of the drug combination, which would have made the drug inaccessible without insurance and a special access program. Patients expressed strong hopes for this combination to be accessible to all Canadian patients with advanced NSCLC with the *BRAF* V600 mutation. Overall, patients indicated that when considering a new treatment, they value delayed progression and prolonged survival, better symptom control, manageable side effects, and an improved QoL.

ECONOMIC EVALUATION

Dabrafenib plus trametinib is available as a combined 2-drug regimen. The recommended dose for dabrafenib is 150 mg twice daily (total daily dose of 300 mg) with trametinib 2 mg daily. Treatment with dabrafenib plus trametinib should be continued until disease progression or unacceptable toxicity. At the sponsor's submitted prices for dabrafenib ($44.88 per 50 mg capsule, $67.32 per 75 mg capsule) and trametinib ($76.98 per 0.5 mg tablet, $307.94 per 2.0 mg tablet) the total drug acquisition cost per patient is $577 or $16,162 for a 28-day course.

The sponsor submitted a cost-utility analysis for the first-line treatment setting, comparing dabrafenib plus trametinib with pembrolizumab plus PDC and a blended strategy of PDCs for adults with metastatic *BRAF* V600-mutant NSCLC who have not received any prior anticancer therapy for metastatic disease (i.e., per the reimbursement request). PDC included 6.7% platinum plus etoposide, 6.7% platinum plus paclitaxel, 6.7% platinum plus gemcitabine, and 80% platinum plus pemetrexed. The sponsor's partitioned survival model consisted of 3 health states: pre-progression (time to the first documented tumour progressed, as per RECIST 1.1, to unacceptable toxicity or to death from any cause), post-progression, and death. Time spent in each state was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis (10 years) using parametric methods. Patients were assumed to be on treatment, according to the modelled extrapolations, until discontinuation or progression, whichever occurred first. Data from the sponsor's ITC of the BRF113928 study and the Flatiron database were used to inform treatment efficacy for dabrafenib plus trametinib, pembrolizumab plus PDC, and PDC alone.

CADTH identified the following key limitations with the sponsor's submitted economic analysis:

- The CADTH Clinical Review identified several limitations with the sponsor-submitted ITC and concluded that the comparative efficacy of dabrafenib plus trametinib is uncertain.
- The parametric function that the sponsor selected to extrapolate the OS curve for dabrafenib plus trametinib (i.e., generalized gamma function) overestimated expected survival at the end of the modelled time horizon according to the clinical experts consulted by CADTH for this review.
- Relevant comparators were excluded: pembrolizumab monotherapy and atezolizumab-based therapies.

CADTH reanalyses addressed the reimbursement population exclusively (no prior anticancer therapy) and included the PFS and OS) outcomes from the BRF113928 study for dabrafenib plus trametinib and all comparators (pembrolizumab plus PDC, PDC alone) and a revised parametric function to characterize the OS extrapolation for dabrafenib plus trametinib. The adjustment to comparative efficacy resulted in equivalent incremental effectiveness for all treatments (dabrafenib plus trametinib, pembrolizumab plus PDC, PDC alone). According to the sequential analysis of the CADTH base case, dabrafenib plus trametinib was dominated by pembrolizumab plus PDC (i.e., was $21,506 more costly; generated equivalent QALYs). The probability that dabrafenib plus trametinib represented the most cost-effective strategy was 28% at a WTP threshold of $50,000 per QALY. A price reduction of at least 88% is needed for dabrafenib plus trametinib to be cost-effective compared to PDC.

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

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact is uncertain
CADTH reanalysis suggests that the sponsor-submitted budget impact of introducing dabrafenib plus trametinib to the market is underestimated, with the 3-year budget impact from the CADTH reanalysis estimated at $34,357,089. Factors with the greatest influence on the estimated budget impact were the market share uptake for dabrafenib plus trametinib and the percentage of NSCLC patients with a *BRAF* V600 mutation.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Michael Crump, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan, who was not present for the meeting
- Dr. Maureen Trudeau, who was excluded from voting due to her role as pERC Chair.

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau, who was excluded from voting due to her role as pERC Chair.

Avoidance of conflicts of interest

All members of the CADTH pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the CADTH website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of dabrafenib plus trametinib for metastatic NSCLC with a *BRAF* V600 mutation, through their declarations, no members had a real, potential, or perceived conflict based on application of the *pCODR Conflict of Interest Guidelines*, and therefore no member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the CADTH website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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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.

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC recommendation
Eligible patient population	
In view of the characteristics of the patient population and exclusion criteria in the BRF113928 phase II trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with dabrafenib in combination with trametinib:	
• Patients with tumours harbouring V600 mutations other than V600E (e.g., V600K, V600R, V600D)	• pERC agreed with the CGP that there are limited data on the efficacy of dabrafenib plus trametinib in NSCLC patients with *BRAF* mutations other than V600E. Despite the limited evidence, pERC agreed with the CGP that it is likely that the combination would be active in NSCLC patients with a range of *BRAF* V600 mutations (as in the case for melanoma), and therefore all patients with tumours harbouring V600 mutations should be eligible for treatment with dabrafenib plus trametinib.
• Patients with active unstable brain metastases	• pERC noted that Study BRF113928 permitted the inclusion of patients with treated or asymptomatic brain metastases. Accordingly, if brain metastases are present, patients should be asymptomatic or have stable symptoms in order to be considered eligible for dabrafenib plus trametinib.
If dabrafenib plus trametinib were recommended for reimbursement, PAG raised that *BRAF* V600 patients currently on first-line chemotherapy or immunotherapy and who have not progressed may need to be addressed on a time-limited basis and seeks advice on switching these patients to dabrafenib plus trametinib.	At the time of implementing a funding recommendation for dabrafenib plus trametinib, jurisdictions may want to consider addressing the short-term, time-limited need for offering the combination to patients who are currently receiving immunotherapy and/or chemotherapy as first-line treatment of *BRAF*-mutated metastatic NSCLC and have not progressed. • pERC agreed with the CGP and registered clinician group feedback that switching patients who are on an effective treatment (i.e., not progressing) is not entirely appropriate, as they may lose access to this treatment again in the future and lose benefit. However, a switch to dabrafenib plus trametinib should be permitted in patients without progressive disease when side effects from toxicities impair quality of life since the combination therapy is usually well tolerated.
Implementation factors	
For both dabrafenib and trametinib, treatment should be continued until disease progression or unacceptable toxicity. PAG seeks a clear definition of disease progression for development of discontinuation criteria.	• pERC discussed that RECIST criteria are usually used as a guideline for therapy continuation. However, pERC agreed with the CGP that the RECIST criteria have limitations for decision-making in clinical practice when presented with certain situations such as oligoprogression. pERC agreed with the CGP that the decision to discontinue treatment should be made by the oncologist and patient, taking into consideration multiple factors and guided by, but not limited to, RECIST criteria.
Sequencing and priority of treatments	
PAG is seeking to confirm the place in therapy of dabrafenib plus trametinib and sequencing with other therapies for NSCLC	

including the scenarios below: Discontinuation of either drug in case of toxicity and continuation of the other for the remainder of the therapy.	• pERC agreed with the CGP that both drugs individually can potentially have therapeutic benefit. As such, pERC agreed that it is reasonable to continue 1 drug if the other has to be discontinued and this should be a clinical decision by the oncologist in discussion with the patient.
Is it common for patients to receive targeted therapy (*EGFR* and *ALK*) adjuvantly and also have a *BRAF* mutation and be treated with dabrafenib plus trametinib in the metastatic setting?	• pERC agreed with the CGP that adjuvant osimertinib is likely to be used increasingly in patients with resected *EGFR*-mutant NSCLC. The CGP noted that it is possible but unlikely that a *BRAF* mutation would be found at recurrence after or during adjuvant osimertinib, and it is highly unlikely that *EGFR* or *ALK* therapy would be used in the adjuvant setting at all if the relevant mutation was not present. Further, it is possible that a very small proportion of patients would develop a new primary lung cancer that had a *BRAF* mutation after receiving adjuvant osimertinib for a resected *EGFR*-mutant NSCLC. Accordingly, very few patients would be candidates to go from 1 therapy to another therapy, and extremely few (if any) would be candidates for both.
Use of targeted *BRAF* therapy to induce a response, then switch to immunotherapy as maintenance. If this were to occur, there may be a desire to use *BRAF*-targeted therapy at the time of disease progression. Therefore, could *BRAF*-targeted therapy be restarted at the time of disease progression?	• pERC agreed with the CGP that there are currently no situations in lung cancer where a targeted therapy is used as induction followed by a switch to immunotherapy maintenance. In usual clinical practice, targeted therapies are typically continued until tumour progression.
Alternative therapy options for patients with a *BRAF* V600 mutation who are unable to tolerate dabrafenib plus trametinib including immunotherapies. Is there evidence to inform whether immunotherapies are effective in *BRAF* V600 mutants?	• pERC agreed with the CGP that limited evidence suggests that immune checkpoint inhibitors may be effective in some NSCLC patients with *BRAF* mutations. In 43 NSCLC patients with *BRAF* mutations, the response rate with immune checkpoint inhibitors was 24%, which is similar to the response rate in NSCLC patients with *KRAS* mutations (response rate 26%) and higher than the response rate with *EGFR* mutations (12%) or *ALK* fusion genes (0%).
Availability of single-agent immunotherapy in subsequent lines. PAG seeks confirmation that patients should first complete chemotherapy prior to being eligible for immune checkpoint inhibitors.	• pERC agreed with the CGP that there are insufficient data to inform sequencing of treatments.
Companion diagnostic testing	
BRAF testing is not routinely performed for patients with NSCLC and would need to be implemented. PAG is seeking clarity on whether *BRAF* testing would be required in all patients and the appropriate timing of *BRAF* testing (e.g., upfront or when progressed with metastatic disease). With the multiple testing of targets required for lung cancer, PAG is seeking clarity on whether this would be performed on 1 tissue sample. Due to the high prevalence of NSCLC, the impact on laboratory budgets may be significant.	• pERC agreed with the CGP that molecular testing is currently considered to be the standard of care for management of non-squamous NSCLC patients and should be completed upfront due to the number of targets that are now relevant and guide treatment decisions. Next-generation sequencing generally reports on *BRAF* mutations at no increased cost over and above testing for the other relevant mutations. For most patients, all molecular testing can be done on a single biopsy sample.

BRAF = v-Raf murine sarcoma viral oncogene homolog B; CGP = Clinical Guidance Panel; NSCLC = non-small cell lung cancer; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; RECIST = Response Evaluation Criteria in Solid Tumors.